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Age and Gender Differences in the Impact of Diabetes on the Prevalence of Ischemic Heart Disease: a Population-Based Register Study

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ABSTRACT

Objective: To explore age and gender differences in the impact of diabetes on the prevalence of ischemic heart disease (IHD) in a defined population.

Methods: Data were obtained from an administrative health care register covering a population of about 415 000. The study included all patients aged 45-74 years diagnosed between 1999-2003 with IHD (n=11 311) and diabetes (n=10 364) by physicians at all primary health care centres (PHCs) and out- and inpatient clinics at all hospitals in the county of Östergötland, Sweden.

Results: In the 45-54 year-old age group, diabetes was associated with an increase in IHD prevalence equivalent to ageing about 20 years in women and 10 years in men. The diabetes/nondiabetes IHD prevalence rate ratio (IPR) decreased with age in both men and women (trend p-values < 0.001). The IPR was higher among women than men in each age group, though the female relative excess decreased from 75% higher in the 45-54 year-old age group to 33% higher in the 65-74 year-old age group (trend p-value = 0.018).

Conclusions: The relative gender difference in the impact of diabetes on IHD in younger middle-aged patients remained up to the age of 65 years, decreasing considerably thereafter.

Key words: aging; coronary disease; diabetes mellitus; prevalence; sex differences
1. Introduction

Diabetes is a major public health problem, and the leading cause of death among patients with diabetes is cardiovascular disease (CVD), particularly ischemic heart disease (IHD) and stroke [1-3]. It is well known that women are generally at much lower risk of IHD than men. However, diabetes mellitus appears to reduce or even obviate the relative protection against IHD conferred by female gender [4-6]. Accordingly, diabetes is a stronger risk factor for women than men and, in a recent meta-analysis, Huxley et al. (2006) [7] found that the relative risk of fatal coronary heart disease associated with diabetes was about 50% higher in women than men. The magnitude of the gender difference varies between studies [8-12]. Furthermore, the gender disparity in the influence of diabetes on IHD may vary with age [13]. However, few studies present age and gender-specific data on the morbidity of IHD among the diabetic and nondiabetic population. The aim of this study therefore was to explore age and gender differences in the impact of diabetes on the prevalence of IHD using information from a population-based register.

2. Methods

2.1. The Care Data Warehouse in Östergötland (CDWÖ)

The Care Data Warehouse in Östergötland (CDWÖ) is a population-based, diagnosis-related administrative database compiled by Östergötland County Council in Sweden. The CDWÖ contains information from the primary health care (PHC) units and hospital out- and inpatient clinics in the county. The CDWÖ was established in 1998 and initially compiled only data on hospital care, but was expanded to include PHC data in 1999. From each consultation with a physician and each hospitalization, there is information on for example date, diagnosis (main diagnosis and up to nine secondary diagnoses), name and the unique personal identification number. Diagnoses are recorded according to the International Classification of Diseases,
10th version (ICD-10). Data from all health care units in the county are transferred to the CDWÖ on a monthly basis.

2.2. Design and study population

The population of Östergötland on 31 December 2003 was 414 897, and all 70 129 men and 71 271 women aged 45-74 years were included in the present study. A case-finding algorithm was used to search a five-year period retrospectively in the CDWÖ database, from 31 December 2003 to 1 January 1999, to identify the patients with at least one health care contact relating to diabetes mellitus (ICD-10 code/s E10-E14) and/or IHD (I20-I25) as a main or secondary diagnosis. Patients deceased before 1 January 2004 were identified by record linkage with the Cause of Death Registry at the National Board of Health and Welfare, Stockholm, Sweden, and omitted from the study population. The remaining patient population was related to the population at risk in Östergötland County on 31 December 2003 [14].

During the study period, there were three hospitals and 42 PHC centres in Östergötland, a county in the southeast of the country. In Sweden, as in the rest of Scandinavia, the integrated health care delivery system is required to serve all residents. In Östergötland, utilization of occupational and private care is very low and negligible in the present study.

2.3. Diabetes and IHD diagnostics

Östergötland County health authority follows the criteria for diabetes mellitus recommended by the WHO [15]. Diagnosis was confirmed if a patient with classic symptoms once had a fasting plasma glucose ≥ 7.0 mmol/l or a non-fasting plasma glucose > 11.0 mmol/l. In patients without symptoms of hyperglycaemia, the diagnosis was confirmed by two fasting values ≥ 7.0 mmol/l or a two-hour value > 11.0 mmol/l in an oral glucose tolerance test after a
standardised 75 g oral glucose load. IHD is characterized by reduced blood supply to the heart and includes myocardial infarction as well as angina pectoris. The diagnostic criteria for myocardial infarction (MI) followed current national guidelines, based on the consensus document of the European Society of Cardiology and the American College of Cardiology [16]. For acute, evolving and recent MI, such criteria include 1) typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) and 2) pathological findings of MI. One of the mentioned biochemical markers of myocardial necrosis should indicate on MI together with either a) ischemic symptoms, b) ECG changes like pathological Q-waves or ST-segment elevation/depression c) or d) coronary artery intervention. For established MI, the diagnostic criteria consist of either 1) developments of new pathologic Q-waves on serial ECG, or 2) pathological findings of MI. Stable angina is characterized by substernal chest discomfort provoked by stress (exertion or emotional) and revealed by rest and/or nitroglycerin [17]. Unstable angina/non-ST-segment elevation MI may present in one of three ways: 1) as rest angina, 2) as new-onset severe angina (less than 2 months and severe enough to cause myocardial injury), and 3) as increasing angina in intensity, duration and/or frequency [18].

2.4. Statistical analyses

The data captures for IHD and diabetes per health care level (i.e. PHC, hospital outpatient and hospital inpatient respectively) are presented as proportions. Estimated prevalence rates are presented as proportions with 95% confidence intervals (CIs) for patients with diabetes and IHD, and for those with IHD who did and did not have diabetes. The rates are given both as totals and by gender in the age groups 45-54, 55-64 and 65-74 years respectively. IHD prevalence rate ratios (IPRs) were calculated as the prevalence of IHD in diabetic versus nondiabetic subjects, and the ratios of female IPRs to male IPRs were also computed. The IPRs and the gender ratios of the IPRs are given with 95% CIs. Binominal CI tails for
prevalence rates were computed via the F-distribution [19], whereas CI tails for the IPRs and the gender ratios of the IPRs were obtained using the normal distribution approximation and the delta method to derive standard errors [20]. P-values for the trend over age in the IPRs and the gender ratios of the IPRs were derived from a log linear regression model in which the age groups were scored 1, 2 and 3 respectively.

The study was approved by the Regional Ethical Review Board of the University of Linköping.

3. Results

In the population aged 45-74 years in Östergötland on 31 December 2003, 6044 (8.6%) men and 4320 (6.1%) women were diagnosed with diabetes mellitus, and 7504 (10.7%) men and 3807 (5.3%) women were diagnosed with IHD (Table 1). Of all identified diabetic patients, 77% were registered with a diabetes diagnosis in PHC, whereas 55% of IHD patients were registered with an IHD diagnosis in PHC. The proportion of patients identified in PHC only was 24% for diabetes and 26% for IHD (Figure 1).

In each age group, men had a higher prevalence of IHD than women, both among diabetic and nondiabetic subjects (Table 2). However, the IHD prevalence rate was higher among diabetic women than among nondiabetic men in each age group.

In the studied age interval, the IHD prevalence ratio of diabetic versus nondiabetic subjects (IPR) was 3.97 (95% CI: 3.69 to 4.27) in women and 2.65 (2.52 to 2.79) in men; the female/male ratio of the IPR was 1.50 (1.39 to 1.61). The IPR decreased with increasing age in each sex (p-values for the trend <0.001). In women, the IPR declined from 6.94 (5.41 to
8.92) in the 45-54 age group to 2.21 (2.02 to 2.43) among those aged 64-75 (Figure 2A); the corresponding decrease in men was from 3.97 (3.35 to 4.71) to 1.66 (1.56 to 1.77) (Figure 2B). The female/male ratio of the IPR was 1.75 (1.38 to 2.21) in the 45-54 age group and 1.71 (1.59 to 1.84) in the 55-64 age group, whereas it was 1.33 (1.26 to 1.40) in the oldest group (Figure 3). Thus, compared to the 45-54 year-old age group, the female relative excess in IPR decreased by 56% in the 65-74 year-old age group (p-value for the trend = 0.018).

We also estimated IPRs using data from hospital clinics only. However, the IPR age trend and gender patterns proved to be similar to the result including PHC data (data not shown).

We further performed an analysis without the angina diagnosis (ICD-10 code I20). This showed virtually identical relationships between the age- and gender-specific IPRs to the analysis including angina (data not shown).

4. Discussion

This population-based study explored the prevalence of IHD in diabetic and nondiabetic subjects in relation to age and sex. In each sex, the IHD prevalence ratio between those with diabetes and those without diabetes (IPR) was higher in younger than in older age groups. The IPR was highest in women aged 45-54 years, where a sevenfold increase of the IHD prevalence in those with versus those without diabetes was observed.

Gender differences in the risk of coronary heart diseases in diabetic and nondiabetic patients have been the focus of numerous studies and, although the reported rates do vary, they all demonstrate higher relative risks of IHD in women than in men. In a meta-analysis of seven prospective studies, Lee et al. (2000) [21] estimated that the pooled relative risk of coronary
death associated with diabetes was 2.58 for women and 1.85 for men, which give a female/male ratio of 1.39. The more recent meta-analysis of 37 prospective studies by Huxley et al. (2006) [7] presented pooled relative risks of 3.50 for women and 2.06 for men, giving a corresponding ratio of 1.69 (95% CI 1.14 to 1.88). In our study, the gender ratio of the IPRs in the 45-74 age group was 1.50 (1.39 to 1.61), which agrees well with the findings of both meta-analyses. The gender ratios of the IPRs were quite similar in the 45-54 and 55-64 year-old age groups, 1.75 and 1.71 respectively, whereas it decreased to 1.33 in the 65-74 year-old age group.

It is important to note that the studies included in the two meta-analyses above were cohort studies based on IHD mortality [7] and both IHD morbidity and mortality data [13], whereas we used information on prevalence for both diabetes and IHD. As the case fatality of IHD is higher in diabetic subjects than in nondiabetic subjects, it is reasonable to assume that prevalence studies would yield weaker associations between diabetes and IHD than corresponding cohort studies. Furthermore, since the relative excess mortality associated with IHD among diabetic subjects decreases with age [3, 22], the age trend in the diabetes and IHD association is probably weaker in a prevalence study than it would have been in a cohort study.

The major strength in using data from an administrative database is the large size of collected data and the population-based information free from recall bias. However, register data can involve misclassification problems caused by unrecorded cases and/or incorrect registration of diagnostic codes, and this limitation may have affected the validity of the data used in our study. In our data, diagnoses were missing for visits to a doctor in about 10% of PHC and approximately 15% of outpatient cases. A secondary diagnosis was registered in a third of all
visits to a doctor, with a slightly lower rate for hospital visits compared to PHC. In a previous study using the same method of data extraction (i.e. a five-year period of data collection, and both main and secondary diagnoses in all out- and inpatient care registered in the CDWÖ), almost the entire population of known diabetes cases in Östergötland was captured [23].

A considerable number of people in the general population have undiagnosed diabetes mellitus. In a population-based sample in northern Sweden, Eliasson et al. (2002) [24] found that the prevalence of unknown diabetes were about equal to that of known diabetes. This seems to be true also in an infarct population [25, 26]. Assuming that the impact of undiagnosed diabetes on IHD equals that of known diabetes, we have underestimated the effect of diabetes to some extent in our study. The underestimation may be slightly greater among women and among those in the oldest age group, assuming that the gender and age distribution of unknown diabetes prevalence in our population corresponds to that found by Eliasson et al. (2002). However, the inclusion of undiagnosed diabetes would only marginally alter the results and would not affect the general conclusions.

To address the possibilities of bias from the broad inclusion of IHD diagnoses, i.e. the inclusion of angina pectoris, and from the inclusion of IHD in PHC, we performed additional analyses. However, the results based on analyses with and without angina cases as well as with and without IHD data from PHC were virtually the same, indicating that our findings are robust in these respects.

It is likely that subjects already diagnosed with one disease, e.g. IHD, tend to be detected in an earlier phase of another disease, e.g. diabetes, since these patients will be under closer scrutiny – a phenomenon known as Berkson’s bias [27]. In our investigation, such bias may
have led to overestimation of the IPRs. However, this would not have affected the trends detected unless there were differences in the bias with respect to gender and age.

The diagnostic coding in the CDWÖ database does not enable differentiation between type 1 and type 2 diabetes. Since type 2 diabetes is the most common form of the disease, and considering that macrovascular complications are confined primarily to type 2 diabetes, it is reasonable to assume that the results of our study can be attributed to type 2 diabetes. The prevalence of diabetes in our county population corresponds very well with previous estimations presented in the Swedish Public Health Report 2005 [28], which refers to a recent follow-up of the project Northern Sweden World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (designated WHO NSW MONICA) [29]. The prevalence rates of diabetes mellitus presented in that report are identical to our data; 5.4% among men and 4.0% among women aged 25–74 years, which strongly supports the validity of the diabetes data in the CDWÖ.

In conclusion, our results indicate that, in women aged 45-54 years, diabetes mellitus is associated with an IHD prevalence similar to that of nondiabetic women about 20 years older. By comparison, the IHD prevalence among diabetic men in the 45-54 year-old age group is close to that of nondiabetic men who are about 10 years older. We found a large relative gender difference in the impact of diabetes on IHD in the younger middle ages, which remained essentially the same up to about 65 years but decreased considerably thereafter. For women, this translates into a reduction due to diabetes of the protective effect against IHD conferred by female gender of 54% and 52% in the 45-54 and 55-64 year-old age groups respectively compared to 34% in the 65-74 year-old age group.
Acknowledgements

We are indebted to Mikael Karlsson for excellent guidance in use of the CDWÖ database. This study was supported by grants from the Research Council of Southeastern Sweden (FORSS).
References


Table 1. Prevalence of diabetes and ischemic heart disease (IHD) by age and sex in the

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of persons in the population</th>
<th>Number of cases</th>
<th>Rate, %</th>
<th>No. of cases</th>
<th>Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>27 058</td>
<td>1123</td>
<td>4.2</td>
<td>940</td>
<td>3.5</td>
</tr>
<tr>
<td>55–64</td>
<td>26 642</td>
<td>2517</td>
<td>9.4</td>
<td>2884</td>
<td>10.8</td>
</tr>
<tr>
<td>65–74</td>
<td>16 429</td>
<td>2404</td>
<td>14.6</td>
<td>3680</td>
<td>22.4</td>
</tr>
<tr>
<td>45–74</td>
<td>70 129</td>
<td>6044</td>
<td>8.6</td>
<td>7504</td>
<td>10.7</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>26 549</td>
<td>754</td>
<td>2.8</td>
<td>403</td>
<td>1.5</td>
</tr>
<tr>
<td>55–64</td>
<td>26 429</td>
<td>1506</td>
<td>5.7</td>
<td>1252</td>
<td>4.7</td>
</tr>
<tr>
<td>65–74</td>
<td>18 293</td>
<td>2060</td>
<td>11.3</td>
<td>2152</td>
<td>11.8</td>
</tr>
<tr>
<td>45–74</td>
<td>71 271</td>
<td>4320</td>
<td>6.1</td>
<td>3807</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Table 2. Prevalence of ischemic heart disease (IHD) by age and sex among subjects with and without diabetes in the county of Östergötland, Sweden, on 31 December 2003

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of cases</th>
<th>Rate, % and (CI)*</th>
<th>No. of cases</th>
<th>Rate, % and (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IHD in subjects with diabetes</td>
<td></td>
<td>IHD in subjects without diabetes</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>138</td>
<td>12.3 (10.4–14.4)</td>
<td>802</td>
<td>3.1 (2.9–3.3)</td>
</tr>
<tr>
<td>55–64</td>
<td>548</td>
<td>21.8 (20.2–23.4)</td>
<td>2336</td>
<td>9.7 (9.3–10.1)</td>
</tr>
<tr>
<td>65–74</td>
<td>816</td>
<td>33.9 (32.1–35.9)</td>
<td>2864</td>
<td>20.4 (19.8–21.1)</td>
</tr>
<tr>
<td></td>
<td>1502</td>
<td>24.9 (23.8–26.0)</td>
<td>6002</td>
<td>9.4 (9.1–9.6)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>68</td>
<td>9.0 (7.1–11.3)</td>
<td>335</td>
<td>1.3 (1.2–1.4)</td>
</tr>
<tr>
<td>55–64</td>
<td>236</td>
<td>15.7 (13.9–17.6)</td>
<td>1016</td>
<td>4.1 (3.8–4.3)</td>
</tr>
<tr>
<td>65–74</td>
<td>472</td>
<td>22.9 (21.1–24.8)</td>
<td>1680</td>
<td>10.3 (9.9–10.8)</td>
</tr>
<tr>
<td></td>
<td>776</td>
<td>18.0 (16.9–19.1)</td>
<td>3031</td>
<td>4.5 (4.4–4.7)</td>
</tr>
</tbody>
</table>

* CI = confidence interval
Figure 1. Percentages of identified subjects aged 45-74 years with diabetes and IHD per health care level – primary health care (PHC), outpatient hospital care and inpatient care – in a five-year period, residents of the county of Östergötland, Sweden (diabetes, n = 10,364; IHD, n = 11,311).
Figure 2. Diabetes/nondiabetes IHD prevalence rate ratios (IPRs) for different age groups with 95% confidence intervals (CIs). Calculations are based on 71,271 women (2A) and 70,129 men (2B) in the county of Östergötland, Sweden, 31 December 2003.
Figure 3. Ratios of the diabetes/nondiabetes IHD prevalence rate ratios (IPRs) for women relative to men for different age groups with 95% confidence intervals (CIs). Calculations are based on 71,271 women and 70,129 men in the county of Östergötland, Sweden, 31 December 2003.