Diabetes mellitus and risk of fatal ischaemic heart disease by gender: 18 years follow-up of 74 914 individuals in the HUNT 1 Study

Ane Cecilie Dale1,3*, Tom Ivar Nilsen2, Lars Vatten2, Kristian Midthjell2, and Rune Wiseth1,3

1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Olav Kyrres gate, N-7006 Trondheim Norway; 2Department of Public Health, Norwegian University of Science and Technology, Olav Kyrres gate, N-7006 Trondheim, Norway; and 3Department of Cardiology, St Olav’s Hospital, Olav Kyrres gate 17, N-7006 Trondheim, Norway

Received 10 May 2007; revised 9 September 2007; accepted 13 September 2007; online publish-ahead-of-print 18 October 2007

Aim To study long-term mortality from ischaemic heart disease (IHD) in subjects with and without diabetes and how the association between diabetes and fatal IHD is influenced by gender and established cardiovascular disease (CVD).

Methods and results In 1984–86, all inhabitants aged 20 years or older in Nord-Trøndelag County, Norway were invited to the HUNT Study. A total of 74 914 participated in our study, 2100 of them with prevalent diabetes. During 18 years of follow-up, 19 967 persons died. Among people without diabetes or CVD at baseline, men had twice (HR 2.20, CI 2.00–2.41) the rate of fatal IHD compared with women. With diabetes present, the gender gap was substantially reduced (HR 1.25, CI 0.9–1.72), and if both diabetes and CVD were present, IHD mortality in men and women was identical (HR 1.1, CI 0.79–1.64). Gender specific analyses showed a stronger association of diabetes with IHD mortality in women (HR 2.71, CI 2.33–3.16) compared with men (HR 1.98, CI 1.70–2.30, test for interaction, \( P < 0.01 \)).

Conclusion Diabetes is a stronger predictor for IHD mortality in women than in men, and diabetes attenuates the usual gender gap in IHD mortality. With both diabetes and established CVD present, the gender gap is fully attenuated.

KEYWORDS Diabetes mellitus; Gender difference; Ischaemic heart disease mortality

Introduction

Diabetes mellitus is associated with increased risk of fatal ischaemic heart disease (IHD).1,2 The association appears to be stronger in women than in men,3–5 indicating that the presence of diabetes may reduce the gender gap in risk for IHD and related mortality. A less favourable cardiovascular risk profile in diabetic women6,7 and less effective treatment strategies in this group6 may explain the different influence of diabetes on IHD mortality between genders.7

Most studies of diabetes and IHD mortality have been of moderate size, with short to moderate follow-up.6,8–10 Also, studies have varied in adjustment for important confounding factors. In many studies, data on women have not been available, and the influence of already established cardiovascular disease (CVD) has often not been considered in the analysis of diabetes and risk for future ischaemic events.

The aims of this prospective study were to assess long-term risk of IHD mortality in individuals with and without diabetes, and to study whether the association is different for men and women. We also wanted to examine how already established CVD may influence the association between diabetes and IHD mortality. To accomplish these objectives, we used data from a large population-based study in Norway, the first wave of the HUNT Study.11

Methods

Study population

During 1984–86, a large general health survey (HUNT 1) was conducted in Nord-Trøndelag County in the middle of Norway (127 000 inhabitants). The county is fairly representative for Norway as a whole; but there is no large city, and the average educational and income levels are somewhat lower than for the country as a whole. The population is stable and ethnically homogenous, with only a small percentage (3%) of people of non-Caucasian origin. Emigration to other countries from this county is negligible.

All inhabitants 20 years of age and older (85 100) were invited to participate in the study. A total of 76 885 responded to the questionnaire and of those, 2242 (3.2%) stated that they had diabetes. A total of 74 977 (88.1%) accepted the invitation and attended a clinical examination that included standardized measurements of blood pressure, pulse, body weight, and height. The investigations were standardized and performed by trained staff who visited the...
various communities according to a defined schedule. Further details of the HUNT 1 Study have been described elsewhere.\textsuperscript{11}

In the analysis, we included 74,914 individuals (36,722 men and 38,192 women; a total of 2100 with diabetes) who were registered with valid responses to at least one of the following variables: body weight and height, systolic or diastolic blood pressure, and a valid response to the question regarding diabetes status.

**Study variables**

Information on diabetes and prevalent CVD was collected from the baseline questionnaire. Persons who answered ‘yes’ to the question ‘Do you have or have you had diabetes?’ were defined as having diabetes. The participants were also asked whether they had experienced angina, myocardial infarction, or stroke and those who answered ‘yes’ to one or more of these questions were classified as having established CVD.

Body weight was measured to the nearest half-kilogram and body height to the nearest cm, and body mass index (BMI) was calculated as weight (kg) divided by the squared value of height (m). BMI was classified according to the definitions given by the World Health Organisation (WHO) (<18.5 kg/m\(^2\)=underweight, 18.5–24.9 kg/m\(^2\)=normal weight, 25–29.9 kg/m\(^2\)=overweight, >30 kg/m\(^2\)=obesity).

Blood pressure was measured using a calibrated mercury manometer. Based on the mean of two measures, people with a blood pressure \(\geq 140/90\) mmHg and/or using antihypertensive medication were classified as hypertensive. Exercise level was divided into three: no regular exercise, exercise 1–2 times a week, or \(\geq 3\) times a week. Based on self-reporting, the participants were classified in three categories of smoking: as current, former, or never smokers. Education was categorized in two groups, according to duration, as \(<13\) years and \(\geq 13\) years.

**Follow-up**

Information on causes of death was obtained by linking data from the HUNT 1 Study to the Cause of Death Registry at Statistics Norway which receives all death certificates of Norwegian citizens. Deaths were classified according to the International Classification of Disease (ICD-9 and ICD-10). IHD was defined by ICD-9: 410–414 and ICD-10: I20–25. CVD was defined by ICD-9: 390–459 and ICD-10: I00–99, and stroke by ICD-9: 430–438 and ICD-10: 160–169.9. In this study, we calculated individual person time at risk from the date of participation at the baseline survey until date of death from IHD or from other causes, or until the end of follow-up at December 31, 2003, whichever occurred first.

**Statistical analysis**

Baseline characteristics of the study population are displayed by means with standard deviations (SD) and proportions, and stratified by sex and diabetes status. The Cox regression analysis was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of death from IHD in participants with and without diabetes. All analyses were stratified by sex, and in supplementary analysis we also stratified by established CVD at study entry. We computed \(P\)-values for interaction between diabetes and sex, and between diabetes and CVD, by including product terms of these factors in the regression model. All analyses were adjusted for age (continuous), and in subsequent multivariable analyses, we adjusted for the following potentially confounding factors: BMI (continuous), presence of hypertension (yes, no), smoking habits, exercise level, and level of education. Departure from the proportional hazards assumption was evaluated using graphical procedures (log-log plots). All statistical tests were two-sided, and all estimates were reported irrespective of their statistical significance level (no correction for multiple testing was conducted). We conducted all statistical analyses using SPSS for Windows (version 12.0 SPSS Inc., Chicago, IL, USA).

**Results**

The study population consisted of 38,192 women and 36,722 men (Table 1). The 1168 (3.1%) women and 932 (2.5%) men who reported diabetes at baseline, were older, had higher BMI and were more frequently hypertensive compared with persons without diabetes. Persons with diabetes, in particular women, had more favourable smoking habits, but less favourable exercise habits. People with diabetes had also more often several concomitant risk factors than others.

During 18 years of follow-up, a total of 19,967 deaths occurred in this population (Table 2). Among participants with known diabetes at baseline, 75.9% of the men and 78.3% of the women had died. About half the deaths among people with diabetes were caused by CVD, and among CVD deaths, about half were due to IHD.

For the diabetes group as a whole, the adjusted HR of IHD mortality when compared with people without diabetes was 2.27 (95% CI 2.04–2.53, data not shown in tables). We found positive associations between diabetes and IHD mortality in both genders. The adjusted HR among men was 1.98 (95% CI 1.70–2.30), and in women, the adjusted HR associated with diabetes was 2.71 (95% CI 2.33–3.16, test for interaction, \(P < 0.01\)) (Table 3). We stratified the analysis according to whether CVD was present or not at baseline, and for both genders the association of diabetes with IHD mortality was weaker when CVD was present (\(P\)-interaction <0.001 for both genders). (Table 3).

The HR of IHD for different combinations of diabetes and CVD status at baseline were estimated using people without known CVD or diabetes as the reference (Table 4). In men, established CVD without diabetes was associated with more than three-fold higher IHD mortality, whereas the mortality among men with diabetes but without CVD was nearly two-fold higher compared with the reference group with neither one of these conditions (Table 4). In women, there was no substantial difference in IHD mortality related to these combinations of diabetes and prevalent CVD. In both genders, established CVD combined with diabetes was associated with much higher IHD mortality (Table 4).

In stratified analysis, we found that among people without established CVD or diabetes at baseline, the adjusted HR was about twice (HR 2.20, 95% CI 2.00–2.41) as high in men (Table 5). If diabetes was present at baseline, the difference in IHD mortality between genders was reduced, and if CVD and diabetes were both present at baseline, there was no difference in mortality from IHD between men and women (adjusted HR 1.11, 95% CI 0.79–1.64) (Table 5).

**Discussion**

In this large, long-term prospective study, we wanted to find out if the difference in IHD mortality between men and women was reduced if diabetes or CVD were present at baseline. In people without CVD or diabetes, IHD mortality was twice as high in men, but in people with established diabetes at baseline, the gender difference was reduced to about 25%. If both diabetes and CVD were present at baseline, IHD mortality was nearly identical for men and women.

These results were based on 18 years mortality follow-up of 2100 individuals with diabetes and 72,814 persons without the disease. The total prevalence of self reported diabetes was 3.1% among women and 2.5% among men, which
corresponds fairly well with the prevalence reported in other studies.\textsuperscript{12,13}

**Potentially confounding factors**

Others have reported that women with diabetes tend to have a greater burden of CVD risk factors\textsuperscript{6,7,14–18} and more often concomitant risk factors\textsuperscript{10,16} than men with diabetes. In the multivariable analyses, we observed a stronger attenuation of the HR of IHD associated with diabetes among women than in men, and this may reflect that women with diabetes could also have a relatively higher burden of risk factors than men in our study. However, adjustment for these factors did not fully attenuate the HR of IHD associated with diabetes, and this finding also corresponds to that of others.\textsuperscript{16,19–21}

We found that hypertension was nearly twice as common in people with diabetes when compared with persons without the disease, and similar findings have been reported by others.\textsuperscript{22} This may indicate hypertension as an important factor to explain the higher IHD mortality associated with diabetes. In our study, obesity (BMI $\geq$ 30) was twice as common in people with diabetes, and obesity was also more common in women than in men, irrespective of diabetes status. It is known that obesity increases the risk for diabetes, and increased BMI alone, or in combination with diabetes, is likely to increase IHD mortality.\textsuperscript{23}

On the other hand, we found that women with diabetes smoked less than other women, suggesting that smoking habits were not among the underlying factors that could explain the higher death rates from IHD associated with diabetes in our study.

**Mortality from ischaemic heart disease**

Over all, IHD mortality was about two-fold higher in people with diabetes compared with people without the disease. This corresponds to the results of the NHANES I Study\textsuperscript{24} and to the results of others.\textsuperscript{2,16,25} In our study, established CVD was more strongly associated with fatal IHD than

---

**Table 1** Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men Diabetes</th>
<th>No diabetes</th>
<th>Women Diabetes</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants (%)</td>
<td>932 (2.5)</td>
<td>35 790 (97.4)</td>
<td>1168 (3.1)</td>
<td>37 024 (96.6)</td>
</tr>
<tr>
<td>Age at inclusion; mean (min-max)</td>
<td>66.2 (21–96)</td>
<td>48.5 (20–100)</td>
<td>69.8 (21–97)</td>
<td>49.4 (20–101)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg; (SD)</td>
<td>154.0 (25.9)</td>
<td>141.2 (21.1)</td>
<td>163.8 (28.4)</td>
<td>138.1 (26.3)</td>
</tr>
<tr>
<td>Antihypertensive medication (%)</td>
<td>28.3</td>
<td>9.4</td>
<td>49.6</td>
<td>14.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>53.4</td>
<td>33.3</td>
<td>64.4</td>
<td>30.9</td>
</tr>
<tr>
<td>Mean body mass index, kg/m$^2$ (SD)</td>
<td>26.3 (3.7)</td>
<td>25.2 (3.2)</td>
<td>27.9 (5.2)</td>
<td>25 (4.4)</td>
</tr>
<tr>
<td>Overweight; BMI $\geq$ 29 kg/m$^2$, %</td>
<td>43.7</td>
<td>41.1</td>
<td>32.1</td>
<td>29.2</td>
</tr>
<tr>
<td>Obese; BMI $\geq$ 30 kg/m$^2$, %</td>
<td>14.6</td>
<td>7.5</td>
<td>31.2</td>
<td>12.8</td>
</tr>
<tr>
<td>Combined risk factors$^a$, %</td>
<td>35.6</td>
<td>21.2</td>
<td>45.9</td>
<td>20.4</td>
</tr>
<tr>
<td>Mean non-fasting glucose, mmol/L (SD)</td>
<td>8.6 (4.2)</td>
<td>5.5 (1.4)</td>
<td>8.4 (4.2)</td>
<td>5.1 (1.2)</td>
</tr>
<tr>
<td>Smoking, % current or former</td>
<td>50.0</td>
<td>54.9</td>
<td>18.0</td>
<td>38.3</td>
</tr>
<tr>
<td>Exercise at least once per week, %</td>
<td>48.8</td>
<td>48.2</td>
<td>29.9</td>
<td>49.2</td>
</tr>
<tr>
<td>Higher education, %</td>
<td>18.1</td>
<td>42.2</td>
<td>7.6</td>
<td>32.7</td>
</tr>
<tr>
<td>History of cardiovascular disease$^c$, %</td>
<td>28.8</td>
<td>7.6</td>
<td>28.1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation.

$^a$Hypertension defined as blood pressure $\geq$ 140/90 mmHg or the use of antihypertensive medication.

$^b$Combined risk factors $=$ hypertension and body mass index $\geq$ 25.

$^c$Cardiovascular disease $=$ history of angina, stroke, or myocardial infarction.

---

**Table 2** Deaths during 18 years of follow-up; given as number of deaths and mortality rate

<table>
<thead>
<tr>
<th></th>
<th>Men Diabetes</th>
<th>No diabetes</th>
<th>Women Diabetes</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>707 (75.9%)</td>
<td>771.4</td>
<td>10 059 (28.1%)</td>
<td>173.0</td>
</tr>
<tr>
<td>Deaths due to CVD</td>
<td>416 (44.6%)</td>
<td>453.9</td>
<td>5069 (14.2%)</td>
<td>87.2</td>
</tr>
<tr>
<td>Deaths due to IHD</td>
<td>239 (25.6%)</td>
<td>260.8</td>
<td>2709 (7.6%)</td>
<td>46.6</td>
</tr>
<tr>
<td>Deaths due to stroke</td>
<td>96 (10.3%)</td>
<td>104.7</td>
<td>1033 (2.9%)</td>
<td>17.8</td>
</tr>
<tr>
<td>Number of deaths$^a$</td>
<td></td>
<td></td>
<td>Number of deaths$^a$</td>
<td></td>
</tr>
<tr>
<td>Death rate per 10 000 pyrs$^b$</td>
<td>771.4</td>
<td>173.0</td>
<td>453.9</td>
<td>87.2</td>
</tr>
<tr>
<td>Number of deaths$^a$</td>
<td></td>
<td></td>
<td>Number of deaths$^a$</td>
<td></td>
</tr>
<tr>
<td>Death rate per 10 000 pyrs$^b$</td>
<td></td>
<td></td>
<td>260.8</td>
<td>46.6</td>
</tr>
<tr>
<td>Number of deaths$^a$</td>
<td></td>
<td></td>
<td>104.7</td>
<td>17.8</td>
</tr>
<tr>
<td>Death rate per 10 000 pyrs$^b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease (history of angina, stroke, or myocardial infarction); IHD, ischaemic heart disease.

$^a$Number of deaths given as numbers and percent.

$^b$Pyrs denotes person years (rates calculated from censored data).
diabetes, in particular for men. Previous studies have not shown consistent results in their comparisons of CVD and diabetes as predictors of IHD death. Haffner et al. found no difference in risk, but others have, similar to us, reported that established CVD is a stronger predictor than diabetes.

Gender differences

We found that the positive association between diabetes and IHD mortality was consistently stronger in women than in men, resulting in a substantial reduction in the mortality gap between genders that is usually observed. In the studies of Liao et al., Hu et al., and in three recent meta-analyses, the presence of diabetes was reported to diminish the female advantage related to IHD mortality. In a meta-analysis by Kanaya et al. and a study by Vilbergsson et al., the gender difference in IHD mortality had fully disappeared, after the adjustment for conventional cardiovascular risk factors.

Different explanations have been proposed to understand the reduced gender gap in IHD mortality related to diabetes. One possibility is that diabetes is associated with less favourable cardiovascular risk profiles in women, and another could be that diabetes induces accelerated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of person years</td>
<td>No. of IHD deaths</td>
<td>HR (95% CI)</td>
<td>No. of person years</td>
</tr>
<tr>
<td>No CVD and no DM</td>
<td>553 625</td>
<td>1797</td>
<td>1.00 (Reference)</td>
<td>607 265</td>
</tr>
<tr>
<td>DM, but no CVD</td>
<td>7332.4</td>
<td>127</td>
<td>1.86 (1.51–2.29)</td>
<td>9251.6</td>
</tr>
<tr>
<td>CVD, but no DM</td>
<td>27 877</td>
<td>912</td>
<td>3.33 (3.04–3.64)</td>
<td>20 188</td>
</tr>
<tr>
<td>Both CVD and DM</td>
<td>1831.3</td>
<td>112</td>
<td>1.60 (1.28–1.99)</td>
<td>2248.4</td>
</tr>
</tbody>
</table>

- Adjusted for age, hypertension, body mass index, smoking, education level, and exercise.
- IHD, ischaemic heart disease.
atherosclerosis to a greater extent in women. Underlying factors could include greater tendency for abnormalities in lipids and lipoproteins and more frequent endothelial dysfunction in women. Pre-menopausal women without diabetes have a robust endothelial-dependent vasodilatation owing to higher release of the vascular protective nitric oxide. However, Steinberg et al. found that in persons with diabetes, this mechanism may be impaired. Other proposed mechanisms include increased arterial stiffness and intimal medial thickness due to excess circulating glucose that may adversely affect the cardiovascular protection of estrogen, possibly resulting in increased vascular tone, platelet aggregation, and enhanced vascular proliferation.

**Influence of established cardiovascular disease**

In men, we found that established CVD contributed to IHD mortality more strongly than diabetes, whereas in women, the two conditions contributed about equally. Other studies have shown conflicting results. Juutilainen et al. reported that diabetes was a stronger predictor of fatal IHD than was CVD for both sexes, but more pronounced for women. Similar findings have been reported by Hu et al. On the other hand, several studies restricted to men have shown results similar to ours, supporting the possibility that history of CVD is a stronger predictor for IHD than diabetes. In the Hoorn study and the Framingham Heart study, findings were similar to ours among men, whereas in women diabetes imposed a similar or greater risk of fatal IHD than could be attributed to establish CVD.

Discrepancy in results may be due to different duration of diabetes between studies, as well as differences in duration of CVD and different length of follow-up. Also, different classifications of causes of death within IHD categories, and differences in adjustment for cardiovascular risk factors may contribute to variation in results between studies. Nonetheless, all studies seem to support our finding that subjects with both CVD and diabetes at baseline are at a substantially higher risk. We found that these persons had five- to six-fold higher risk of dying from IHD compared with persons without these conditions. This finding emphasizes the need for aggressive risk factor intervention in this high-risk group.

**Limitations of the study**

During the 18 years of follow-up, the prevalence of diabetes gradually increased in this population, and a number of individuals who did not have diabetes at baseline, did subsequently develop the disease. Therefore, the association between diabetes and IHD mortality is probably underestimated in our study.

Diabetes was defined by self-reporting which could underestimate the prevalence. However, in a separate study it was demonstrated that the self-reported diagnosis of diabetes in the HUNT population was correct in 96.5%. Others have also demonstrated that self-reporting of diabetes is trustworthy, verifying the diagnosis in 97% of the cases. Serum lipids were not measured in this study. Dyslipidemia in diabetes differs from that in subjects without the disease. With adjustment for lipid levels, the HR for IHD mortality associated with diabetes is therefore likely to be further attenuated for both genders. On the other hand, it can be argued that the particular lipoprotein profile in diabetes is part of the diabetic syndrome, and thus, it may not be appropriate to adjust for differences in serum lipids.

It has been claimed that undertreatment may occur in women with IHD and that this may explain the excess mortality. Our data on medical treatment during the follow-up period are sparse as are our data on whether different treatment strategies according to gender have been employed. Thus, we cannot explore the possibility that women with coronary artery disease do not always receive appropriate treatment.

**Conclusions**

In this long-term mortality follow-up, we found that diabetes was a stronger predictor for IHD mortality in women than in men, and that the presence of diabetes strongly attenuated the gender gap in IHD mortality. For people with both diabetes and established CVD, the gender gap was fully eliminated. Our results argue for more aggressive IHD risk factor intervention in women with diabetes. For optimal intervention, the mechanisms for the gender differences related to the association of diabetes with IHD mortality need to be better understood.

**Funding**

This study was supported by grants from The Liaison Committee for Central Norway Regional Health Authority and the Norwegian University of Science and Technology.

**Conflict of interest:** none declared.

**References**


