The Effects of Diabetes on the Risks of Major Cardiovascular Diseases and Death in the Asia-Pacific Region

Asia Pacific Cohort Studies Collaboration

OBJECTIVE — To provide reliable age- and region-specific estimates of the associations between diabetes and major cardiovascular diseases and death in populations from the Asia-Pacific region.

RESEARCH DESIGN AND METHODS — Twenty-four cohort studies from Asia, Australia, and New Zealand (median follow-up, 5.4 years) provided individual participant data from 161,214 people (58% from Asia) of whom 4,873 had a history of diabetes at baseline. The associations of diabetes with the risks of coronary heart disease, stroke, and cause-specific mortality during follow-up were estimated using time-dependent Cox models, stratified by study cohort and sex and adjusted for age at risk.

RESULTS — In all, 9,277 deaths occurred (3,635 from cardiovascular disease). The hazard ratio (95% CI) associated with diabetes was 1.97 (1.72–2.25) for fatal cardiovascular disease; there were similar hazard ratios for fatal coronary heart disease, fatal stroke, and composites of fatal and nonfatal outcomes. For all cardiovascular outcomes, hazard ratios were similar in Asian and non-Asian populations and in men and women, but were greater in younger than older individuals. For noncardiovascular death, the hazard ratio was 1.56 (1.38–1.77), with separately significant increases in the risks of death from renal disease, cancer, respiratory infections, and other infective causes. The hazard ratio for all-causes mortality was 1.68 (1.55–1.84), with similar ratios in Asian and non-Asian populations, but with significantly higher ratios in younger than older individuals.

CONCLUSIONS — The relative effect of diabetes on the risks of cardiovascular disease and death in Asian populations is much the same as that in the largely Caucasian populations of Australia and New Zealand. Hazard ratios were severalfold greater in younger people than older people. The rapidly growing prevalence of diabetes in Asia heralds a large increase in the incidence of diabetes-related death in the coming decades.

Diabetes Care 26:360–366, 2003

The World Health Organization estimated that, in 1997, there were 143 million people with diabetes worldwide (1). The two countries with the largest diabetic populations were India (21 million) and China (17 million). The total number with diabetes is likely to reach about 300 million by 2025 (1,2). A disproportionate amount of this increase is anticipated in low- and middle-income countries, many of which are expected to experience severalfold increases in the number with diabetes. In the Asia-Pacific region, which includes several low- and middle-income countries, numbers are predicted to rise from 58 million in 1997 to 136 million in 2025. To inform health care planners in this region about the eventual consequences of such increases, local evidence is required about the effects of diabetes on cardiovascular and other diseases.

In Western countries, two- to threefold increases in the risks of atherosclerotic diseases have been reported among individuals with diabetes (3,4). In these populations, cardiovascular disease is the leading cause of death among those with diabetes (5). In some lower-income population groups, however, chronic renal failure and infection are more common causes of death among such people (6,7). In most populations from the Asia-Pacific region, there is very little evidence available about the effects of diabetes on the risks of cardiovascular disease or other common causes of death.

The Asia Pacific Cohort Studies Collaboration was established to provide reliable evidence about the effects of a variety of modifiable risk factors, including diabetes, on the risks of major cardiovascular diseases and other common causes of death in populations from this region. The Collaboration includes the large majority of all prospective observational studies conducted in both Asian and Caucasian populations in the region. This report describes the effects of diabetes on the risks of major cardiovascular diseases and cause-specific mortality in these populations.

RESEARCH DESIGN AND METHODS

Participating studies

The Asia Pacific Cohort Studies Collaboration is an overview (meta-analysis) conducted by the principal investigators of longitudinal observational studies conducted in the region. Details of the methods of study identification and data collection are described elsewhere (8). Briefly, studies were eligible for inclusion in the Collaboration if they were conducted prospectively in a population from the Asia-Pacific region, measured blood pressure at baseline and vital status at the end of the follow-up, and continued follow-up for at least 5,000 person-years. Studies were not eligible if entry was dependent on having a particular medical condition or risk factor. Studies were classified as Asian if their participants were recruited from China, Japan, Korea, or...
southeast Asia or Australasian if their participants were recruited from Australia and New Zealand. All datasets were checked centrally for consistency and, where necessary, further details were sought from collaborating investigators.

**Variables measured at baseline**
The diabetic status of individual participants was determined on the basis of a reported history of diabetes at baseline, except in the 1992 Singapore National Health Survey, where status was also dependent on diagnosis by an oral glucose tolerance test. In most studies, blood pressure was measured at rest in the seated position using a standard mercury sphygmomanometer and total cholesterol was measured from fasting serum. BMI was calculated as weight (kg) divided by height (m)^2. Smoking status was recorded as either current smoker or nonsmoker of cigarettes.

**Outcomes**
All outcomes were classified according to the ninth revision of the International Classification of Diseases (ICD-9). Each death was ascribed to its underlying cause as reported on the death certificate. The primary end points considered here are death was ascribed to its underlying cause (ICD-9). Each group defined by geographical area (Asia/Australasia), sex, and age were investigated by adding interaction terms to the Cox model (9). Analyses of composite fatal and nonfatal outcomes were restricted to those studies that provided information on both types of outcomes.

**RESULTS**

**Data available**
By the end of 2000, 38 studies involving about half a million participants and 4 million person-years of follow-up had been recruited to the Collaboration. The major characteristics of the participating studies are described elsewhere (8). Information on diabetes at baseline and dates of death was available from 24 studies involving 161,214 individuals, of whom 5% were women (Table 1). The median follow-up time was 5.4 years. Additional data on nonfatal strokes were available from nine studies, and data on nonfatal myocardial infarction were available from six studies.

**Variables measured at baseline**
Among the 161,214 participants, 4,873 (3.0%) were classified as having diabetes at baseline: 2,697 (2.9%) in Asia and 2,176 (3.2%) in Australasia; age standardization made no difference to these estimates of prevalence. The age-adjusted prevalence of diabetes was 2.8% for women and 3.2% for men. The prevalence of diabetes was 2.1% among those <60 years old; 5.3% in those 61–74 years old; and 6.1% in those ≥75 years old. In both Asian and Australasian studies, those with diabetes tended to be older and have higher systolic blood pressure and BMI than those without diabetes (Table 2). In Asia, those with diabetes were less likely to smoke. Mean systolic blood pressure, total cholesterol, and BMI and the percentage smoking cigarettes were higher in Australasia than in Asia. Mean diastolic blood pressure was slightly higher in Asia.

**Outcomes**
During follow-up, 9,277 deaths were recorded, of which 3,635 were ascribed to cardiovascular disease (including 1,414 deaths from coronary heart disease and 1,154 from cerebrovascular disease), 4,983 were ascribed to noncardiovascular diseases, and 659 were of unknown cause. The crude annual death rate was 2.4% among those with diabetes and 1.1% among those without diabetes. Cardiovascular disease accounted for 46% of the known causes of death among those with diabetes and 42% of such deaths among those without diabetes. The leading cardiovascular cause of death in Asia was stroke (42%), whereas in Australasia it was coronary heart disease (59%). In the studies with data on nonfatal outcomes, 747 nonfatal strokes and 486 nonfatal myocardial infarctions were reported.

**Coronary heart disease**
For death from coronary heart disease, the age-, sex-, and study-adjusted hazard ratio associated with diabetes was 2.19 (95% CI 1.81–2.66), with similar ratios for Asian and Australasian populations (Fig. 1). There was no material change in this hazard ratio after further adjustment for systolic blood pressure (decreased by 2.0%), total serum cholesterol (0%), BMI (decreased by 4.5%), smoking status (increased by 2.3%), or all four together (decreased by 3.4%). The hazard ratios were similar in men (2.03; 95% CI 1.60–2.59) and women (2.54; 95% CI 1.84–3.49) (P for interaction = 0.27). Moreover, in neither the Asian nor the Australasian subgroup was there any significant sex difference in the hazard ratios (P for interaction > 0.1). Hazard ratios declined with age at risk (P = 0.0003 for homogeneity), ranging from 4.38 (98% CI 2.63–7.31) in those aged <60 years to 1.57 (95% CI 1.14–2.16) in those aged ≥75 years (Fig. 2). The hazard ratio for the composite outcome of death from coronary heart disease or nonfatal myocardial infarction, 1.73 (95% CI 1.34–2.22), was similar to that for the fatal event alone.

**Cerebrovascular disease**
The age-, sex-, and study-adjusted hazard ratio for death from cerebrovascular disease was 2.02 (95% CI 1.57–2.59) among individuals with diabetes, with similar ratios in Asian and Australasian subgroups. Further adjustment for other risk factors
hazard ratios declined with age (P = 2.64 (95% CI 1.78–3.92)) and for hemorrhagic stroke (271 events), 1.13 (0.55–2.36).

Deaths from other cardiovascular diseases

The hazard ratio for deaths ascribed to cardiovascular disease other than coronary heart disease and cerebrovascular disease was 1.61 (95% CI 1.22–2.13), with similar ratios in Asian and Australasian subgroups. Too few deaths were recorded to allow more detailed analysis of cause-specific cardiovascular mortality. The hazard ratio for deaths from any cardiovascular cause was 1.97 (95% CI 2.19–2.63). The hazard ratio for deaths from cancer was smaller, but still conventionally significant (1.21; 95% CI 1.01–1.45). Although numbers were generally too small to allow meaningful analyses of site-specific cancers, there was some evidence of excess mortality from pancreatic cancer (125 deaths) among those with diabetes (2.08; 95% CI 1.04–4.17).

Deaths from nonvascular causes and total mortality

Increased hazard ratios were observed for death from renal disease (not including cancer) (2.93; 95% CI 1.70–5.04); death from respiratory infections, mostly pneumonia (1.52; 95% CI 1.03–2.24); and death from nonrespiratory infections (not renal) (2.19; 1.15–4.16) (Fig. 3). The hazard ratio for all deaths from infective or inflammatory causes was 1.98 (95% CI 1.49–2.63). The hazard ratio for deaths from cancer was smaller, but still conventionally significant (1.21; 95% CI 1.01–1.45). Although numbers were generally too small to allow meaningful analyses of site-specific cancers, there was some evidence of excess mortality from pancreatic cancer (125 deaths) among those with diabetes (2.08; 95% CI 1.04–4.17).
In each case, there was no clear difference in the hazard ratios for women and men (data not shown) or between Asian and Australasian subgroups. The hazard ratios for total mortality were inversely related to age at risk (P < 0.0001 for homogeneity).

**CONCLUSIONS** — This analysis demonstrates that individuals with diabetes were also associated with an increased risk of death from causes unknown (hazard ratio 1.59; 95% CI 1.21—2.09), from any noncardiovascular cause (1.56; 95% CI 1.38—1.77), and from all causes (1.68; 95% CI 1.55—1.84). In each case, there was no clear difference in the hazard ratios for women and men (data not shown) or between Asian and Australasian subgroups. The hazard ratios for total mortality were inversely related to age at risk (P < 0.0001 for homogeneity).

**Table 2**—Mean (or percentage) values of baseline variables, by diabetes history status and geographical area

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asia</th>
<th>Australia &amp; New Zealand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean 95% CI</td>
</tr>
<tr>
<td>Age (years)</td>
<td>2,697</td>
<td>59.3 (58.8—59.7)</td>
</tr>
<tr>
<td>Females (%)</td>
<td>2,697</td>
<td>47.5 (46.6—49.4)</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>2,684</td>
<td>26.7 (24.3—29.1)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)*</td>
<td>2,697</td>
<td>134.9 (134.2—135.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)*</td>
<td>2,697</td>
<td>77.8 (77.3—78.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>2,543</td>
<td>23.9 (23.7—24.0)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)*</td>
<td>1,617</td>
<td>5.21 (5.16—5.27)</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex.

---

**Figure 1**—Sex-, study-, and age-adjusted hazard ratios (on a log scale) for major cardiovascular diseases (diabetic versus nondiabetic), overall and by geographic area. The horizontal lines and (for totals) width of diamonds are 95% confidence limits; the boxes are proportional to the number of events.
tes in the Asia-Pacific region are at increased risk of death from a variety of causes. Overall, diabetes was associated with a twofold increase in the risk of death from cardiovascular disease, a one-half increase in the risk of noncardiovascular death, and a two-thirds increase in the risk of death from all causes. For all outcomes, there were no discernible differences between the hazard ratios in Asian and Australasian populations or between those in men and women. However, there was a strong effect of age on the hazard ratios for coronary heart disease, stroke, total cardiovascular death, and all-cause death, each of which decreased with increasing age at risk. All cardiovascular associations were maintained after

<table>
<thead>
<tr>
<th>Number of deaths/person-years</th>
<th>No diabetes</th>
<th>Diabetes</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>137,679,016</td>
<td>19,123,29</td>
<td>4.38 (2.62-7.31)</td>
</tr>
<tr>
<td>50-74</td>
<td>518,321,04</td>
<td>62,143,55</td>
<td>2.44 (1.84-3.23)</td>
</tr>
<tr>
<td>75+</td>
<td>639,562,252</td>
<td>42,229,77</td>
<td>1.67 (1.14-2.46)</td>
</tr>
</tbody>
</table>

| **Cerebrovascular disease**   |            |          |                       |
| <50                           | 854,795,16  | 61,232,9 | 2.57 (1.00-6.59)      |
| 50-74                         | 448,921,04  | 41,143,55 | 2.69 (1.91-3.80)      |
| 75+                           | 552,562,25  | 25,229,77 | 1.30 (0.80-1.96)      |

| **All cardiovascular disease**|            |          |                       |
| <50                           | 2,031,132,16 | 229,132,29 | 2.37 (1.00-5.21)      |
| 50-74                         | 1,395,521,304 | 127,143,55 | 2.27 (1.67-2.75)      |
| 75+                           | 1,710,562,25 | 94,229,77  | 1.49 (1.20-1.84)      |

| **All-cause mortality**       |            |          |                       |
| <50                           | 1,274,680,076 | 71,123,63 | 2.43 (1.63-3.12)      |
| 50-74                         | 3,751,532,171 | 309,145,05 | 1.78 (1.56-2.01)      |
| 75+                           | 3,643,595,86 | 219,242,7  | 1.40 (1.21-1.61)      |

---

**Figure 2**—Sex-, study-, and age-adjusted hazard ratios (on a log scale) for deaths from major cardiovascular diseases and all causes (diabetic versus nondiabetic), by age group. For conventions see Fig. 1.

**Figure 3**—Sex-, study-, and age-adjusted hazard ratios (on a log scale) for noncardiovascular deaths and deaths from all causes (diabetic versus nondiabetic), overall and by geographic area. For conventions see Fig. 1.
adjustment, both individually and in total, for the major established risk factors—systolic blood pressure, cholesterol, obesity, and smoking—some of which may, themselves, be influenced by diabetes. Additional adjustments (not reported here) of all associations for 10-year calendar time (decade of observation) made virtually no difference.

The proportion of deaths attributed to cardiovascular disease (46%) among individuals with diabetes in these populations from the Asia-Pacific region is similar to that observed in other studies, based on death certificates, in Australia (50%) (10) and the United States (48%) (5). The sizes of the associations of diabetes with cardiovascular diseases in these populations are also very similar to those found in earlier North American (11–14), Asian (15), and Pacific (16) studies, after allowing for the age differences between study populations. For instance, in the Honolulu Heart Program (16), among males of similar average age to those included in this study, relative risks associated with diabetes were 2.0 for ischemic stroke, 1.0 for hemorrhagic stroke, and 1.8 for all strokes—outcomes virtually identical to those reported here. The particularly high relative risks for stroke reported in both Finland (4.8 for 30–59 year olds) (17) and Sweden (3.9 for 51-to 59-year-old men) (18) are consistent with the hazard ratios observed in this study among younger people. The much higher relative risks for coronary (6.2) and cardiovascular (5.1) death among those free of coronary disease at baseline in the Nurses Health Study (19) appear to be at odds with the results of most other major studies, including this one, although higher cardiovascular relative risks associated with diabetes in women have been reported in some other studies, such as the Framingham Study (12). For coronary heart disease, the findings for women and men in this study are remarkably similar to those from a meta-analysis (20), which reported relative risks of 2.58 (compared with 2.53 here) for women and 1.85 (compared with 2.02 here) for men. Most studies have been too small or too age-restricted to explore age-specific associations of diabetes. Exceptions are the Physicians (14) and Nurses (19) Health Studies, both of which found an attenuation of coronary heart disease relative risk with increasing age, and NHANES-I (11), which reported a similar trend for all-cause mortality. Each of these findings is consistent with the results of the current analyses.

Overall, the association of diabetes with death from noncardiovascular causes was less strong than that with cardiovascular disease. However, the hazard ratio for death from chronic renal failure, a common vascular complication of diabetes, was somewhat higher than that for death from stroke or coronary heart disease, albeit with much smaller absolute numbers of deaths in both Asian and Australasian populations. The hazard ratios for death from respiratory infections, mostly pneumonia, and other (nonrenal) infections were also increased, a finding consistent with reports from the United States (21,22). The increased cancer risk observed here is consistent with a small, though nonsignificant, excess reported among 51- to 59-year-old Swedish men (18).

The definition of diabetes used here was almost entirely based on self-report. This would be expected to have a high positive predictive value but limited sensitivity, as there must be others in these populations who had diabetes but were unaware of it. Although results of oral glucose tolerance tests were not available from most studies, some studies collected fasting blood glucose measurements; such measurements were available for 55,422 participants (34% of the total study population). Using World Health Organization criteria (23) for classification of diabetes by glucose level, 1,390 (3%) of the 53,032 in this subsample who reported no history of diabetes met the criteria for diabetes. When these individuals were added to the group classified as having diabetes at baseline, the hazard ratio for death from cardiovascular disease was virtually unchanged (1.83; 95% CI 1.47–2.27). In this study, no separate data were available about subtypes of diabetes (type 1 or 2) or duration of diabetes, nor were data available about treatments received. Whereas these characteristics may vary between regions, the consistency of the hazard ratios observed here suggests that any net effect of such differences on disease risk is unlikely to be large.

Diabetes is a serious health problem and a major risk factor for cardiovascular disease in both sexes and all adult age groups. Its prevalence is increasing in the Asia-Pacific region (2,24), where nearly half of those with diabetes reside and where nearly half of all cardiovascular deaths occur worldwide (25). Within such populations, precise estimates of the associations of diabetes with its major cardiovascular and noncardiovascular complications are a critical prerequisite for informed decisions about strategies for the prevention and control of diabetes-related mortality and morbidity. The results provided here suggest that diabetes has similar proportional effects on disease risk in Eastern and Western populations in the region and in men and women but is more strongly related to disease risk in younger than older individuals. This is of particular relevance to lower- and middle-income countries, since the average age at which people suffer major cardiovascular events in such countries is much lower than that in higher-income countries (26). Taken together with the evidence of rapidly increasing numbers of people with diabetes in countries such as India and China, the findings from this project suggest that unless preventive action is taken, the absolute impact of diabetes on the health of the populations of Asia will be enormous.

Acknowledgments—This project was funded by grants from the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand. Federica Barzi is a Fellow from Instituto di Ricerche Farmacologiche Mario Negri, Milano, Italy.

APPENDIX—Asia Pacific Cohort Studies Collaboration

Writing committee
M. Woodward, X. Zhang, F. Barzi, W. Pan, H. Ueshima, A. Rodgers, S. MacMahon

APCSC investigators
Statistical analyses F. Barzi, D. Bennett, V. Parag, S. Van der Hoorn, M. Woodward

Asia Pacific Cohort Studies Collaboration
References


