The diabetes-cardiovascular risk paradox: results from a Finnish population-based prospective study

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Aims
To assess changes in coronary heart disease (CHD) event rates and CHD mortality rates among diabetic and non-diabetic individuals between two large study cohorts with baseline assessments 10 years apart and followed up for 10 years.

Methods and results
Four population surveys were carried out in 1972, 1977, 1982, and 1987 in a randomly selected independent population in Finland. For the analyses, we combined the 1972 and 1977 cohorts (cohort 1) and similarly also the 1982 and 1987 cohorts (cohort 2). A total of 16,779 men and 18,235 women were followed up for 10 years. Whereas the risk of first cardiovascular disease event in women did not change between the two cohorts, the risk in diabetic men aged 25–49 years and men of all age groups with incident diabetes during the follow-up decreased compared with the earlier cohort. The relative risk of CHD mortality in men with baseline diabetes or incident diabetes compared with non-diabetic individuals increased (from 1.67 to 1.75 and 1.00 to 1.92, respectively). CHD event rates and CHD mortality rates decreased among non-diabetic individuals between the two study cohorts.

Conclusion
Special attention should be given to prevent the onset of diabetes in the population and to intensify the management of patients with diabetes.

Keywords
Coronary heart disease • Diabetes • Population-based study • Mortality

Introduction
The increasing prevalence of obesity and sedentary lifestyle are the major underlying causes that type 2 diabetes became one of the fastest growing public health problems worldwide imposing a high financial burden on health care costs.1,2 The World Health Organization has estimated that the number of adults with diabetes will more than double from an estimated 143 million in 1997 to 300 million by 2025.3 Diabetes is a major cause of cardiovascular disease (CVD) and most people with diabetes sooner or later develop CVD.4

Medalie et al.5–7 previously presented a developmental cycle model of diabetes and cardiovascular conditions in populations that are becoming more urbanized and industrialized. Infectious diseases decrease in stage 1. Diabetes and other CVD risk factors are proposed to increase in stage 2 but no increase in CVD morbidity was however observed. In stage 3, higher rates of diabetes and increased CVD morbidity are expected, and in stage 4, the high rates of diabetes will start to decrease. Finally, it was predicted that lower rates of diabetes and CVD as an adjustment phase will occur in stage 5.

Diabetes is a well-known risk factor for coronary heart disease (CHD) and it also increases the case fatality in acute coronary events.6,9 Hypertension, hypercholesterolaemia, and smoking are other major risk factors for CHD and CVD.10 The Framingham study reported an exponential relationship between the risk...
factor clustering and the probability of a CVD event.\textsuperscript{11} During the last decades, mortality from CHD and CVD has been decreasing in developed countries,\textsuperscript{12} including Finland.\textsuperscript{13} In Finland, this decrease has been largely related to the decrease in prevalence of smoking, hypertension, and hypercholesterolaemia.\textsuperscript{14} However, recent analysis of the trend data from the WHO MONICA project suggested that also other factors such as introduction of new treatments seem to play a significant role in determining the change in CHD incidence and mortality.\textsuperscript{15} Study results from the USA recently showed that in non-diabetic subjects, CHD and CVD mortalities have continued to fall, whereas in diabetic patients there has been no decrease.\textsuperscript{16} When diabetes is increasing in many populations, it may result in a levelling off of the decrease in CHD mortality. This may be called ‘diabetes-cardiovascular risk paradox’. As CHD is often a fatal disease, it is important to intensify efforts of health promotion and medical care in groups at a particularly high risk of CHD such as diabetic patients.\textsuperscript{17}

The aim of this study was to assess and compare the CHD event and mortality rates among diabetic and non-diabetic individuals between two large study cohorts studied 10 years apart and followed up for 10 years.

Methods

Study population

Four independent cross-sectional population surveys were carried out in 1972, 1977, 1982, and 1987 to evaluate the levels and trends in cardiovascular risk factors in the provinces of North Karelia and Kuopio in eastern Finland.\textsuperscript{18,19} A random sample of 6.6\% of the population born between 1913 and 1947 was selected in both provinces in 1972 and 1977. In 1982 and 1987, the sample comprised people aged 25 to 64 years. The samples were stratified according to the World Health Organization monitoring trends and determinants in cardiovascular disease (MONICA) protocol,\textsuperscript{20} with at least 200 subjects of each sex and each 10 year age group chosen from each province. In this study, the population samples from 1972 and 1977 were combined into cohort 1 and those from 1982 and 1987 were combined into cohort 2, respectively. Both cohorts were followed up for 10 years. The relative changes in 10 year CHD incidence and mortality were calculated between two cohorts. Subjects who participated in more than one survey were included in the first study cohort only. Sample sizes and baseline characteristics of the study cohorts are presented in Table 1. The final study population consisted of 16,779 men and 18,235 women. This study complies with the Declaration of Helsinki and the ethical guidelines of the National Public Health Institute. Informed written consent has been obtained from all study subjects.

Assessment of diabetes

The patients developing incident diabetes during the follow-up or having diabetes at baseline were derived from the national drug reimbursement records of the Social Insurance Institution and the hospital admission records of the National Hospital Discharge Register by computer-based record linkage. All Finnish residents have a unique personal identification number that is used in all databases in the country. The Hospital Discharge Register has reported the codes for type 1 and type 2 diabetes separately since 1987. Anti-diabetic drugs prescribed by a physician are free of charge in Finland and subject to the approval of the Social Insurance Institution on the basis of the patient’s application and a review of each case history provided by the treating physician. The physician’s diagnosis of diabetes was based on the World Health Organization criteria.\textsuperscript{21,22} All approvals of patients receiving free of charge medication (either oral antidiabetic agents or insulin) are entered into a register maintained by the Social Insurance Institution.

Assessment of coronary heart disease

Mortality and non-fatal event data of the first acute CHD were obtained from death records of the Statistics Finland and from the national Hospital Discharge Register. The data were linked to registers in December 1998. As to mortality, the Internal Classification of Diseases, Injuries and Causes of Death (ICD) codes 410–414 were classified as CHD deaths. Hospital discharges with ICD codes 410 and 411 were used to ascertain non-fatal acute CHD events. Mortality and the non-fatal event data of the two cohorts were linked by computer to the earlier-mentioned sources of events using the national identification numbers. The cumulative rate of the first acute CHD events includes either acute fatal or non-fatal first acute CHD event.

Statistical analysis

Each study cohort was followed up for 10 years. Age-specific incidence and mortality rates of the first acute CHD events were estimated per 1000 person-years stratified by age (25–49 and 50 – 64 years), cohort, sex, and the diabetes status. The variance of the event rate per person-years was evaluated by the standard method.\textsuperscript{24} The direct method was used to calculate age-adjusted mortality rates. The relative change in rates between cohort 1 and cohort 2 was calculated as the rate ratio (RR) for the first acute CHD events, CHD mortality, and the case fatality observed in cohort 2 divided by those in cohort 1, respectively. The variance of the RR and the variance of the relative risk due to diabetes were computed by a Taylor series approximation by estimating the variance of a ratio from a sample.\textsuperscript{24} All tests were two-sided and the level of confidence was set to $\alpha = 0.05$.

Results

A total of 16,779 men and 18,235 women were followed up for 10 years. Whereas there was a statistical significant higher risk of first CHD event in cohort 1 compared with cohort 2 in men [RR 1.7, 95% confidence interval (CI) 1.0–2.8], no changes in the risk of the first CHD event were observed in female (RR 1.0, 95% CI 0.6–1.7) patients with diabetes at baseline (Table 2). The risk of first CHD event in all diabetic men decreased from 1.67 per 1000 person-years in cohort 1 to 1.37 in cohort 2. In diabetic women, the risk of first CHD event increased from 2.33 to 3.42 between the two cohorts. The rate of the first acute CHD event was significantly higher in non-diabetic men (RR 1.4, 95% CI 1.2–1.6) and women (RR 1.4, 95% CI 1.2–1.7) in cohort 1 compared with cohort 2.

The RR regarding mortality from CHD did not change in diabetic men and women. The RR of 10 year CHD mortality between cohort 1 and cohort 2 was 1.7 (95% CI 0.5–6.1) in men and 5.1 (95% CI 0.7–231.3) in women, respectively (Table 3). CHD mortality increased in diabetic men from 1.67 per 1000 person-years in cohort 1 to 1.75 in cohort 2. In diabetic women, the risk of CHD mortality decreased from 4.2 to 2.00 per 1000 person-years. In individuals without diabetes at baseline, however, there was a statistically significant higher RR of CHD
### Table 1: Age-standardized baseline characteristics of the study cohorts according to gender

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1</td>
<td>Cohort 2</td>
</tr>
<tr>
<td>Number of people followed up (n)</td>
<td>9985</td>
<td>6794</td>
</tr>
<tr>
<td>Age groups (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–49 years</td>
<td>77</td>
<td>68</td>
</tr>
<tr>
<td>50–64 years</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.75 (0.03) a</td>
<td>26.29 (0.05) a</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>145 (0.18) a</td>
<td>143 (0.25) a</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>90 (0.11) a</td>
<td>86 (0.17) a</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>6.68 (0.01) a</td>
<td>6.12 (0.02) a</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>Diabetes at baseline (%)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>New diabetes in the 10 year follow-up (%)</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

*Mean and standard errors.

### Table 2: Ten year cumulative rate of the first acute coronary heart disease event per 1000 person-years (95% confidence interval) in cohort 1 and cohort 2 by the baseline diabetes status and age

<table>
<thead>
<tr>
<th>Age group</th>
<th>CHD event rate (95% CI)</th>
<th>RR (cohort 1/cohort 2) (95% CI)</th>
<th>Relative risk of CHD event for diabetic compared with non-diabetic people</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1</td>
<td>Cohort 2</td>
<td>Cohort 1</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–49</td>
<td>11.9 (7.6–17.9)</td>
<td>3.7 (1.4–8.1)</td>
<td>3.2 (1.3–9.6)</td>
</tr>
<tr>
<td>50–64</td>
<td>37.0 (25.3–52.2)</td>
<td>33.7 (20.6–52.0)</td>
<td>1.1 (0.6–2.0)</td>
</tr>
<tr>
<td>All</td>
<td>19.7 (14.8–25.7)</td>
<td>11.8 (7.7–17.3)</td>
<td>1.7 (1.0–2.8)</td>
</tr>
<tr>
<td>Without diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–49</td>
<td>6.8 (6.2–7.4)</td>
<td>2.9 (2.3–3.6)</td>
<td>2.3 (1.8–2.9)</td>
</tr>
<tr>
<td>50–64</td>
<td>28.1 (25.9–30.3)</td>
<td>23.2 (20.4–26.2)</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>All</td>
<td>11.8 (11.2–12.5)</td>
<td>8.6 (7.7–9.6)</td>
<td>1.4 (1.2–1.6)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–49</td>
<td>4.4 (1.9–8.6)</td>
<td>2.7 (0.7–6.8)</td>
<td>1.6 (0.4–7.4)</td>
</tr>
<tr>
<td>50–64</td>
<td>22.4 (15.2–31.7)</td>
<td>30.8 (19.8–45.9)</td>
<td>0.7 (0.4–1.3)</td>
</tr>
<tr>
<td>All</td>
<td>12.1 (8.6–16.6)</td>
<td>12.3 (8.2–17.8)</td>
<td>1.0 (0.6–1.7)</td>
</tr>
<tr>
<td>Without diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–49</td>
<td>2.2 (1.8–2.5)</td>
<td>0.7 (0.4–1.1)</td>
<td>3.3 (2.0–5.6)</td>
</tr>
<tr>
<td>50–64</td>
<td>12.2 (11.1–13.5)</td>
<td>9.7 (8.1–11.5)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>All</td>
<td>5.2 (4.8–5.6)</td>
<td>3.6 (3.1–4.3)</td>
<td>1.4 (1.2–1.7)</td>
</tr>
</tbody>
</table>
mortality in cohort 1 compared with cohort 2 (RR in men 1.7, 95% CI 1.2–2.3; in women 1.9, 95% CI 1.0–4.2).

Non-diabetic participants at baseline who developed incident diabetes during the follow-up period had a higher relative risk of the first acute CHD event than those who remained free of diabetes, and this difference increased over time in women from 6.36 to 6.50 (women) per 1000 person-years, but decreased in men from 3.53 to 3.18 (Table 4). In men who remained free of diabetes, the first acute CHD event rate significantly decreased from 11.3 to 8.1 in men and from 4.5 to 3.2 in women between the two cohorts, respectively. The relative change in the CHD event RR (cohort 1/cohort 2) in people without incident diabetes during the follow-up was 1.4 (95% CI 1.2–1.6) in men and 1.4 (95% CI 1.2–1.7) in women.

The relative risk of CHD mortality at the first acute CHD event increased in individuals who developed incident diabetes compared with those who remained free of diabetes from 2.1 to 1.2 in men and from 0.4 to 0.2 in women, respectively.

### Discussion

Our results showed that CHD event rates and CHD mortality rates decreased among non-diabetic individuals between the two study cohorts, but the CHD mortality rates among people with either incident diabetes during the follow-up or diabetes at baseline did not change during the 10 year period. Whereas the risk of first CVD event in women did not change between the two cohorts, the risk in diabetic men aged 25–49 years and men of all age groups with incident diabetes during the follow-up decreased compared with the earlier cohort.

There may be different possible explanations to our results. First, the incidence rate of diabetes in cohort 1 was lower than that in cohort 2, i.e. the more recent birth cohorts had a higher risk of diabetes. Second, the age of onset of diabetes might have been higher in the past so that the exposure time to effects of hyperglycaemia has also been shorter in the older cohort. Third, even though the target of glycaemic control has become tighter over time compared with the situation in the past, it may not have been sufficiently efficient in order to affect high CHD risk associated with diabetes.

Thomas et al. observed that mortality associated with diabetes increased owing to higher diabetes incidence and smaller declines in mortality for persons with diabetes relative to those without diabetes. Furthermore, the outcomes of our study partly differ from the one previously observed in the USA reporting a
decline in CHD mortality among diabetic men.\textsuperscript{16} Among US women with diabetes, neither all-cause nor CVD mortality declined, and the all-cause mortality rate difference between diabetic and non-diabetic women more than doubled. However, in accordance with their findings, the Finnish non-diabetic patients’ mortality from CHD decreased in both men and women in our study as well. Possible explanations for this discrepancy are likely due to differences in study methods and populations as well as diabetes diagnosis. In contrast to these findings, Fox \textit{et al.}\textsuperscript{27} reported that adults with and without diabetes had benefited similarly from the decline in CVD rates in the Framingham Heart Study, but it should be remembered that the Framingham cohort was very intensively investigated with repeated examinations, not representing a usual general population.

We think that many factors favourable to health may explain the decrease in all CHD events among non-diabetic individuals between cohort 1 and cohort 2. These include changes in several CVD risk factors in the population, advances in medical care and treatment, and emergency transport system to coronary care units. Mortality from CVD has been decreasing in Finland during the last three decades.\textsuperscript{28,29} The decline in the incidence of first CHD events, in recurrent coronary events and in the case fatality rate all contributed to decreasing trend in CHD mortality.\textsuperscript{29} The case fatality did not differ much between south-western and eastern Finland even though the incidence of acute myocardial infarction was \textasciitilde 40\% higher in eastern Finland.\textsuperscript{30}

Our cohort data are unique since we were also able to ascertain incident diabetes during the follow-up of the cohorts. Such information was not available in the previous US studies. Our results indicated that the case fatality of acute CHD events in Finland is decreasing in general, but that newly diagnosed diabetes during the follow-up period might deteriorate this improvement in case fatality as we have shown earlier.\textsuperscript{31} The recent results from the Euro Heart Survey on Diabetes and Heart revealed that two-thirds of patients with acute myocardial infarction and chronic CHD have either diabetes or glucose metabolism disorders.\textsuperscript{32} Asymptomatic hyperglycaemia, in particular, post-prandial hyperglycaemia is a significant risk factor for CHD and mortality even without progressing to diabetes.\textsuperscript{33–35} Thus, it is not surprising that the development of diabetes during the follow-up seemed to have a strong effect on the deterioration of the case fatality in the first CHD event from cohort 1 to cohort 2.

A prior myocardial infarction is a risk factor for CHD,\textsuperscript{36} but diabetes is also a major risk factor for CHD among our study subjects. This seems to be particularly important for women whose risk of CHD was drastically increased in the presence of diabetes, as also shown in earlier studies.\textsuperscript{35,37} Hu \textit{et al.}\textsuperscript{38} recently reported that the association between diabetes and mortality was stronger than that between myocardial infarction and mortality in women, whereas the converse was true among men. The incidence and mortality of the first acute CHD did not improve in diabetic subjects. These data imply that it would be important to manage patients

\begin{table}[h]
\centering
\caption{Ten year cumulative rate of the first acute coronary heart disease event per 1000 person-years (95\% confidence interval) in subjects without diabetes at baseline according to incident diabetes during the follow-up}
\begin{tabular}{|l|l|l|l|l|l|l|l|}
\hline
\textbf{Age group} & \multicolumn{2}{|c|}{\textbf{CHD event rate (95\% CI)}} & \multicolumn{2}{|c|}{\textbf{RR (cohort 1/cohort 2) (95\% CI)}} & \multicolumn{2}{|c|}{\textbf{Relative risk of CHD event for incident diabetes compared with non-diabetic people (95\% CI)}} \\
\cline{2-7}
 & \multicolumn{1}{|c|}{\textbf{Cohort 1}} & \multicolumn{1}{|c|}{\textbf{Cohort 2}} & \multicolumn{1}{|c|}{\textbf{Cohort 1}} & \multicolumn{1}{|c|}{\textbf{Cohort 2}} & \multicolumn{1}{|c|}{\textbf{Cohort 1}} & \multicolumn{1}{|c|}{\textbf{Cohort 2}} \\
\hline
\multicolumn{7}{|c|}{Men} \\
\hline
With incident diabetes & & & & & & \\
25–49 & 24.2 (15.7–35.3) & 8.7 (2.4–22.4) & 2.8 (1.0–10.9) & 3.72 & 3.12 \\
50–64 & 61.2 (45.3–81.0) & 37.5 (24.3–55.4) & 1.6 (1.0–2.8) & 2.28 & 2.00 \\
All & 39.9 (31.4–50.0) & 25.8 (17.3–37.0) & 1.5 (1.0–2.5) & 3.53 & 3.18 \\
\hline
Without incident diabetes & & & & & & \\
25–49 & 6.5 (6.0–7.1) & 2.8 (2.3–3.5) & 2.3 (1.8–2.9) & — & — \\
50–64 & 26.9 (24.8–29.1) & 22.3 (19.5–25.3) & 0.8 (0.7–0.9) & — & — \\
All & 11.3 (10.6–12.0) & 8.1 (7.3–9.1) & 1.4 (1.2–1.6) & — & — \\
\hline
\multicolumn{7}{|c|}{Women} \\
\hline
With incident diabetes & & & & & & \\
25–49 & 15.5 (9.0–24.9) & 6.9 (0.8–25.0) & 2.2 (0.5–20.1) & 7.75 & 11.5 \\
50–64 & 37.0 (28.4–47.3) & 26.8 (15.9–42.3) & 1.4 (0.8–2.5) & 3.43 & 3.05 \\
All & 28.6 (22.7–35.6) & 20.8 (12.7–32.1) & 1.4 (0.8–2.4) & 6.36 & 6.50 \\
\hline
Without incident diabetes & & & & & & \\
25–49 & 2.0 (1.7–2.3) & 0.6 (0.3–1.0) & 3.3 (2.0–5.9) & — & — \\
50–64 & 10.8 (9.7–12.1) & 8.8 (7.2–10.6) & 1.2 (1.0–1.5) & — & — \\
All & 4.5 (4.1–5.0) & 3.2 (2.7–3.8) & 1.4 (1.2–1.7) & — & — \\
\hline
\end{tabular}
\end{table}
with diabetes more intensively in order to decrease CHD incidence, mortality, and case fatality among them. Although health promotion activities and the progress in treatment methods have resulted in decreasing mortality for CHD, it is still difficult to prevent CHD in diabetes patients as also documented by the United Kingdom Prospective Diabetes Study. On the other hand, lifestyle factors such as physical activity can provide significant protection against CVD even in diabetic patients.

One of the main strengths of our study was that our analyses were conducted among large, representative population samples of middle-aged men and women. The participation rates were high and the follow-up period was relatively long, which makes it possible to apply the results directly to the general population. However, several limitations of this study need to be considered. CVD risk factors were assessed only at the beginning of the follow-up as usual in observational studies of this size. Thus, possible individual changes in the levels of CVD risk factors and other predictors of the disease onset and mortality during the follow-up may have influenced the results. Furthermore, people lost to follow-up owing to having moved abroad changing citizenship or not supplying information to hospital or the Social Insurance Institution may have biased the results because they were classified as being alive and without an event. However, these scenarios are very rare in Finland and very unlikely to have influenced the main findings of this study. Finally, we are aware that during the last 10 years, however, the progress not only in the treatment of CVD in the acute situation but also in the chronic condition including the overall cardiovascular risk reduction by multi-factorial therapy was in particular striking. Our follow-up of the second cohort ended in 1997 and it can be argued whether the results are still pertinent in 2007. This, however, can be addressed in further publication as soon as data linkage will be performed between the different registers enabling a comparison between even three population cohorts.

In conclusion, even though the incidence and mortality of CHD have been decreasing in non-diabetic individuals in Finland in our two study cohorts, no changes in CHD mortality were observed in men and women with diabetes. Thus, more effort is needed to prevent the onset of diabetes and to decrease the incidence of diabetes and glucose metabolism disorders in the population, and it is necessary to intensify the management and medical care of diabetes patients to decrease all events and mortality from CHD among them.

Conflict of interest: none declared.

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References


The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.