Long-term population-based trends in the incidence of cardiovascular disease in individuals with type 1 diabetes from Finland : a retrospective, nationwide, cohort study

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Decrease in incidence of cardiovascular disease in individuals with type 1 diabetes - long-term population-based trends

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Abstract

Background Cardiovascular disease (CVD) is the main determinant of premature mortality in type 1 diabetes (T1D). However, time trends regarding different types of CVD in childhood onset T1D with a long time-span from the diagnosis of diabetes are not well established. This study therefore investigated the cumulative incidence of CVD in individuals with T1D in a population-based cohort.

Methods The entire cohort of 11,766 individuals diagnosed with T1D under the age of 15 years during the period 1965-1999 in Finland was followed for the occurrence of CVD until the end of 2016 and CVD mortality until 2017. Cumulative incidences of CVD were defined by 5-year calendar year of diagnosis cohorts. The excess risk of CVD was estimated by comparison with the risk in the Finnish background population by calculating standardized incidence ratios (SIRs) and their time trends.

Findings During 361,033 person-years of follow-up and 29·6 (IQR 22·3-37·9) years of median follow-up time a total of 1,761 individuals had experienced single or multiple types of CVD events; 864 events of coronary artery disease (CAD) of which 663 were acute myocardial infarctions, 497 strokes, 854 peripheral artery disease of which 498 lower extremity amputations and 471 heart failure events as well as 1,467 deaths. The hazard ratio for any CVD was 1·99 (95% CI 1·67-2·36) in the earliest cohort (1965-69) and decreased to 0·63 (0·42-0·97) in the latest cohort (1995-99) compared with the mid-point cohort (1980-84) (p<0·0001 for trend). The decrease was more pronounced in the cohorts from 1960 to 1980, but only modest after that. There was decrease in the SIRs for both CAD and stroke within all 10-year age groups under 65 years, except for stroke in the oldest age group. However, the SIR was still 8·9 (95% CI 7·4-10·6) for CAD and 2·9 (1·3-5·7) for stroke in those diagnosed in the 1990s. Finally, the CVD mortality rate decreased constantly by diagnosis year.

Interpretation The risk of CVD has decreased over time in Finland in individuals with childhood-onset T1D. However, there is still considerable excess CVD risk in individuals with T1D compared to the background population. These results highlight the need for studies on the mechanisms of atherosclerosis from the time of diagnosis of diabetes in order to facilitate early and effective prevention of CVD.

Research in context

Evidence before this study

We searched PubMed for articles published up to May 20, 2020, using the search terms "type 1 diabetes", "type 2 diabetes", or "diabetes" in combination with "diabetes complications", "cardiovascular disease", "coronary artery/heart disease", "peripheral artery disease", "stroke", "heart failure", "trend", "secular", "decrease", "long-term", "incidence", "morbidity", "mortality". We also hand-searched reference lists of identified publications to determine additional eligible articles. The search was limited to articles in the English language. We aimed to identify articles of investigations of long-term trends of CVD in type 1 diabetes. We identified, however, only a few such studies conducted in type 1 diabetes (T1D).

Several studies have shown a decline in the incidence and the mortality of CVD over time in individuals with diabetes. However, the type of diabetes was either not specified, the data covered short-term trends, or did not take the duration of diabetes, age or age at onset of diabetes into account. There is also a lack of contemporary data on CVD outcomes in childhood-onset T1D.

Added value of this study

This study provides for the first time a comprehensive picture of the trends in the cumulative incidence of different types of CVD in childhood onset T1D with to date the longest observation period of over 50 years. This study also provides for the first time the time trends in the excess risk of coronary artery disease and stroke. The comparison covered the diagnosis of diabetes over the decades 1960s, 1970s, 1980s and 1990s, where the follow-up started from the date of diagnosis. There was significant risk reduction for each CVD type over time; coronary artery disease (CAD), stroke, peripheral arterial disease and heart failure (HF). Although the observed decrease in the CVD events could be explained by the concomitant decrease in the incidence of diabetic nephropathy (DN), our analyses have shown that DN was not the only factor contributing to the decrease in CVD events. Independently of DN, age and sex, receiving a T1D diagnosis during the more recent calendar years was associated with a decrease in the CVD incidence. However, this study revealed only a modest further decrease in those diagnosed in the 1990s compared to those diagnosed in the 1980s, especially for HF and in women not significant decrease was seen. Moreover, the incidence of low extremity

amputations even slightly increased. Despite the attenuated decrease in CVD morbidity in the more recent cohorts, the CVD mortality had decreased. Finally, despite the increased risk of CVD in those with T1D compared to the background population, the excess risk in T1D had decreased in the more recent cohorts.

Implications of all the available evidence

Over the past four decades, alongside the microvascular complications also the CVD burden has decreased. However, despite the decrease in the long-term trends, the excess risk of coronary artery disease in those under the age of 35 years compared to the general population was still 8.9-fold increased. These results highlight the need for studies of the natural course of atherosclerosis in children and young adults from the time of diagnosis of diabetes in order to facilitate early and effective prevention of CVD.

Introduction

Cardiovascular disease (CVD) is the main determinant of premature mortality in type 1 diabetes (T1D)[1]. The risk of CVD is several-fold higher in individuals with diabetic nephropathy (DN), but even those without any signs of kidney disease are at increased risk [2].

CVD morbidity and mortality have decreased in individuals with type 2 diabetes (T2D) and in the general population [3]. However, it is not well-established whether a similar decrease has occurred in individuals with T1D. Unfortunately, previous studies conducted in diabetes populations often do not distinguish between individuals with T1D and T2D [4], thus probably masking differences in the trends in these two populations. The Pittsburgh Epidemiology of Diabetes Complications (EDC) study suggests that despite of a remarkable decrease in end stage renal disease (ESRD) and mortality, the incidence of coronary heart disease has been stable [5,6]. However, these data originated from cohorts, diagnosed with T1D in years 1965 to 1980 and therefore more recent cohorts of individuals with T1D were not included. Recently, treatment and monitoring of hyperglycemia has improved, together with diagnostic and therapeutic approaches for CVD, offering possibilities for further CVD decrease. Data from the Swedish National Diabetes Register Study indeed showed a decrease in CVD morbidity and mortality from 1998 through to 2014 [7], but their study did not show long-term trends with follow-up from the diagnosis of diabetes. Also, previous studies may not be representative of the childhood-onset T1D. Furthermore, very little is known about the trends for heart failure (HF) or peripheral artery disease (PAD) in T1D. Finally, data on CVD risk in those who have been diagnosed with T1D after the year 1990 are missing.

Therefore, the aim of this study was to evaluate the cumulative incidence of CVD, including coronary artery disease (CAD), stroke, PAD and HF, according to the calendar year of diabetes diagnosis and the presence of DN in the country with the world's highest incidence of T1D [8,9] based on nationwide data from reliable registries with up to 50 years of follow-up. In addition, we studied the time trends regarding the excess risk of CAD and stroke as well as of CVD mortality.

Methods

This is a population-based cohort study of 11,766 individuals diagnosed with T1D before the age of 15 years (Supplementary Figure 2) between the calendar years 1965 and 1999, and who

were included in the database of the National Institute for Health and Welfare (NIHW). This database is compiled from successive cohorts of individuals with childhood onset T1D in Finland. It is virtually complete, since it includes data from the National Social Insurance Institution on all individuals that require insulin and that have received their medication for free since 1965 and these individuals with T1D can thus be identified from this register [10,11]. History of CVD and DN was identified from the Finnish Care Register for Health Care and the Cause of Death Register until the end of year 2016. The Finnish Care Register for Health Care is one of the oldest individual level hospital discharge registers in the world and covers information on all hospitalizations in Finland since 1967 including day-surgical procedures codes since 1996 and specialized outpatient care since 1998 [12].

The first CVD events (either non-fatal of fatal) were defined as a history of CAD that includes acute myocardial infarction (AMI) or coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft), ischemic or hemorrhagic stroke, PAD defined as lower extremity amputation (LEA) or revascularization (either open surgical or endovascular) and HF. Separate analysis for each CVD subtype included the first event of the CVD type. The dates for diagnosis of DN/CVD were defined as the first admission date of hospitalization, day-care angioplasty, or visit to the specialized outpatient care (DN) or death. To get the most accurate onset time of DN/ESRD we furthermore utilized the data from the Finnish Diabetic Nephropathy Study that partly overlap with these data [13]. Specific codes for CVD and DN are listed in Supplementary Table 1.

Statistical methods

The date of the diabetes diagnosis was specified as the entry date, and the date of the CVD event, death or the 31st of December 2016 as the exit date of follow-up. The follow-up since diabetes diagnosis was expressed as median (interquartile range, IQR). Cumulative incidence rates for CVD were defined by the Fine and Gray method [14] instead of the Kaplan-Meier method that are generally biased upwards [15]. Death from other causes than the type of CVD that is investigated are considered as competing events. However, another type of CVD event was not considered as a competing event. First, the relationship and form of the trend between incident CVD events or CVD-mortality and diabetes diagnosis year as a continuous variable was assessed allowing for nonlinearity by using restricted cubic splines. Then, the Wald test was used to test for the presence of nonlinearity. Cumulative incidences were calculated combining any type of CVD (the first) and also separately for CVD subtypes stratified by 5-year calendar year of diagnosis cohorts 1965-69, 1970-1974, 1975–1979, 1980-84, 1985-89,

1990-1995 and 1995-99. Trends in CVD event rates were analyzed by Fine and Gray competing risks regression models considering the year of diagnosis of diabetes as a continuous variable and adjusting for age at onset of diabetes, sex and DN status before the incident CVD event. Interaction between sex and diagnosis cohort was incorporated into the models to assess whether the trends were different between the sexes. If no interaction was detected, the trends were similar for both sexes. However, we conducted also the analyses separately for women and men and they are shown in the Supplementary Table 2. Cumulative CVD-mortality (due to CAD or stroke) analyses were conducted using other causes of death as competing risk.

In order to quantify the excess CAD and stroke morbidity in individuals with T1D the data were compared with the Finnish background population drawn from the Cardiovascular Disease Register of the NIHW that contains data annually for the years 1991-2014 in 10-year age groups and is publicly available [16,17]. Standardized incidence ratios (SIRs) were calculated as ratios of observed and expected number during the same time period, 1991-2014. The expected numbers were derived by multiplying the number of person-years at risk by sex-, 10-year age- and 1-year period-specific morbidity rates observed in the background population [18]. Changes in SIRs across time periods were evaluated by Poisson regression using a log of the expected counts as an offset and adjusting for sex and age.

All analyses were performed using the Statistical Analysis System version 9.4 (SAS Institute, Cary, NC, USA) and the R open source software version 3.2.2 (http://www.r-project.org). The study was approved by the Finnish National Institute for Health and Welfare (THL/786/6.02.00/2016) and Statistics Finland (TK53-26-16).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the study population according to the 5-year calendar year of diagnosis cohorts. The median follow-up time (duration of diabetes) for any CVD was 47·3 (IQR 35·2 to 49·4)

years in the earliest diagnosis cohort (1965-69), while it was 19·3 (18·0-20·6) years in the latest cohort (1995-99). In the earliest cohort, the 50-year survival was 63·6% (62·6 to 64·5). During 361,033 person-years of follow-up and 29·6 (IQR 22·3 to 37·9) years of median duration of diabetes a total of 1,761 individuals had experienced a first ever CVD event. There were 864 CAD events of which 663 were AMIs, 497 strokes, 854 PADs of which 498 LEAs, and 471 HF events until 2016 and 1,467 deaths until 2017. Most of the CVD events occurred in those with DN, n=1,068. The vast majority of the individuals having CVD had a single type of CVD event (n=1,125, 63·9%), but 399 (22·6%) had two, 195 (11·1%) three and 42 (2·4%) four different types of CVD (Supplementary Figure 1A). The most prevalent combination of different CVD events was CAD and PAD with or without HF (7·6% and 6·7%). When DN was present, the degree of clustering of CVD events was higher, 46·1% (Supplementary Figure 1B) versus without DN, 20·8% (Supplementary Figure 1C).

Cumulative incidence of any CVD, CAD, stroke, PAD, and HF

The 50-year cumulative incidence of any CVD was 45·8% (43·0 to 48·6) in the individuals diagnosed in 1965-69 (Figure 1A), and was higher in men than in women, 47·6% (95% CI 43·9 to 51·5) vs 43·8% (95% CI, 39·7 to 47·9). The hazard ratio for men compared to women with diabetes for all individuals was 1·23 (1·12-1·35, P<0·0001). The 25-year cumulative incidences were 7·5% (6·2 to 9·0), 5·2% (4·1 to 6·5), 6·0% (4·9 to 7·3), 3·8% (3·0 to 4·8), 3·3% (2·5 to 4·2), 3·1% (2·3 to 4·0) and 1·8% (1·0 to 2·9) for the diagnosis cohorts from the earliest to the latest, respectively. According to the Fine and Gray regression model adjusted for sex and age at diagnosis of diabetes the CVD risk decreased by 3·8% (95% CI 4·0 to 4·5, P<0·0001) by later calendar year of diabetes diagnosis (p<0·0001, Table 2). The relationship between the calendar year of diabetes diagnosis and the CVD events did not deviate from linearity (Figure 2A). The downward trend was similar for men and women (p=0·65 for interaction between sex and diagnosis cohort).

The pattern of the cumulative incidence of CAD was similar as for any CVD type (Figure 1B). Thus the 50-year cumulative incidence was 26·5% (24·2-29·1) in the earliest cohort, while the 25-year cumulative incidence was 2·6% (1·9 to 3·6), 1·7% (1·1 to 2·5), 1·7% (1·2 to 2·5), 1·0% (0·6 to 1·5), 0·9% (0·5 to 1·5), 0·7% (0·4 to 1·2) and 0·2% (0·06 to 0·4) for the diagnosis cohorts from the earliest to the latest, respectively. The CAD risk decreased continuously by 5·1% (95% CI 4·8 to 7·2, p<0·0001) per later calendar year of diabetes diagnosis (Table 2, Figure 2B).

The shape of the decrease was similar for men and women (p=0·67 for interaction). Supplementary Table 4 shows the proportions of AMIs and revascularizations and Supplementary Table 5 28-days case fatality, 1-year survival rate and median survival time in AMI.

Figure 1D shows the cumulative incidence of stroke by diagnosis cohort. The 50-year cumulative incidence of stroke was 13·6% (11·8 to 15·6) in the individuals diagnosed in 1965-69. The 25-year cumulative incidence decreased from 2·5% (1·7 to 3·4) in the earliest cohort to 1·1% (0·6 to 1·7) in the latest cohort 0·2% (0·008 to 0·5). The greatest difference in the risk was seen between the earliest cohort (1960s) and the rest of the cohorts. The flattening decrease could be seen also in the Figure 2D. There was no interaction between sex and year of diagnosis year (p=0·46) indicating similar trends for men and women. The Supplementary Table 5 shows 28-days case fatality, 1-year survival rate and median survival time in stroke.

The 50-year cumulative incidence of PAD was 23·6% (21·2-26·0) in the individuals diagnosed in 1965-69. The 25-year cumulative incidence was 2·3% (1·6-3·2) in the earliest cohort while to 0·8% (0·3 to 1·8) in the latest cohort. Contrary to the other types of CVD, the greatest fall in the risk of PAD was observed after the 1970s (Figure 1E), a further decrease was seen in the cohort of 1980-84 and also after 1985. Figures 1F and 2F show the results separately for LEA. Despite the overall decrease in the LEA incidence in the later diabetes diagnosis cohorts, there was a slight increase observed in the 1990s cohort.

Finally, the decrease by time in the HF risk was less prominent than for any of the other CVD types (p=0.056 for differences between cohorts, Figure 1G). When calendar year of diabetes diagnosis was analyzed as a continuous variable, a significant decrease in the HF risk was seen in the later calendar years (Figure 2G, p=0·005). The interaction between sex and the calendar year of diagnosis was not significant (p=0·34). However, the decrease in women did not reach statistical significance while it did in men (Supplementary Table 2).

Standardized incidence ratio (SIR) of CAD and stroke

The SIR for CAD was 10·9 (95% CI 10·1 to 11·8) in the entire cohort, 25·5 (22·5 to 28·9) in women and 8·0 (7·2 to 8·8) in men. The SIR was the highest, 25·1 (20·6-30·3) in the youngest age group 25-34 years and decreased to 13·5 (11·9-15·3), 8·1 (7·1-9·3) and 6·7 (5·1-8·7) in the age groups 35-44, 45-54 and 55-64 years, respectively. In men the age-group specific SIRs were 16·1 (12·2-20·9), 9·9· (8·4-11·5), 6·4 (5·4-7·5) and 4·6 (3·1-6·5) while in women 58·8

(44·3-76·5), 35·0 (28·4-42·7), 17·1 (13·5-21·3) and 15·2 (10·1-22·2) from the youngest to the oldest age group, respectively.

Figure 3A illustrates the decrease in SIRs for CAD within each 10-year attained age group by diabetes diagnosis cohorts. The SIR in the youngest age group 25-34 years decreased from 36·3 (23·3 to 54·0) in those diagnosed in the 1970s to 8·9 (3·9 to 17·5) in the individuals, who were diagnosed during the 1990s.

The SIR for stroke was 5·9 (95% CI 5·3 to 6·5) for the entire cohort, 6·1 (5·3 to 6·9) for men and 5·7 (4·8 to 6·7) for women. Figure 3B shows the decrease in SIRs for stroke. In contrast to CAD, the differences in SIRs between the age groups were less striking, and the highest SIR peak was observed in the age group 35-44 years, 7·7 (6·6-8·9), while it was 5·4 (4·1-6·8), 5·2 (4·4-6·2) and 3·5 (2·3-5·2) in the age groups 25-34, 45-54 and 55-64 years, respectively. There was a decrease in the SIRs for stroke in the age groups of 25-34, 35-44 ($p<0·0001$) and 45-54 years ($p=0·02$), but not in 55-64 years (0·19). The decrease in the SIRs was most prominent in the age group 35-44 years in which the SIR decreased from 10·3 (7·7-13·4) in those diagnosed during the 1960s to 3·9 (1·6-8·2) in those diagnosed in the late 1980s.

CVD mortality

There was a total of 538 deaths in which CVD (either CAD or stroke) was the cause of death from a total of 1467 deaths until 2017. Notably, there was only one death due to CVD in those diagnosed during the 1990s. Figure 4 shows the cumulative CVD mortality curves and Figure 2H the decreasing HRs. The 50-year cumulative CVD mortality was 17·7% (15·7-19·8) in the earliest cohort, and the 35-year cumulative mortality was 7·5% (6·1-9·0), 5·1% (4·0-6·3), 3·6% (2·7-4·6), 2·0% (1·4-2·9) in the four earliest cohorts. There was an increase in the median survival time after AMI and stroke observed, but not for the short-term mortality (Supplementary Table 5).

Discussion

This study demonstrates a considerable decrease in CVD morbidity and mortality in childhood onset T1D over the last five decades in Finland. The decrease was observed in the absolute morbidity, the excess morbidity (SIR) and the mortality. Notably, the decrease in SIRs indicates a steeper reduction in CVD morbidity in individuals with T1D than in the general population. However, CVD morbidity is still several-fold increased compared with the general population. It is of concern that the decrease in CVD morbidity in the individuals, who were

diagnosed in the 1990s compared to those who were diagnosed in the early 1980s, has been only modest.

Some previous studies have also shown a decline in the diabetes related vascular complications, although the decline has mainly been limited to the microvascular complications or did not distinguish between T1D and T2D [4, 19-21]. Our results are to a large extent in concordance with recently published data from the Swedish National Diabetes Register. However, their data were restricted to the period from 1998 to 2014 [7] and did not account for the calendar year of diabetes diagnosis. In line with the Swedish study, there was a greater reduction in the CVD burden in individuals with diabetes than in the general population. Similarly, a greater proportional reduction was observed in the rates of mortality, AMI and stroke in the individuals with T1D compared to the nondiabetic population in a Canadian study [20]. This greater relative CVD risk reduction in T1D compared to the general population could be the consequence of a higher initial risk present in those with T1D, being especially high in those with ESRD [22]. The Epidemiology of Diabetes Complications (EDC) study provided trends for individuals with longstanding T1D with the earliest diagnosis cohort comparable with ours, 1965-69, but the EDC did not include any cohorts from the 1990s. In contrast to our results, no reduction in the incidence of CAD was found over time [6]. This difference may be due to their smaller sample size and lack of cohorts with a more recent diabetes onset. Nevertheless, recent reports from the US show an increase in some diabetes complications, especially the LEAs, that may be influenced by broader social and economic factors [23].

Very few studies report data on PAD in T1D. We here show that PAD events are as common as CAD events in the T1D population. The decrease in the PAD incidence is seen throughout the years and is at least partly driven by the decline in DN/ESRD that has been shown previously in this population [24]. However, the rate of LEA was not reduced after diabetes diagnosis year 1985, although there was an overall significant decrease observed from the 1960s.

Besides the LEA, heart failure is the complication with the smallest decrease in its incidence observed during the years of follow-up, both being tightly associated with glycemic control and DN [25]. In line with our results, there was no significant reduction in risk of hospitalization for HF in individuals with T1D in the Swedish study [7]. On the contrary, a greater decrease in

the HF risk in T1D individuals than in non-diabetic individuals was reported from Scotland during the years 2004-2013 [26].

It is of note that the decline in CVD has been accompanied by a corresponding decline in ESRD in Finland [24]. However, the calendar year of T1D diagnosis remained a significant predictor of the decline in CVD after adjusting for the DN status, suggesting that also other factors are explaining the decline. The observed decline could possibly be connected to two main reasons. First, as a similar pattern is seen in the background population, it could be associated with intensified lipid-lowering and antihypertensive treatment, as the use of statins and the inhibition of the renin-angiotensin-aldosterone system are now cornerstones of the standard of care. Second, it could also be related to the improvement of diabetes care given the major advances in blood glucose monitoring and insulin therapy. Improvement in diabetes care has had a substantial impact on the decreased risk of ESRD [24], a major risk factor for CVD [22,27]. It is of note that the changes in CVD morbidity and mortality have been favorable and have decreased also in the Finnish background population in which CVD morbidity and mortality in the 1960s and early 1970s was the highest in the world [28]. Major changes with respect to the CVD risk factors have taken place; serum total cholesterol as well as systolic and diastolic blood pressure levels have decreased, and the proportion of smokers has declined [29]. It can be assumed that these changes have also taken place in the individuals with diabetes [29, 30] as we observed a substantial decraese in the CVD mortality and an increase in the median survival time after the AMI or stroke. Surprisingly, there was only a trend in early mortality improvement after the AMI, but no improvement of early mortality after stroke.

The CVD events were mainly non-fatal in those diagnosed in the 1990s; there was only one CVD death, although the oldest patient reached the age of 40 during follow-up. Also, in more recent cohorts the same clinical event was more likely to be diagnosed (e.g. following the introduction of troponins or natriuretic peptides) and intervened on (e.g. advances in percutaneous interventions). This may not affect SIRs substantially, where comparisons are only made within the same calendar years, but certainly would affect direct comparisons among the different cohorts. However, we demonstrated that this might be true for CAD with a steeper decrease seen for AMI compared to all aspects of CAD with a concomittant increase in revascularistion procedures, however, that was not seen for PAD, where the incidence of LEAs did not decrease with later calendar year of diabetes diagnosis, in line with the report from the US. These data could also suggest that the major improvements in CVD prevention are due to

the inhibition of the renin-angiotensin-aldosterone system and the subsequent reduced risk of DN and not so much to the improved hyperglycemia treatment that also took place after the 1980s. Similarly, studies from Canada and USA show that CVD reduction may not be consistent across the age spectrum, as individuals under the age of 40 years did not experience the same decline as the earlier population [23,31].

As observed in the current study and also in our previous study, early CAD events still occur in relatively young individuals and even in those without DN [22]. This is highlighted by the excess early morbidity (SIR 8·9) in the ages 25-34 years in those who were diagnosed in the 1990s. Interestingly, a recent study from the DCCT/EDIC suggests a role for autoimmune mechanisms in the development of CVD in T1D [33] that partly differentiates the mechanism from that in T2D and typically may increase the risk of CVD at younger ages. Autoimmunity was most pronounced in the individuals with poor glycemic control [34]. Unfortunately, we are not able to provide any clinical data in this study that could detect changes in the key risk factors for CVD. However, a Finnish study that consisted of a random sample of adult individuals with T1D all around Finland between 1993 and 2009 revealed that the glycemic control had not improved as desired in the individuals with T1D as the HbA_{1c} was on average 8.4% [35]. Similarly, the blood pressure had not changed significantly either. Although there was a decrease in total and LDL-cholesterol, no changes were seen in triglycerides or HDL-cholesterol. In contrast, BMI had increased and half of the individuals with T1D had a BMI over 25 kg/m^2 [35]. Thus, the changes in risk factors between the diagnosis cohorts could affect the CVD trends over time.

Of note, our study underlines the effect of some unmodifiable risk factors for CVD. Interestingly, for AMI, stroke and HF, the male sex remained a risk factor even after the adjustment for DN. However, we did not have complete data on microalbuminuria in the current study, which could explain the discrepancy with our recently published study where we showed that male sex was not an independent risk factor for CVD, when DN was accurately accounted for [22]. Also, in the present study we have shown that increasing age at diabetes onset increases the CVD risk, independently of DN. This is partly due to the fact that with increasing age at onset of diabetes with the same duration of diabetes the attained age increases. This finding is in line with the EDC data [36] and also the findings reported from the Swedish Diabetes Registry with respect to the absolute CVD risk [37].

Strengths and limitations of this study

These data are unique in many aspects. First, the studied population contains virtually a complete capture of the individuals, who were diagnosed with T1D before the age of 15 in Finland without selection bias. Second, the time span of the diagnosis of diabetes covers a continuum of 35 years (1965-1999). Third, the follow-up is long and comprehensive with a maximum follow-up time over 50 years. Fourth, we were able to link the data on diabetes to the nationwide registries with reliable data on CVD morbidity and mortality [12, 17] including HF [38]. Finally, Finland has a unique nationwide CVD register from year 1991 and this provided the opportunity to compare the CVD morbidity in the individuals with T1D with data from the general population. The main limitation of this study is that we did not have access to any clinical data. However, we were able to identify the most important risk factor, the presence of DN, from the health registers and the numbers of ESRD are comparable to published data from Finland [24]. Nevertheless, we acknowledge that the incidence of DN may be underestimated since information about the DN diagnosis might not always be acknowledged, especially from the visits at the outpatient clinic and in earlier cohorts, where albuminuria detection may not be as common as in later cohorts. Also, we provided cumulative incidence of CVD depending on diabetes duration and not on the attained age. Yet our 5-year calendar year of diagnosis cohorts had comparable time of T1D onset, and therefore the cumulative incidence curves were similar if plotted against the attained age (Supplementary Fig 3). It can be hypothesized that the curves would differ if individuals with a late-onset T1D would be included, too, since at a comparable diabetes duration a higher age would be a stronger driver of the CVD events.

In conclusion, the CVD risk has decreased remarkably over time in Finland. Despite of a declining risk of CVD, there is still excess early CVD morbidity and mortality in individuals with T1D compared to the background population. Our results highlight a need for studies on the natural history of atherosclerosis in children and young adults from the diagnosis of diabetes and furthermore studies on effective early prevention of CVD.

Contributors

V.H. was responsible for the study design, data acquisition, statistical analyses, data interpretation and writing the manuscript. D.P.B. participated in the data interpretation and writing and critical revision of the manuscript. P-H.G. participated in the data interpretation and critical revision of manuscript. V.H. is the principal investigator of the study, participated in the study conception, data interpretation and critical revision of manuscript for important intellectual content.

Declaration of interest: P-H.G. reports receiving lecture honorariums from Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Peer Voice, Sanofi and being an advisory board member of AbbVie, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Novartis, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Data sharing

Study data will not be available as the GDPR does not allow to distribute the patient level data.

Figure 1. Cumulative incidence of A) any CVD event, B) coronary artery disease (CAD), C) acute myocardial infarction AMI, D) stroke, E) peripheral artery disease (PAD), F) lower extremity amputation LEA, and G) heart failure (HF) in a nationwide cohort of individuals with childhood onset type 1 diabetes by 5-year calendar year of diagnosis cohorts.
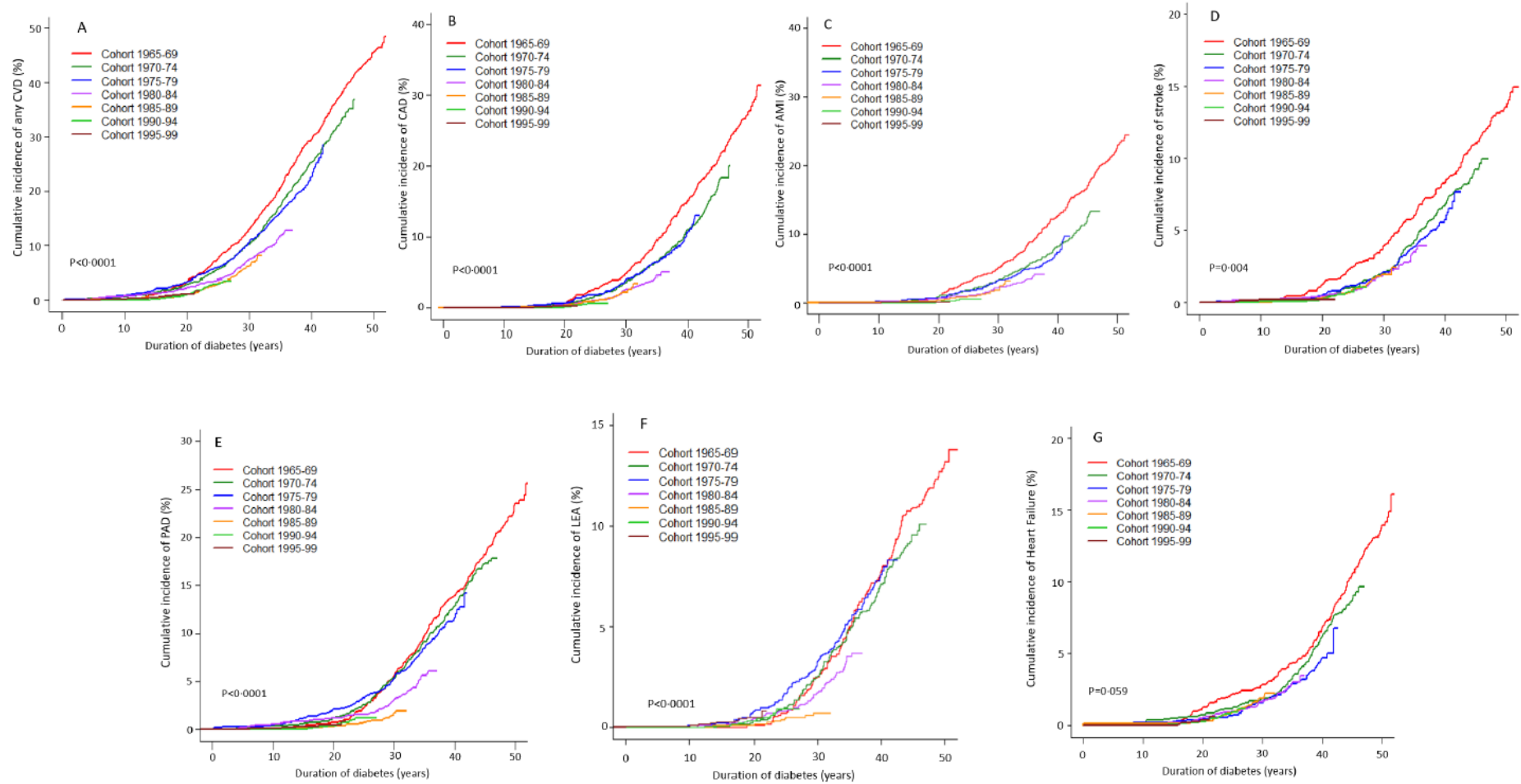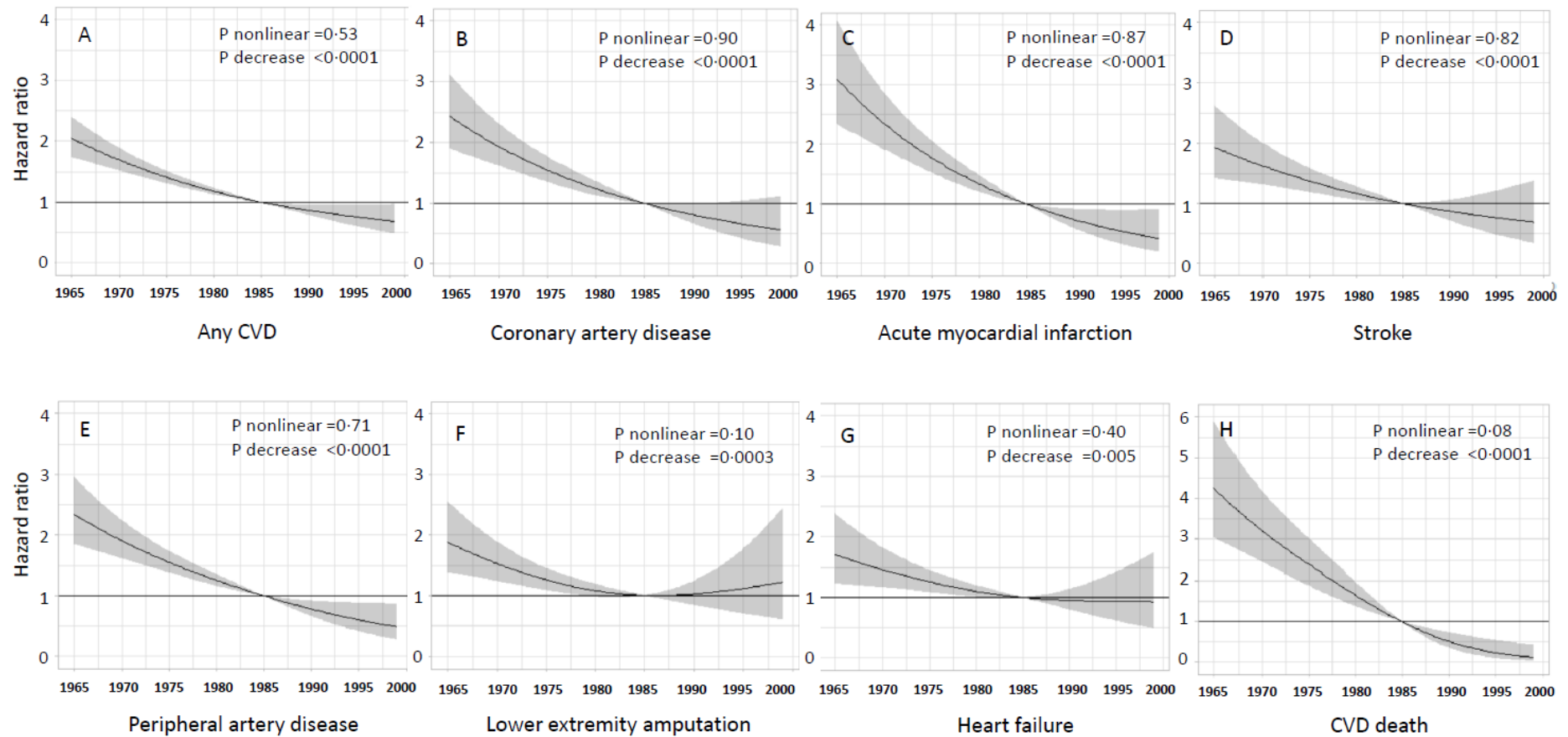
Figure 2. Spline curves for hazard ratios (HRs) for the risk of A) any CVD event, B) coronary artery disease (CAD), C) acute myocardial infarction (AMI), D) stroke, E) peripheral artery disease (PAD), F) lower extremity amputation LEA, G) heart failure (HF), and H) CVD mortality.
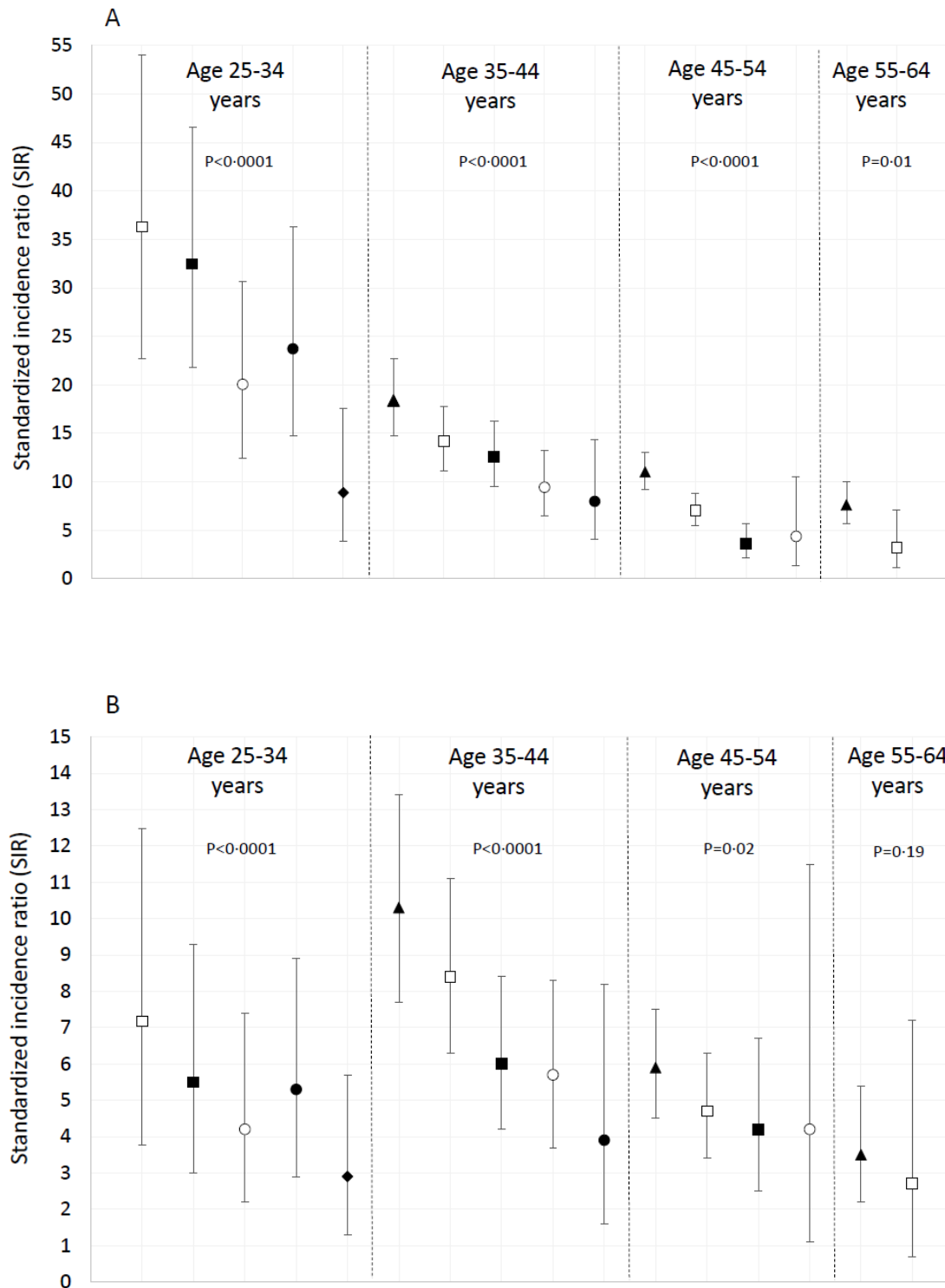
Figure 3. Time trends in the standardized incidence ratios (SIRs) by 5-year diagnosis of diabetes cohorts and 10-year attained age groups A) coronary artery disease (CAD), B) stroke in individuals with childhood onset type 1 diabetes. ▲denotes the diagnosis cohort 1965-69, □ 1970-74, ■ 1975-79, ○ 1980-84, ● 1985-59, ◆ 1990-94 and 1995-99 combined. SIR of 1 means a similar incidence. P values stand for differences in SIRs among the diagnosis cohorts at the attained age intervals.
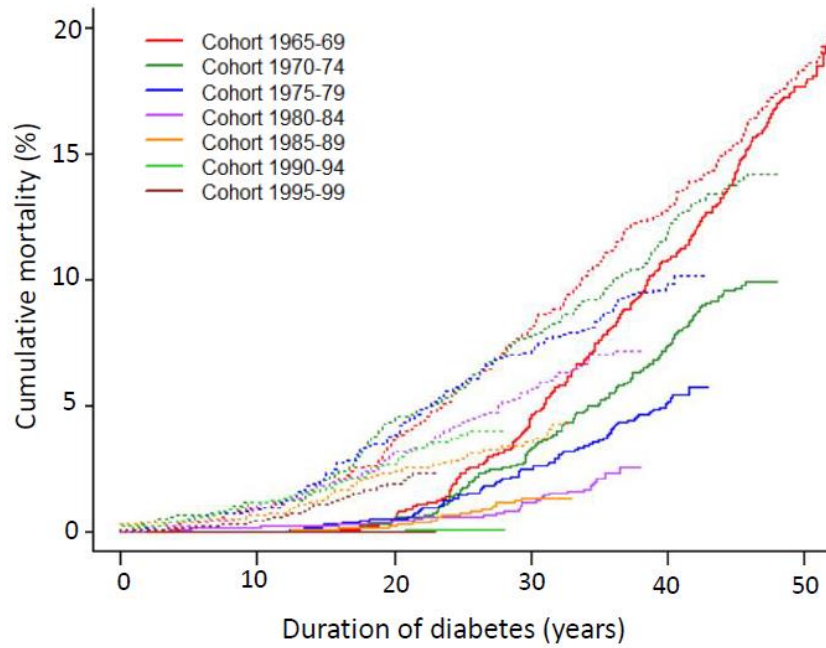
Figure 4. Cumulative CVD-mortality due to CAD or stroke (solid line) cohorts and other couses of death as competing risk (dashed line) in individuals with type 1 diabetes by 5-year diagnosis of diabetes.

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Supplementary Table 1. Specific codes used for the ascertainment of the cardiovascular disease outcomes and diabetic nephropathy from the relevant registries.

Outcome	ICD-code	Nordic Classification of Surgical Procedure codes	Purpose
Coronary artery disease (CAD)	ICD-10: I20-I25, I46, R96, R98 in any cause of death ICD-8/9: 410-414, 798 in any cause of death ICD-10: I121, I22 in hospitalization ICD-8/9: 410 in hospitalization		SIR*
Coronary artery disease (CAD)	In hospitalization or cause of death ICD-10: I21, I22, Z951, Z955 ICD-9: 410 ICD-8: 410-414	TFN 40, FN1AT, FN1BT, FN1YT, FNF, FNG, FNA, FNB, FNC, FND, FNE, FN2, Before 1996: 5311-5315	Cumulative incidence of CAD
Myocardial infarction (AMI)	In hospitalization or cause of death ICD-10: I21, I22 ICD-9: 410 ICD-8: 410-414		Cumulative incidence of AMI
Stroke	In hospitalization or cause of death ICD-10: I60-I64 ICD-8, ICD-9: 430-434		Cumulative incidence of stroke and SIR*
Heart failure	In hospitalization or cause of death		Cumulative incidence of heat failure

	ICD-10: I50 ICD-9: 428 ICD-8: 4270, 7824		
Peripheral artery disease (PAD)	ICD-10: S78, S88, S98, I702 ICD-9: 4402A, 4442A, 7854A, 7071A ICD-8: 44399, 25006, 44020, 44500	NFQ10,20, NGQ10,20, NHQ10,20,30,40,48; PDF05, 20-22; PDH50-55, 99; PDN05, 20-22; PDW99; PEF23-25; PEH 56,57; PEN 23-25; PEW99; PGH41-47,49; PFH58-67; PDQ05, 20-22; PD1AT; PD1BT; PD1YT; PD3AT; PD3BT;PEQ23-25; PEQ99; PE1AT; PE1BT; PFQ26; PFQ99; PF1AT; PF1BT Before 1996: 9571-75, 5561-5568, 5579, 5581, 5583	Cumulative incidence of PAD
Diabetic nephropathy **	ICD-10: E102, N083, N180 ICD-9: 581, 585, 2503 ICD-8: 582, 789, 792, 25004		Presence of diabetic nephropathy
End stage renal disease	ICD-10: Z940, T824, Z992, Y841, T861 ICD-9: 5850B ICD-8: 582, 792	KAS10,KAS20,KAS40,KAS60,KAS61,TJA33,TJA35,TK800,TK820 Before 1996: 7151,6112,7158	Presence of end stage renal disease

* Based on the same definition of ascertaiment as in the the Cardiovascular Disease Register ** plus codes for end stage renal disease
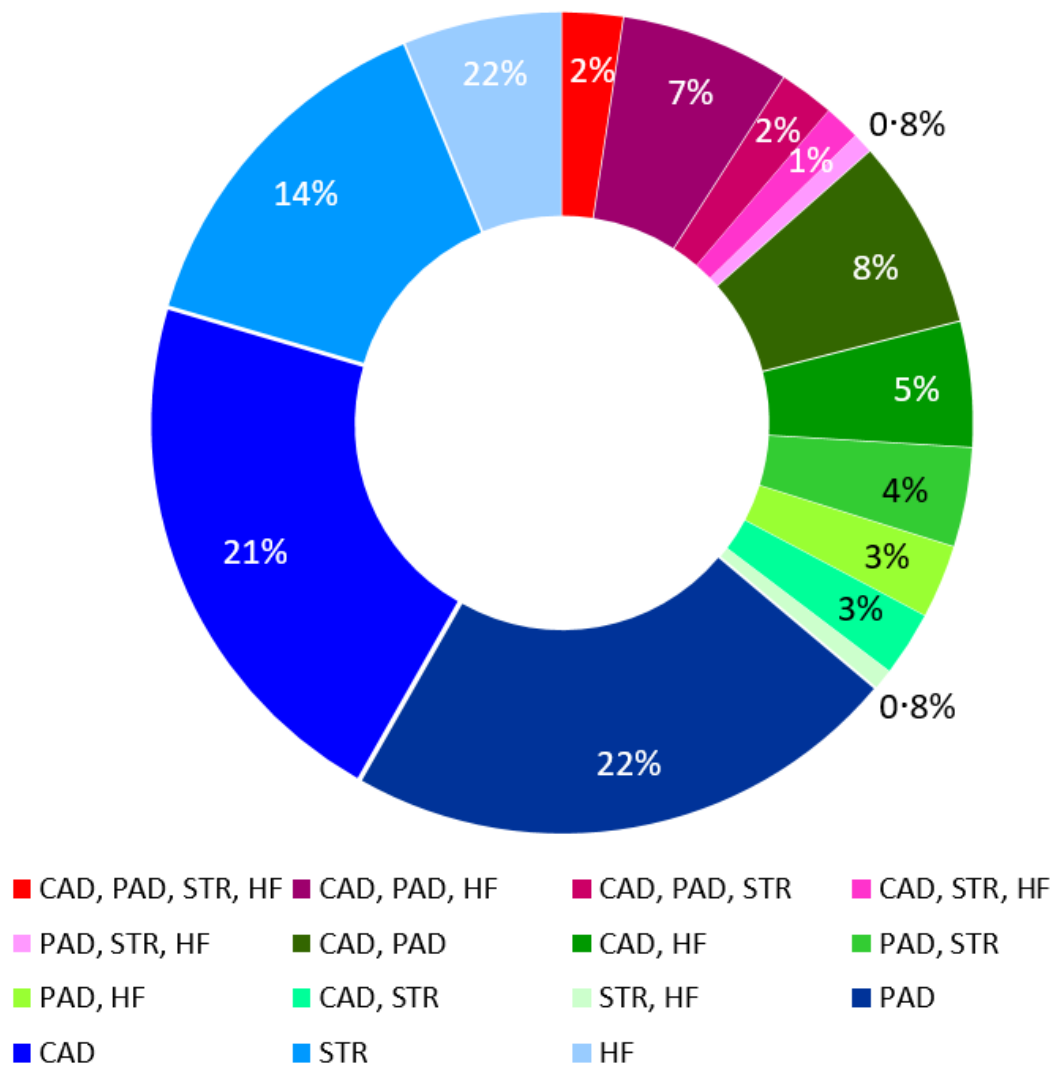
Supplementary Figure 1A. Proportions of individuals having CVD with a single type of CVD (blue shades) or combination of two (green shades), three (violet shades) or four (red) different types of CVD events. PAD denotes peripheral artery disease, STR stroke, HF heart failure, and CAD coronary artery disease.
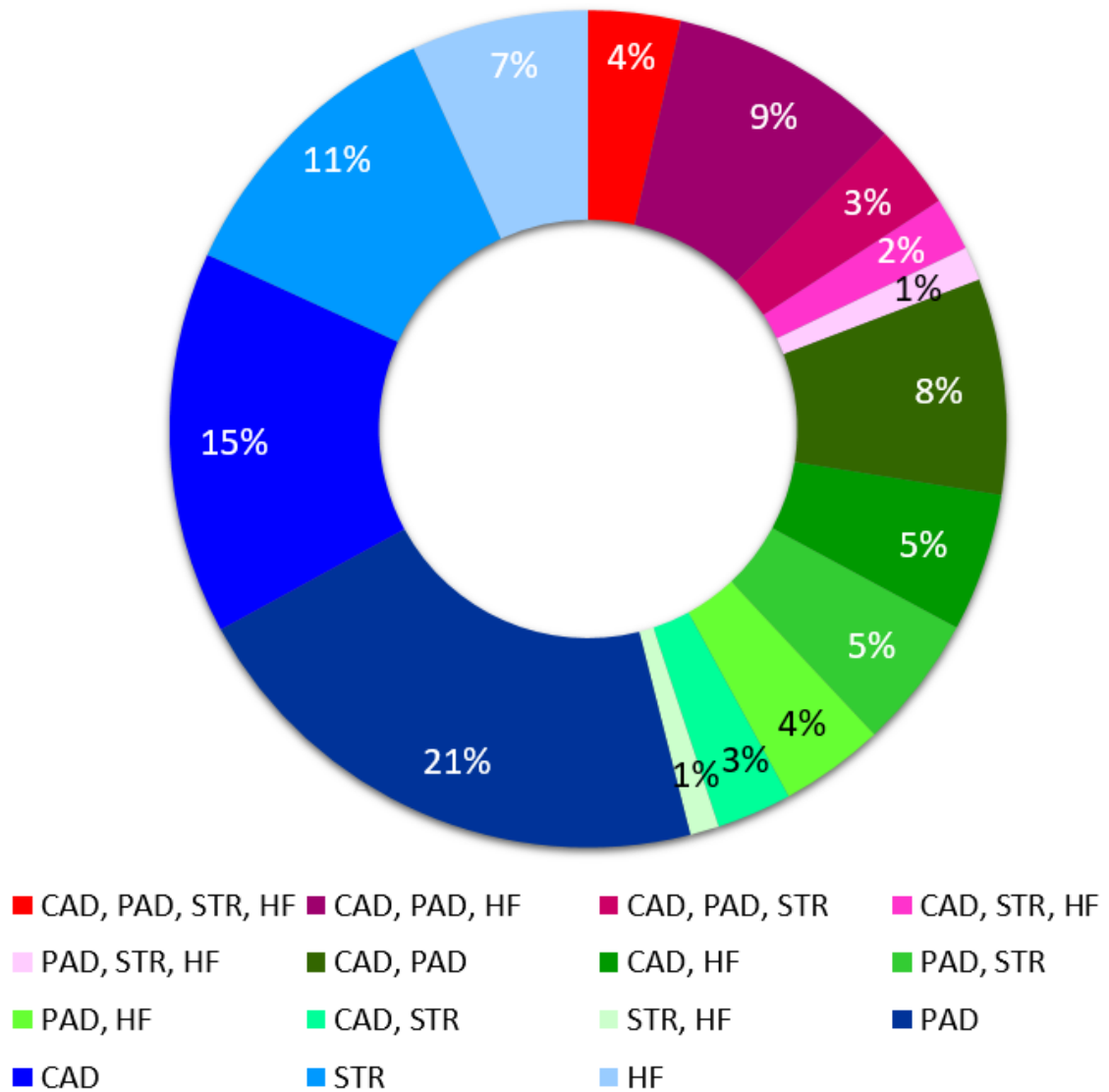
Supplementary Figure 1B. Proportions of individuals having CVD in individuals with diabetic nephropathy; with a single type of CVD (blue shades) or combination of two (green shades), three (violet shades) or four (red) different types of CVD events. PAD denotes peripheral artery disease, STR stroke, HF heart failure, and CAD coronary artery disease.
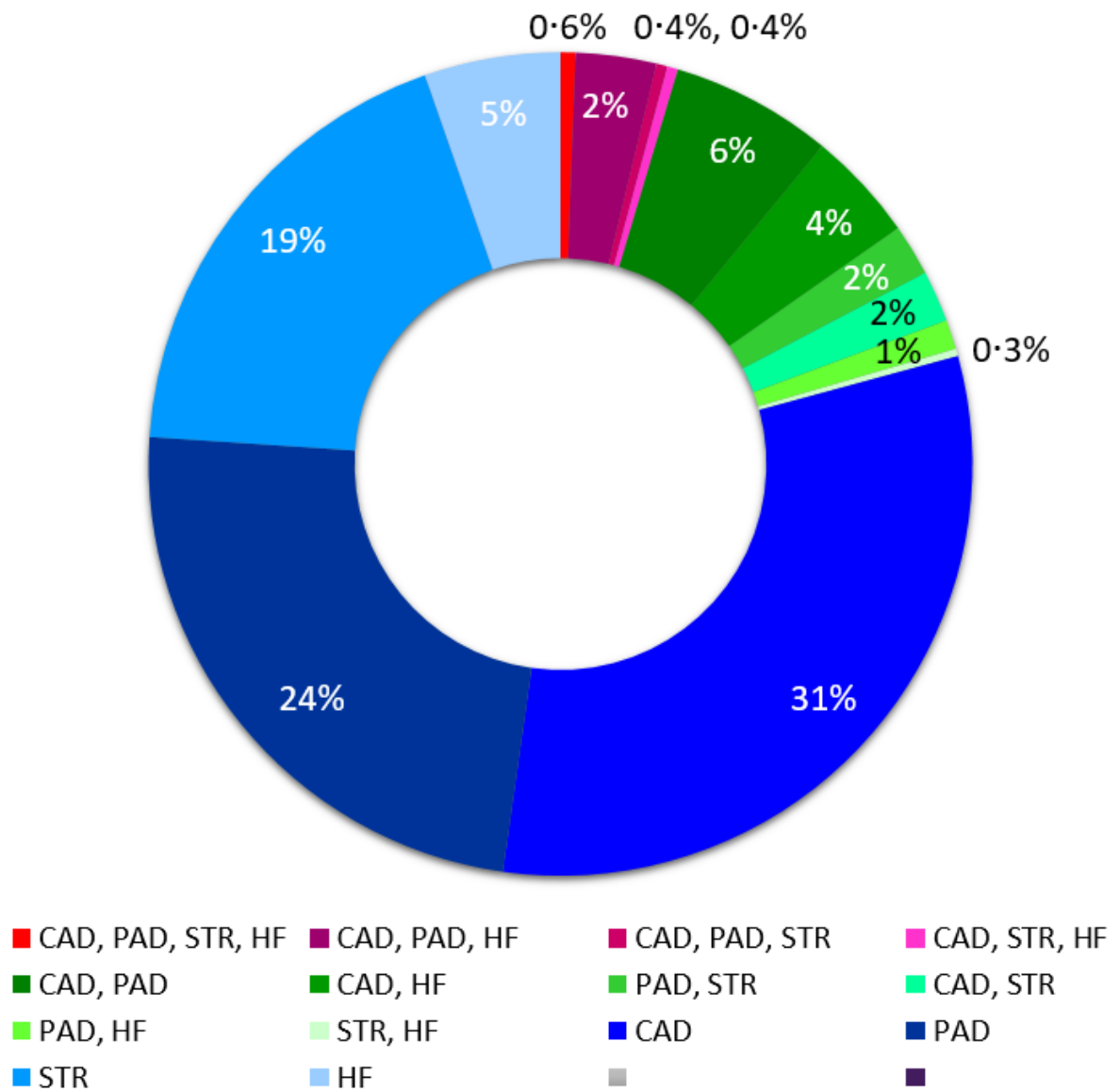
Supplementary Figure 1C. Proportions of individuals having CVD in individuals without diabetic nephropathy; with a single type of CVD (blue shades) or combination of two (green shades), three (violet shades) or four (red) different types of CVD events. PAD denotes peripheral artery disease, STR stroke, HF heart failure, and CAD coronary artery disease.
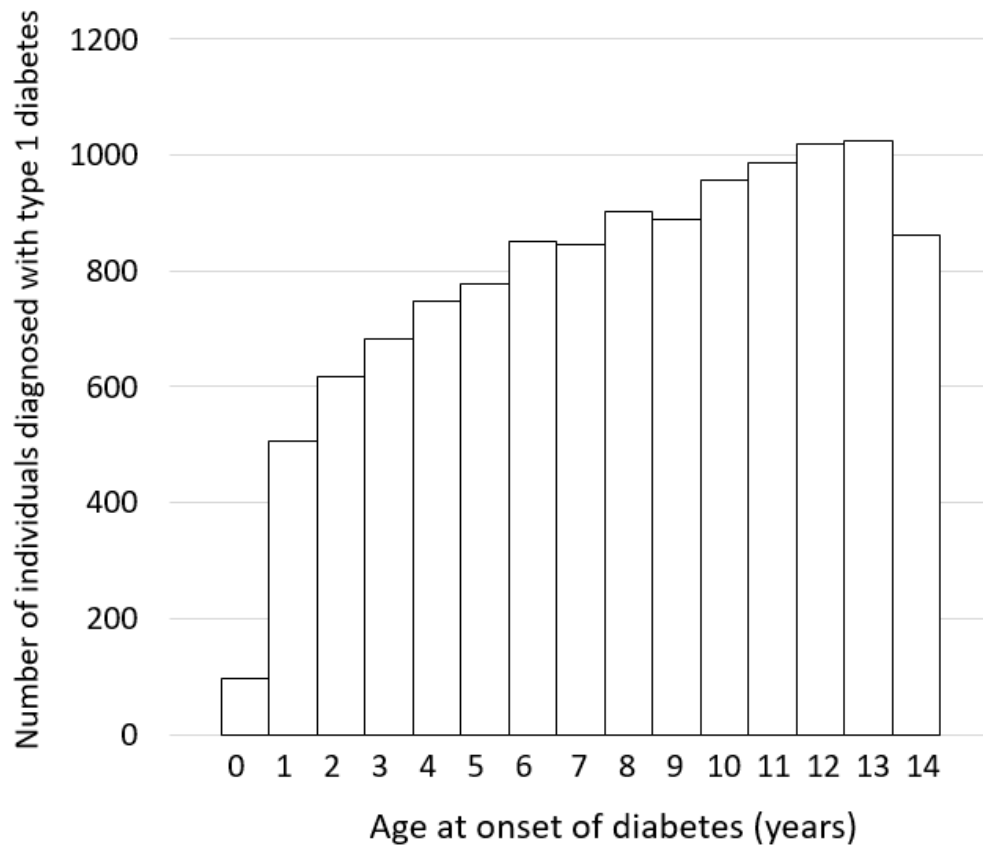
Supplementary Figure 2. Age at onset of diabetes distribution.
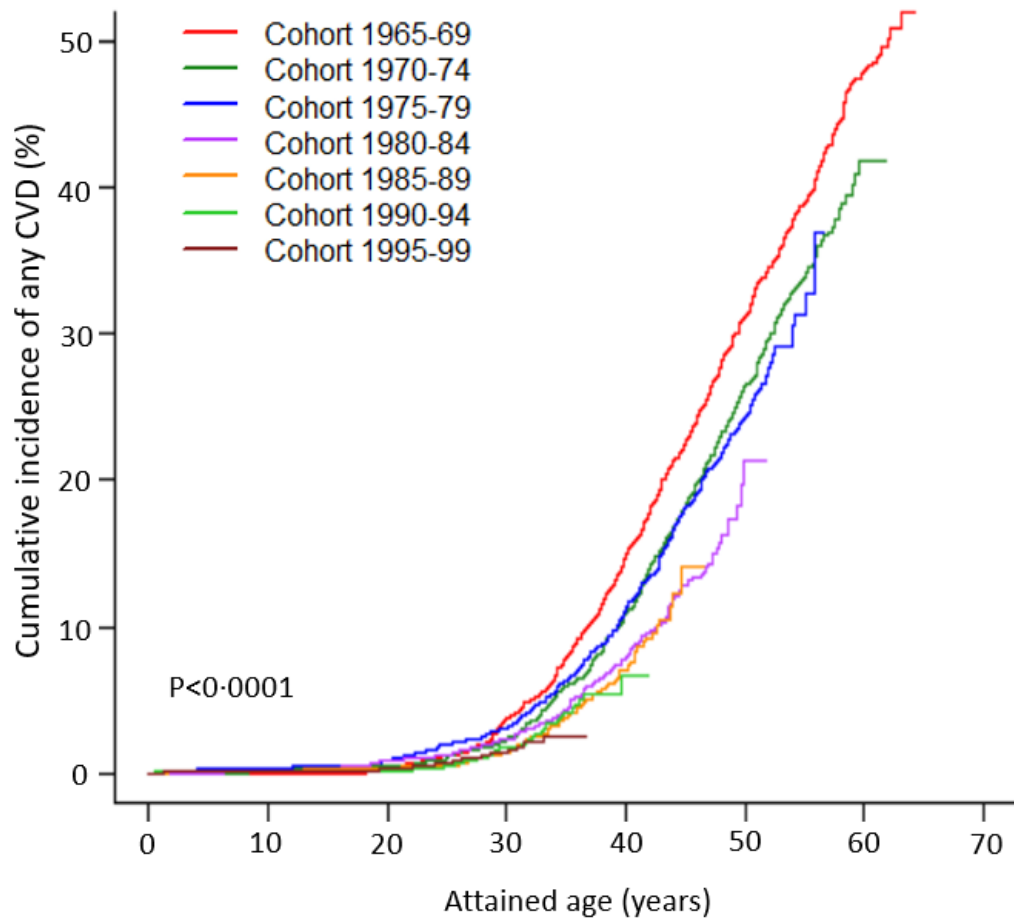
Supplementary Figure 3. Cumulative incidence of any CVD by attained age according to 5-year diagnosis cohorts

Supplementary Table 2. Hazard ratios (HRs) for year of diagnosis of diabetes as a continuous variable, age at onset of diabetes and DN status for different types of cardiovascular disease (CVD) derived from Fine and Gray competing risks regression models in women and men separately.

|	Any CVD		CAD		AMI		Stroke		PAD		LEA		HF	
Model 1	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at onset of diagnosis Women	1·05 (1·03-1·07)	<0·0001	1·06 (1·03-1·09)	<0·0001	1·04 (1·01-1·08)	0·005	1·02 (0·98-1·06)	0·27	1·06 (1·03-1·09)	<0·0001	1·05 (1·01-1·09)	<0·0001	1·05 (1·1-1·09)	0·02
Year of diagnosis Women	0·963 (0·953-0·974)	<0·0001	0·954 (0·937-0·970)	<0·0001	0·942 (0·923-0·961)	<0·0001	0·954 (0·933-0·975)	<0·0001	0·956 (0·942-0·971)	<0·0001	0·973 (0·951-0·996)	<0·0001	0·981 (0·958-1·004)	0·10
Age at onset of diagnosis Men	1·07 (1·06-1·09)	<0·0001	1·10 (1·07-1·13)	<0·0001	1·10 (1·08-1·13)	<0·0001	1·04 (1·01-1·07)	0·004	1·08 (1·05-1·10)	0·0005	1·07 (1·04-1·10)	<0·0001	1·06 (1·03-1·10)	<0·0001

	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Year of diagnosis Men	0·959 (0·951-0·967)	<0·0001	0·945 (0·931-0·959)	<0·0001	0·937 (0·922-0·952)	<0·0001	0·968 (0·952-0·998)	<0·0001	0·950 (0·938-0·962)	<0·0001	0·963 (0·948-0·978)	<0·0001	0·961 (0·945-0·978)	<0·0001
Model 2	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DN without ESRD Women	2·20 (1·86-2·59)	<0·0001	1·96 (1·55-2·47)	<0·0001	1·87 (1·41-2·48)	<0·0001	2·07 (1·48-2·90)	<0·0001	2·24 (1·75-2·88)	<0·0001	3·64 (2·51-5·28)	<0·0001	4·06 (2·92-5·64)	<0·0001
ESRD Women	4·14 (3·36-5·10)	<0·0001	3·07 (2·36-3·99)	<0·0001	3·27 (2·44-4·38)	<0·0001	3·92 (2·74-5·60)	<0·0001	5·74 (4·43-7·45)	<0·0001	9·06 (6·19-13·27)	<0·0001	4·21 (2·80-6·33)	<0·0001
Year of diagnosis Women	0·973 (0·962-0·984)	<0·0001	0·961 (0·944-0·978)	<0·0001	0·950 (0·931-0·969)	<0·0001	0·965 (0·943-0·987)	<0·0001	0·970 (0·955-0·986)	0·0002	0·994 (0·971-1·019)	0·65	0·993 (0·970-1·017)	0·59
Age at onset of diagnosis Women	1·06 (1·04-1·08)	<0·0001	1·07 (1·04-1·09)	<0·0001	1·05 (1·02-1·08)	<0·0001	1·03 (0·99-1·07)	0·21	1·07 (1·04-1·10)	<0·0001	1·06 (1·01-1·10)	0·01	1·06 (1·01-1·10)	0·008
DN without ESRD Men	1·91 (1·65-2·20)	<0·0001	2·05 (1·67-2·52)	<0·0001	2·34 (1·85-2·95)	<0·0001	2·22 (1·71-2·90)	<0·0001	2·01 (1·61-2·51)	<0·0001	2·04 (1·53-2·73)	<0·0001	3·02 (2·28-4·00)	<0·0001

ESRD Men	3·04 (2·57-3·60)	<0·0001	2·33 (1·85-2·94)	<0·0001	2·54 (1·96-3·28)	<0·0001	2·51 (1·88-3·36)	<0·0001	4·42 (3·58-5·45)	<0·0001	5·42 (4·20-6·99)	<0·0001	4·39 (3·26-5·91)	<0·0001
Year of diagnosis Men	0·967 (0·958-0·975)	<0·0001	0·951 (0·937-0·965)	<0·0001	0·945 (0·929-0·961)	<0·0001	0·978 (0·961-0·995)	0·01	0·962 (0·949-0·974)	<0·0001	0·977 (0·962-0·993)	0·004	0·976 (0·958-0·994)	0·009
Age at onset of diagnosis Men	1·07 (1·06-1·09)	<0·0001	1·10 (1·07-1·13)	<0·0001	1·10 (1·07-1·13)	<0·0001	1·04 (1·01-1·07)	0·01	1·08 (1·05-1·10)	<0·0001	1·06 (1·03-1·09)	<0·0001	1·06 (1·03-1·09)	<0·0001

Model 1 is adjusted for age at onset of diabetes; model 2 is adjusted for age at onset of diabetes, and diabetic nephropathy (DN) status: no DN, DN without end-stage renal disease (ESRD) or with ESRD. CI denotes confidence interval, CAD coronary artery disease, AMI acute myocardial infarction, PAD peripheral artery disease, LEA lower extremity amputation and HF heart failure.

Supplementary Table 3. Numbers (%) of acute myocardial infarction (AMI) and revascularization in first coronary artery disease (CAD) according to 5-year diabetes diagnosis cohorts.

	Total number of individuals with CAD	AMI only	Revascularization only	AMI with revascularization
Total follow-up time				
1965-69	362	135 (37·3)	73 (20·2)	154 (42·5)
1970-74	233	75 (32·2)	67 (28·8)	91 (39·1)
1975-79	150	50 (33·3)	44 (29·3)	56 (37·3)
1980-84	67	22 (32·8)	16 (23·9)	29 (43·3)
1985-89	36	16 (44·4)	6 (16·7)	14 (41·7)
1990-94	11	2 (18·2)	3 (27·3)	6 (54·5)
1995-99	5	1 (20·0)	2 (40·0)	2 (40·0)
Total	864	301	211	352
During the 30 years duration				
1965-69	65	58 (89·2)	3 (4·6)	4 (6·2)
1970-74	50	40 (80·0)	7 (14·0)	3 (6·0)
1975-79	58	34 (58·6)	13 (22·4)	11 (19·0)

1980-84	41	17 (41·5)	8 (19·5)	16 (39·0)
1985-89	32	16 (50·0)	7 (21·9)	9 (28·1)
1990-94	11	2 (18·2)	4 (36·4)	5 (45·5)
1995-99	5	1 (20·0)	2 (40·0)	2 (40·0)
Total	262	168	44	50

Supplementary Table 4. Incidence rates of different types of CVD per 10,000 person years during the first 20-years of duration of diabetes (follow-up) / attained age of 20-34 years by 5-year diagnosis cohorts.

	1965-69	1970-74	1975-79	1980-84	1985-89	1990-94	1995-99
Any CVD							
Number of events	45	35	52	38	22	20	26
Incidence rate (95% CI)	17·2 (12·6-23·1)	12·5 (8·7-17·7)	17·9 (13·4-23·5)	11·9 (8·4-16·3)	6·7 (4·2-10·2)	5·3 (3·3-8·2)	5·9 (3·8-8·6)
Incidence rate ratio (95% CI)	1·00	0·7 (0·5-1·1)	1·0 (0·7-1·6)	0·7 (0·5-1·1)	0·4 (0·2-0·7)	0·3 (0·2-0·5)	0·3 (0·2-0·6)
Coronary artery disease							
Number of events	12	11	10	10	8	2	5
Incidence rate (95% CI)	4·6 (2·4-8·0)	3·9 (2·0-7·0)	3·4 (1·6-6·3)	3·1 (1·5-5·7)	2·4 (1·1-4·8)	0·5 (0·1-1·9)	1·1 (0·4-2·6)
Incidence rate ratio (95% CI)	1·00	0·9 (0·4-1·9)	0·8 (0·3-1·7)	0·7 (0·3-1·6)	0·5 (0·2-1·3)	0·1 (0·03-0·5)	0·3 (0·1-0·7)
Acute myocardial infarction							
Number of events	12	11	10	10	6	1	3
Incidence rate (95% CI)	4·6 (2·4-8·0)	3·9 (2·0-7·0)	3·4 (1·6-6·3)	3·1 (1·5-5·7)	1·8 (0·7-4·0)	0·3 (0·01-1·5)	0·7 (0·1-2·0)
Incidence rate ratio (95% CI)	1·00	0·9 (0·4-1·9)	0·8 (0·3-1·7)	0·7 (0·3-1·6)	0·4 (0·2-1·1)	0·1 (0·01-0·5)	0·2 (0·04-0·5)
Stroke							

Number of events	17	6	9	7	5	4	5
Incidence rate (95% CI)	6·5 (3·8-10·4)	2·1 (0·8-4·7)	3·1 (1·4-5·8)	2·2 (0·9-4·5)	1·5 (0·5-3·6)	1·1 (0·3-2·7)	1·1 (0·4-2·6)
Incidence rate ratio (95% CI)	1·00	0·3 (0·1-0·8)	0·5 (0·2-1·1)	0·3 (0·1-0·8)	0·2 (0·1-0·6)	0·2 (0·06-0·49)	0·2 (0·1-0·5)
Peripheral artery disease							
Number of events	10	17	31	19	5	8	11
Incidence rate (95% CI)	3·8 (1·8-7·0)	6·1 (3·5-9·7)	10·6 (7·3-15·1)	5·9 (3·6-9·3)	1·5 (0·5-3·6)	2·1 (0·9-4·2)	2·5 (1·2-4·5)
Incidence rate ratio (95% CI)	1·00	1·6 (0·7-3·5)	2·8 (1·4-5·7)	1·6 (0·7-3·3)	0·4 (0·1-1·2)	0·6 (0·2-1·4)	0·6 (0·3-1·5)
Lower extrimity amputation							
Number of events	1	4	12	7	1	6	10
Incidence rate (95% CI)	0·4 (0·1-2·1)	1·4 (0·4-3·6)	4·1 (2·1-7·1)	2·2 (0·9-4·5)	0·3 (0·01-1·7)	1·6 (0·6-3·5)	2·3 (1·1-4·2)
Incidence rate ratio (95% CI)	1·00	3·7 (0·4-33·4)	10·7 (1·4-82·6)	5·7 (0·7-46·3)	0·8 (0·1-12·8)	4·2 (0·5-34·9)	11·8 (1·5-92·2)
Heart failure							
Number of events	17	11	7	10	7	5	7
Incidence rate (95% CI)	6·5 (3·8-10·4)	3·9 (2·0-7·0)	2·4 (1·0-4·9)	3·1 (1·5-5·7)	2·1 (0·9-4·4)	1·3 (0·4-3·1)	1·6 (0·6-3·3)
Incidence rate ratio (95% CI)	1·00	0·6 (0·3-1·3)	0·4 (0·2-0·9)	0·5 (0·2-1·05)	0·3 (0·1-0·8)	0·2 (0·1-0·6)	0·2 (0·1-0·6)

Supplementary Table 5. 28-days case fatality, 1-year survival rate and median survival time in acute myocardial infarction (AMI) and stroke by age and diagnosis cohorts.

Age group	1965-69	1970-74	1975-79	1980-84	1985-89	1990-94	1995-99	Total	P for trend
AMI									
Case fatality Fatal /Total No, %	75/295 25·4%	48/169 28·4%	25/107 23·4%	7/53 13·2%	7/32 21·9%	0/8 0%	0/3 0%	162/667 24·3%	0·10
1-year mortality, % (95% CI)	33·2% (29·5-36·7)	36·1% (31·3-40·5)	27·1% (20·7-33·0)	22·6% (13·4-30·9)	25·0% (12·9-35·4)	0	0	31·2% (28·7-33·6)	0·12
Median survival time, years (95% CI)	5·4 (3·5-7·4)	6·1 (0·8-11·5)	13·4 (6·8-20·1)	NA	NA	NA	NA	7·3 (5·3-9·2)	0·001
Stroke									
Case fatality Fatal /Total No, %	27/181 14·9%	18/127 14·2%	12/87 13·8%	5/52 9·6%	6/30 20·0%	1/15 6·7%	0/5 0%	69/497 13·9%	0·53
1-year mortality, % (95% CI)	23·8% (0·19-0·28)	23·6% (17·8-29·1)	21·8% (14·7-28·3)	13·5% (5·1-21·1)	20·0% (7·7-30·7)	13·3% (0·73-1·0)	0%	21·5% (18·5-24·3)	0·61
Median survival time, years (95% CI)	7·6 (4·9-10·2)	9·9 (4·2-15·7)	10·8 (5·9-15·6)	NA	NA	NA	NA	10·4 (8·3-12·5)	0·07