Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study

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Summary

Background **Adults with diabetes are thought to have a high risk of cardiovascular disease (CVD), irrespective of their age. The main aim of this study was to find out the age at which people with diabetes develop a high risk of CVD, as defined by: an event rate equivalent to a 10-year risk of 20% or more; or an event rate equivalent to that associated with previous myocardial infarction.**

Methods **We did a population-based retrospective cohort study using provincial health claims to identify all adults with (n=379 003) and (n=9 018 082) without diabetes mellitus living in Ontario, Canada, on April 1, 1994. Individuals were followed up to record CVD events until March 31, 2000.**

Findings **The transition to a high-risk category occurred at a younger age for men and women with diabetes than for those without diabetes (mean difference 14·6 years). For the outcome of acute myocardial infarction (AMI), stroke, or death from any cause, diabetic men and women entered the high-risk category at ages 47·9 and 54·3 years respectively. When we used a broader definition of CVD that also included coronary or carotid revascularisation, the ages were 41·3 and 47·7 years for men and women with diabetes respectively.**

Interpretation **Diabetes confers an equivalent risk to ageing 15 years. However, in general, younger people with diabetes (age 40 or younger) do not seem to be at high risk of CVD. Age should be taken into account in targeting of risk reduction in people with diabetes.**

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Introduction

Diabetes is a common cause of morbidity and premature loss of life.[1] People with diabetes are up to four times more likely to have cardiovascular disease (CVD) as people without diabetes; CVD accounts for a large proportion of the excess mortality related to diabetes.[2–4] Evidence suggests that even in the absence of pre-existing vascular disease, middle-aged people with type 2 diabetes have a similar risk of coronary heart disease (CHD) to those without diabetes who have had a myocardial infarction.[5] The idea of diabetes as a coronary equivalent led to widespread changes in the approach to reduction of CVD risk in this population.[6–8] In the past 5 years, increasing evidence has emerged that lends support to the use of cardioprotective agents in patients with diabetes, including lipid-lowering therapy, aspirin, and angiotensin-converting-enzyme inhibitors, and the adoption of all of these strategies simultaneously.[9–12]

An issue that concerns many practitioners is the age at which vascular-protection strategies should be started in people with diabetes. Although randomised controlled trials on this topic have rarely included participants under the age of 40 years, many clinical practice guidelines recommend application of existing evidence when treating these individuals. National cholesterol guidelines in several countries recommend use of the same therapeutic targets for people with type 2 diabetes as those recommended for secondary prevention of coronary-artery disease.[6–8] In this respect, all adults with type 2 diabetes, irrespective of their age, are regarded as being at high risk of fatal or non-fatal coronary events. In 2005, the International Diabetes Federation published global guidelines suggesting that people with type 2 diabetes should be judged as being at high risk of CVD if older than 40 years, even in the absence of pre-existing CVD or coronary risk factors.[13] The American Diabetes Association takes a similar approach; however, their recommendations do not distinguish between people with type 1 or type 2 diabetes.[14] By contrast, the UK National Institute for Health and Clinical Excellence uses risk-assessment tables to select individuals with type 2 diabetes for primary-prevention strategies.[15] In the absence of an appropriate prediction tool for type 1 diabetes, these guidelines use an age threshold of 35 years for recommendation of primary prevention with statins in people with type 1 diabetes without pre-existing vascular disease or other high-risk features.[16]

The relation between age and risk of CVD in people with diabetes has not been fully elucidated. Predictive algorithms created from diabetic cohorts have shown that age is a strong predictor of CHD, but little is known about the absolute risk of these events in younger people with diabetes.[17] Moreover, the appropriateness of existing age thresholds for identification of people with diabetes who are at high risk of CVD is not known. Therefore, we used a population-based approach to

investigate the age at which individuals with and without diabetes develop a high risk of CVD. We postulated that the absolute rate of cardiovascular events in adults younger than 40 years with diabetes would be less than the rate conventionally characterised as high risk. We explored this issue using two commonly used definitions of high risk: a fatal or non-fatal CHD-event rate equivalent to a 10-year risk of 20% or more; and a rate of CHD equivalent to that of previous myocardial infarction. Our secondary aims were to ascertain: the ageing equivalent of diabetes-associated cardiovascular risk; and the effect of diabetes on sex-related differences in CHD.

Methods

Patients

We used the Registered Persons Database to identify all residents of Ontario aged 20 years and older who were eligible for coverage under the Ontario Health Insurance Plan on April 1, 1994. As in other Canadian provinces, hospital, laboratory, and physicians' services are funded through a single-payer system administered through the Ontario Government; therefore these data sources include records for almost all residents in the province.

We used the Ontario Diabetes Database to identify individuals with and without diabetes.[18] This database uses health claims from hospital admissions and outpatient services to identify people with diabetes. A person with a claim for one or more admissions to hospital or two or more claims for visits to a physician (within 2 years), which lists a diagnosis of diabetes is included in the database. Once individuals have been included in the database, they remain in it until they move out of the province or die. This algorithm is highly sensitive (86%) and specific (98%) for identification of patients in whom diabetes was recorded in primary-care charts.[18] We linked records for individuals across data sets by use of a unique anonymous identifier, thus retaining confidentiality. Individuals in our cohort who were included in the Ontario Diabetes Database on or before April 1, 1994, were classified as having diabetes. Those in the comparison, non-diabetic group who developed diabetes and were entered into the database after this date were excluded from the analysis. The final sample size was 9 397 085.

Procedures

We followed up members of the cohort from April 1, 1994, to March 31, 2000, for recording of cardiovascular events. Hospital records were used to identify admissions for which the main diagnosis was listed as acute myocardial infarction (AMI; International Classification of Diseases, ninth revision codes 410·0–410·9) or stroke (ICD-9 codes 431, 434, and 436), and to identify in-hospital deaths.[19] The Registered Persons Database was used to document deaths that took place out of hospital. Disease-specific mortality data are not available from either of these databases, thus, all-cause mortality was used as a surrogate for CHD deaths. Information on revascularisation procedures (percutaneous coronary intervention, coronary-artery bypass graft surgery, and carotid endarterectomy) was also obtained from hospital records.[20,21] We ascertained baseline AMI status using records from the 3 years before April 1, 1994. Any record of AMI during this 3-year period was categorised as a recent AMI. The assignment of health-card numbers was changed on April 1, 1991; therefore, earlier health records could not be linked to those generated on or after this date.

In the first component of this analysis, we examined the relation between age and the 6-year incidence of CHD (AMI or death from any cause) and of CVD (AMI, stroke, or death from any cause) according to diabetes status and sex. Rates were calculated on the basis of the number of events per 1000 person-years for age categories defined by 1-year increments. We used regression techniques to plot the relation between age (x) and cardiovascular event rates (y), using a linear ($y=a+bx$), exponential ($y=ab^x$), or polynomial (quadratic) equation ($y=a+bx+cx^2$). We used the line of best fit between these two variables to establish the average age at which men and women with or without diabetes

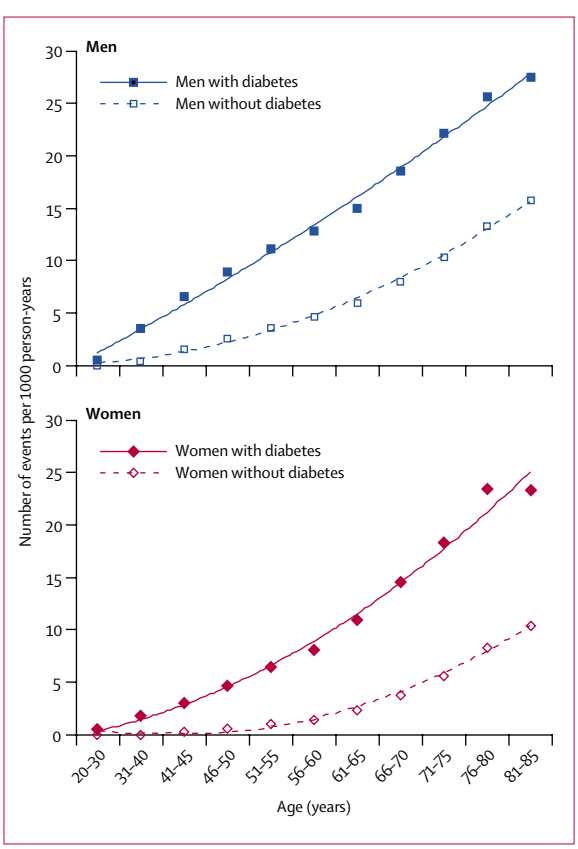

Figure 1: **Relation between age and rates of AMI by diabetes status and sex**
All lines fitted according to a polynomial equation. R^2 >0·99 for each fitted line.

	Age (years) at transition*					
	Men			Women		
	Diabetes	No diabetes	Difference	Diabetes	No diabetes	Difference
AMI or death from all causes						
Moderate-risk category†	38·6	54·8	−16·2	46·1	61·7	−15·6
High-risk category‡	49·3	62·2	−12·9	56·0	68·7	−12·7
Mean difference AMI/death from all causes			−14·6			−14·2
Moderate-risk category†	34·5	54·1	−16·6	44·6	60·5	−15·9
High-risk category‡	47·9	61·5	−13·6	54·3	67·5	−13·2
Mean difference AMI/stroke/death from all causes			−15·1			−14·6
Moderate-risk category†	32·7	51·4	−18·7	38·6	58·4	−19·8
High-risk category‡	41·3	58·8	−17·5	47·7	65·4	−17·7

*Age at which risk crosses to moderate-risk or high-risk categories based on the equation derived from the line of best fit between age and event rate.†Moderate risk: 10–19% 10-year risk. ‡High risk: 20% or greater 10-year risk.

Table: **Association between age and CVD risk**

moved from low risk (less than ten events per 1000 person-years) to moderate risk (ten to 19 events per 1000 person-years); and from moderate to high risk (20 or more events per 1000 person-years) for each set of outcomes.

The above thresholds for moderate and high risk were chosen on the basis of corresponding 10-year-risk estimates for fatal or non-fatal CHD events (10%–19% for moderate risk and 20% or more for high risk) used by various clinical practice guidelines in conjunction with the Framingham risk algorithm.[6,7] The inclusion of stroke and overall mortality as outcomes in our analysis would tend to overestimate the cardiovascular risk calculated with use of this definition. Similarly, we used a history of AMI in the preceding 3 years as a surrogate for baseline CHD; thus, a small proportion of individuals with AMI before that time would have been classified as having no history of AMI. This systematic overestimation would bias our results towards the null hypothesis; that young adults with diabetes are at high risk of CHD. As a further sensitivity analysis, we used a broader definition of CVD (AMI, stroke, death from any cause, or coronary or carotid revascularisation).

We then assessed whether the rate of fatal or non-fatal coronary events in people with diabetes was equivalent to that among people with previous myocardial infarction. We used a Cox's proportional hazards model to calculate age-adjusted and sex-adjusted hazard ratios for the rates of myocardial infarction in people with diabetes but no recent AMI relative to those with a history of recent AMI but without diabetes. Sex-specific hazard ratios were calculated for comparisons of men and women in the two populations overall and in the age categories 20–34 years, 35–49 years, 50–64 years, 65–74 years, and 75 years or older. Because coronary deaths out of hospital might not result in hospital admission for AMI, we repeated the same analysis for deaths from any cause. We compared this same diabetic subset with the subset without diabetes or recent AMI. To assess the ageing equivalent of diabetes-related CVD risk, we compared the age at which individuals with

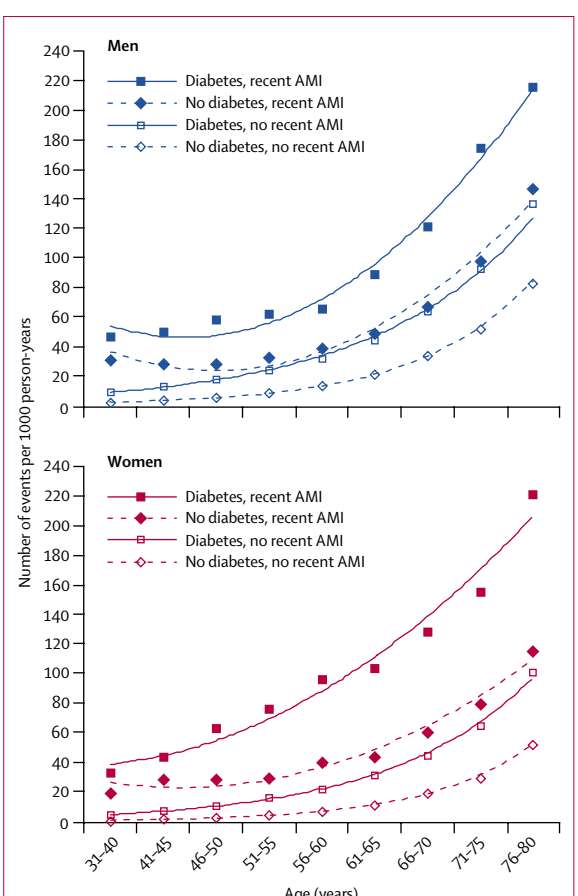

Figure 2: **Relation between age and rates of AMI or death from any cause in men and women according to presence of diabetes and previous AMI**
Recent AMI: polynomial distribution. No recent AMI: exponential distribution. R^2 >0·97 for each fitted line. Recent AMI=within 3 years of baseline.

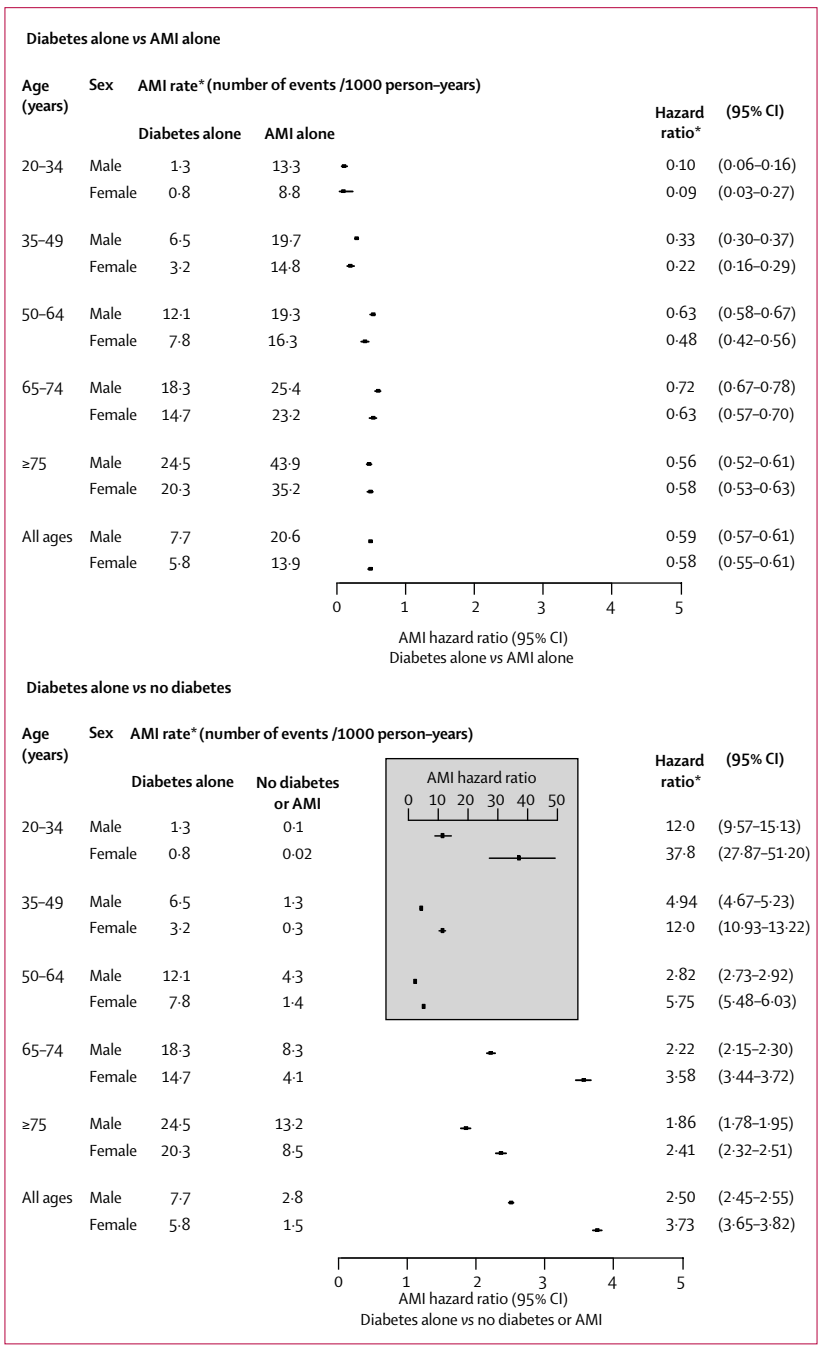

Figure 3: **Age-adjusted rates of new myocardial infarction in people with diabetes without recent AMI versus those without diabetes**

and without diabetes moved from low to moderate risk and from moderate to high risk for CHD or CVD events. The age difference between the groups was averaged across each category of change.

We also examined the effect of sex on cardiovascular risk in the groups with and without diabetes by comparing the age-adjusted hazard ratio of AMI for men versus women in each population separately. Additional models examined the effect of age and sex on AMI rates in people with diabetes after adjustment for baseline AMI status, comorbidity, outpatient service use, and residential information previously shown to influence AMI in this population (area income, urban or rural status, and region).[20] We used the Johns Hopkins Ambulatory Care Groups assignment software to assign comorbidity on the basis of hospital and physicians' services claims from the year before baseline.[22] Clinical variables, such as blood pressure or serum cholesterol concentrations, were not available in these data sources and were therefore not included in our model. We used SAS version 8.2 for all analyses. This protocol was approved by the Institutional Review Board at Sunnybrook and Women's College Health Sciences Centre.

Role of the funding source

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

Results

The study population consisted of 379 003 people with diabetes and 9 018 082 without this disease. People with diabetes were older than those without the disease (60·8 *vs* 42·6 years, p<0·0001); a substantially lower proportion of them were younger than 40 years (9·6% *vs* 51·3%), and a higher proportion were 65 years or older (44·7% *vs* 12·6%). 573 515 individuals in our cohort had one or more outcome events during the 6-year follow-up period, 18·3% (n=104 702) of whom had diabetes.

In both populations, the rate of AMI rose with age (figure 1). Diabetes was associated with earlier CVD; diabetic men and women were about 15 years younger than those without diabetes in the same risk category (table). For the outcome of AMI, stroke, and death from any cause, the transition from moderate to high risk of CVD took place at about age 48 years for men with diabetes and 54 years for women with diabetes (table). Even with use of a broader definition of CVD that included the need for revascularisation, the ages at which men and women with diabetes entered the high-risk category were about 41 and 48 years respectively. Similar figures for CHD alone (AMI or death from any cause) were much higher (table).

Figure 2 shows the relation between age and rates of CHD in men and women with and without diabetes according to previous cardiovascular status. In men aged 50–65 years, the lines of best fit representing this relation for men without diabetes who had had a recent AMI and for those with diabetes who had not were almost identical. However, in younger men and women

of all ages, those with diabetes had consistently lower CHD-event rates than those with recent AMI alone. Age-specific rates of AMI were significantly lower for all groups with diabetes without recent AMI than for those with a recent AMI but without diabetes (figure 3). The relative disparity between these groups was greatest in younger members of the population. By contrast, the risk of death from any cause for diabetes was equivalent to that for recent AMI only for the subset of men who were aged 50 years or older (figure 4).

Age-adjusted rates for AMI and all-cause mortality were about two to four times higher in men and women with diabetes than in those without diabetes or recent AMI (figures 3 and 4). The relative difference in rates between the two populations was again most pronounced in the youngest age groups. For instance, women aged 20–34 years with diabetes had rates of AMI nearly 40 times higher than their age-matched non-diabetic counterparts. By contrast, absolute rates of AMI and death rose with age and were consistently higher in men than women. AMI rates rose more steeply with age for people without diabetes (hazard ratio 2·10 per decade, 95% CI 2·09–2·11) than for those with diabetes (1·50 per decade, 95% CI 1·48–1·51).

Differences in relative risk by sex were greatly reduced, but not eliminated, by the presence of diabetes. In people without diabetes, the age-adjusted hazard ratio for incident AMI was 2·56 for men compared with women (95% CI 2·53–2·60). The same comparison in the diabetic population yielded a hazard ratio of only 1·40 (1·36–1·43). After adjustment for sociodemographic factors, comorbidity, and use of health-care services, men with diabetes were 1·22 times more likely to have an AMI than women with diabetes (1·18–1·25). There were no differences between men and women in CHD rates in the subset of patients with both diabetes and recent AMI (figure 5).

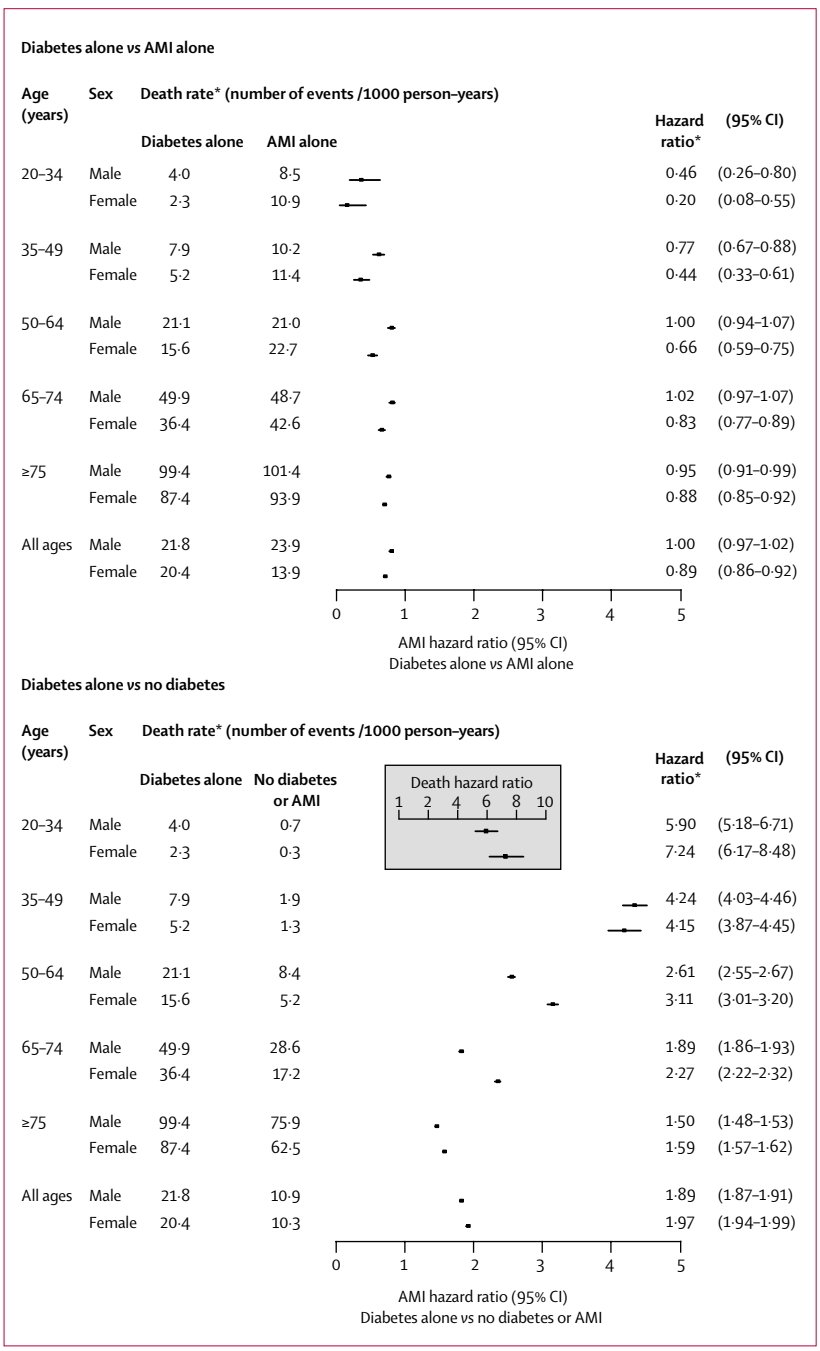

Figure 4: **Age-adjusted rates of death from any cause in people with diabetes without AMI versus those without diabetes**

Discussion

Our findings highlight the higher CVD risk in people with diabetes than in those without diabetes, both in relative and absolute terms. We showed that both for men and women, diabetes confers an equivalent degree of risk as ageing about 15 years. Age also seems to be an important predictor of CVD in people with diabetes, with younger people being at lower risk than older people. Even with use of the broadest definition for CVD, our data suggest that the CVD risk in people with diabetes does not reach the threshold conventionally regarded as high until the early to late 40s, both for men and for women. In those without established coronary disease, men have higher rates of CVD than women. However, diabetes greatly attenuates the usual protective effect afforded by female sex, thereby narrowing the relative gap in cardiovascular risk between the sexes.

Several studies have examined factors contributing to CHD in young people with diabetes; however, few have included a comparison with people without diabetes.[23–25] We showed that young adults with diabetes have rates of CHD 12–40 times higher than those in people without diabetes. However, absolute rates of coronary events, or of CVD in general, were lower in this younger group than the rates conventionally regarded as high risk, and lower than those of people without diabetes with established CHD. Relative-risk estimates strongly

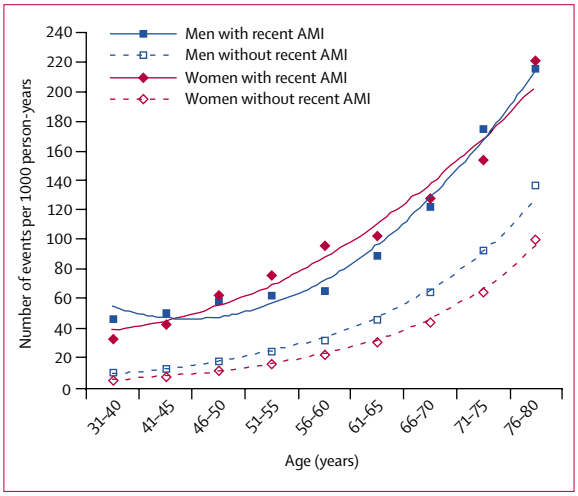

Figure 5: **Relation between age and rates of AMI or death from any cause among men and women with diabetes**
All lines fitted according to a polynomial equation. R^2 >0·97 for each fitted line.

depend on the risk of the underlying reference group. In young adults without diabetes, the risk of CHD is very low in the absence of pre-existing vascular disease but might be disproportionately raised in those who have suffered a premature coronary event because of the presence of risk factors such as a genetic predisposition or heavy smoking.[26]

We showed that in older men the presence of diabetes alone conferred a similar risk of death from any cause, as did a recent history of AMI, probably because of the effect of diabetes on fatal CHD. The same was not true for women and men younger than 50 years, in whom the risk of CHD was lower for people with diabetes alone than for those with a recent history of AMI (though still substantially higher than that for people without diabetes or recent AMI). Other studies lend support to the finding that diabetes is not a coronary equivalent in all circumstances. Data from a population-wide registry in Tayside, Scotland, showed that middle-aged patients with type 2 diabetes had a lower risk of coronary events and of death from all causes than those without diabetes who had had a previous myocardial infarction.[27] By contrast, other studies have suggested that in certain populations, the excess cardiovascular risk imparted by type 2 diabetes clearly rivals that of established CHD.[5,28–31] Some reports have shown diabetes to be a coronary equivalent for predicting mortality from all causes, but not from CHD,[32–34] whereas others showed diabetes to be an equivalent or stronger risk factor for stroke.[5,35] We used all-cause mortality as a surrogate for CHD-related deaths, which might explain why we noted similar rates of these events in middle-aged men with either diabetes or history of AMI alone. Differences in sample size, selection criteria, underlying population characteristics, and how diabetes status was assigned could have contributed to the discrepancies between studies. Disease duration is a potent risk factor for coronary events in patients with type 2 diabetes;[31,36] which might explain why studies of those with more advanced diabetes yield higher population estimates of CHD, whereas those including newly diagnosed patients yield lower estimates.[5,31,37] Our analysis differed from many others because we used health information from the whole population, thereby avoiding selection bias and providing a large enough sample to examine CVD risk across a broad range of ages.

There are several limitations to our analysis that merit discussion. Our definition of diabetes requires the patient to have interacted with the health-care system, and therefore, use of our algorithm would not have identified people with undiagnosed diabetes. However, the omission of such cases would lead to higher estimates of CVD in people with diabetes because those excluded would be asymptomatic, thus biasing our results towards our null hypothesis. A second limitation is that we were unable to discern use of cardioprotective drugs in patients of all ages. However, reports show that between 1994 and 1999, only 8–25% of Ontario residents aged 65 years and older with diabetes, whose drug costs are covered under a provincial insurance plan, received lipid-lowering drugs, and 25–37% received angiotensin-converting-enzyme inhibitors; the proportions based on all ages might be even lower.[38–40] Therefore, substantial use of these drugs in younger groups with diabetes is unlikely to explain the low rates of CVD in this population. Lastly, we were unable to account for diabetes duration or to distinguish between type 1 and type 2 diabetes. CVD rates might vary between young adults with type 1 diabetes and their age-matched counterparts with type 2 diabetes. However, if this premise were true, it would lend further support to the use of individualised risk-reduction efforts in younger people with type 1 and type 2 diabetes. Our findings challenge present practices that view all adults with diabetes as being at high risk of CVD irrespective of age or diabetes subtype.

Age is a strong risk factor for CVD in people with or without diabetes. Our analysis showed that diabetes confers an equivalent risk to ageing 15 years, a finding that could be applied to existing risk algorithms. Middle-aged and older people with diabetes seem on average to be at high risk of CVD, thus aggressive risk-reduction strategies are warranted for them. Appropriate thresholds for younger people with diabetes are less clear. At least in the short term, many individuals with diabetes who are younger than 40 years seem to have a low to moderate absolute risk of CVD; thus the number-needed-to-treat to prevent an acute cardiovascular event would be substantially higher in this population than in older groups with diabetes. Our data support present guidelines recommending that risk-reduction efforts be individualised in patients with diabetes who are less

than 40 years of age.[7,15,16] However, further work to develop appropriate algorithms for CVD risk in young adults with type 1 and type 2 diabetes is crucially important to guide therapeutic decisions in these individuals.

Contributors

G L Booth obtained funding, contributed to study conception and design, data analysis, data interpretation, and drafting, revision, and final approval of the manuscript. M K Kapral contributed to data analysis, data interpretation, and revision and final approval of the manuscript. K Fung participated in data collection, data analysis, reviewed drafts of the report, and approved the final version. J V Tu contributed to data analysis, data interpretation, and revision and final approval of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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