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

From the Asia Pacific Cohort Studies Collaboration (see Appendix).

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Received for publication 3 June 2002 and accepted in revised form 10 October 2002.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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 deaths from coronary heart disease (ICD 410–414); cerebrovascular disease (430–438); all cardiovascular causes; renal disease (excluding cancer) (403–404, 580–593); cancer (140–239); respiratory infections (460–466, 480–487); other infections (not renal) (001–139, 390–392, 540–543, 680–686, 690–698), all infective or inflammatory causes; all noncardiovascular causes; and total mortality. From the studies that collected data on nonfatal cardiovascular outcomes, data are reported on two composite end points: nonfatal myocardial infarction or death from coronary heart disease and nonfatal stroke or death from cerebrovascular disease.

Statistical methods

Analyses used individual participant data and were restricted to participants aged ≥20 years at the time of the baseline survey. Baseline cardiovascular risk factor levels in those with and without diabetes were compared after adjustment for age and sex using least-squares methods for continuous variables and standardization for binary variables (9), with the total study population as the standard population. The prevalence of diabetes in Asian and Australasian study populations was compared using similar methods. Time-dependent Cox models, stratified by study and sex and adjusted for age at risk, were used to assess risks associated with diabetes. In some analyses, further adjustments were made for systolic blood pressure, total cholesterol, BMI, and smoking status at baseline. Homogeneity between groups 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 50% 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

Table 1—*Characteristics of participating studies

Cohort name	Country	*n*	Age (years)	Females (%)	Diabetes (%)	Median follow-up (years)	Fatal events				Nonfatal events	
							All	CVD	CHD	Stroke	MI	Stroke
Asia												
Aito	Japan	1,718	20–77	56.7	2.7	15.2	181	59	16	25	—	—
Akabane	Japan	1,828	40–69	55.7	1.4	11.0	137	36	7	12	21	26
CISCH	China	2,163	34–64	50.9	2.5	3.3	7	1	1	0	14	9
Civil Service	Japan	9,318	40–55	33.1	1.8	6.7	99	13	1	2	—	—
East Beijing	China	1,135	20–84	51.2	5.6	17.1	121	65	20	28	—	—
Hong Kong	Hong Kong	2,960	66–107	57.2	8.6	2.5	632	197	83	72	—	—
Kinmen Island	Taiwan	2,522	50–93	48.9	8.7	2.9	165	96	10	12	—	—
Konan	Japan	1,226	20–96	55.4	3.0	6.4	82	26	3	13	—	—
Miyama	Japan	1,071	40–80	55.8	5.0	6.6	90	26	2	10	—	—
Ohasama	Japan	2,240	27–91	63.8	10.0	4.1	88	27	7	8	—	48
Saitama	Japan	3,624	20–94	62.2	1.7	10.3	365	120	24	55	—	—
Seven Cities	China	37,353	35–98	53.1	1.1	2.5	811	472	78	173	—	145
Shibata	Japan	2,350	40–89	57.7	1.1	20.0	833	346	67	209	—	—
Shigaraki	Japan	3,757	29–94	59.5	5.4	4.4	117	29	3	13	—	—
Singapore Heart	Singapore	2,368	20–89	48.9	9.5	14.6	167	59	31	21	39	68
Singapore 92	Singapore	3,332	20–70	51.8	9.6	6.2	71	33	22	6	15	41
Tanno/Soubetsu	Japan	1,957	39–65	53.4	6.2	16.4	247	72	23	33	—	0
CVD FACT	Taiwan	5,729	20–92	55.4	2.7	6.0	230	60	13	29	—	—
Yunnan	China	6,570	35–84	3.1	0.5	4.5	630	220	17	106	—	—
Subtotal		93,221	20–107	48.7	2.9	4.6	5,073	1,957	428	827	89	337
Australasia												
Busselton	Australia	5,283	20–96	51.8	1.9	17.5	1,674	897	506	193	326	336
Canberra	Australia	879	70–97	47.2	6.8	7.7	391	105	55	23	—	—
Fletcher Challenge	New Zealand	10,326	20–89	28.1	2.5	4.8	230	110	70	16	71	74
Melbourne Cancer	Australia	41,286	27–75	58.9	3.7	5.6	1,096	254	161	32	—	—
Perth	Australia	10,219	20–90	48.3	2.1	14.4	813	312	194	63	—	—
Subtotal		67,993	20–97	51.9	3.2	5.6	4,204	1,678	986	327	397	410
Total		161,214	20–107	50.0	3.0	5.4	9,277	3,635	1,414	1,154	486	747

*Restricted to studies and subjects with information on history of diabetes at baseline and duration of follow-up. CHD, coronary heart disease; CVD, total cardiovascular disease; MI, myocardial infarction.

made no substantial difference. The hazard ratios were almost exactly the same in women (2.00; 95% CI 1.37–2.92) and men (2.04; 95% CI 1.46–2.84). Once again, in neither the Asian nor the Australasian subgroups were there any significant sex differences in the hazard ratios (P for interaction > 0.4). However, the hazard ratios declined with age ($P = 0.008$ for homogeneity). The hazard ratio for the composite outcome of death from cerebrovascular disease or nonfatal stroke was 2.09 (95% CI 1.65–2.64). In some cases, it was possible to classify stroke by subtype—ischemic or hemorrhagic. Overall, the hazard ratio for ischemic stroke (328 fatal or nonfatal events) was 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 1.72–2.25), with similar ratios, once again, in Asian and Australasian subgroups, and for women and men. The size of the hazard ratio decreased with age at risk ($P < 0.0001$ for homogeneity): from 3.47 (2.30–5.21) among individuals <60 years old to 1.49 (1.20–1.84) among those ≥75 years old.

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). Diabe-

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

	Asia						Australia & New Zealand					
	Diabetes			No diabetes			Diabetes			No diabetes		
Variable	*n*	Mean	95% CI	*n*	Mean	95% CI	*n*	Mean	95% CI	*n*	Mean	95% CI
Age (years)	2,697	59.3	(58.8–59.7)	90,524	52.1	(52.0–52.2)	2,176	58.8	(58.3–59.2)	65,817	51.2	(51.1–51.3)
Females (%)	2,697	47.5	(45.6–49.4)	90,524	48.7	(48.4–49.0)	2,176	46.9	(44.8–49.0)	65,817	52.1	(51.7–52.5)
Current smoking (%)*	2,684	26.7	(24.3–29.1)	89,803	32.7	(32.4–33.1)	2,169	37.6	(34.4–40.8)	65,668	35.3	(34.8–35.8)
Systolic blood pressure (mmHg)*	2,697	134.9	(134.2–135.7)	90,524	128.9	(128.7–129.0)	2,176	142.7	(141.9–143.5)	65,817	137.1	(136.9–137.3)
Diastolic blood pressure (mmHg)*	2,697	77.8	(77.3–78.2)	90,524	77.3	(77.2–77.4)	2,176	76.9	(76.4–77.4)	65,817	76.7	(76.6–76.8)
BMI (kg/m^2)*	2,543	23.9	(23.7–24.0)	88,850	22.1	(22.1–22.2)	2,094	28.4	(28.3–28.6)	64,576	25.8	(25.7–25.8)
Cholesterol (mmol/l)*	1,617	5.21	(5.16–5.27)	55,970	4.85	(4.83–4.86)	2,084	5.45	(5.40–5.50)	63,997	5.50	(5.48–5.51)

*Adjusted for age and sex.

tes was 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).

CONCLUSIONS — This analysis demonstrates that individuals with diabe-

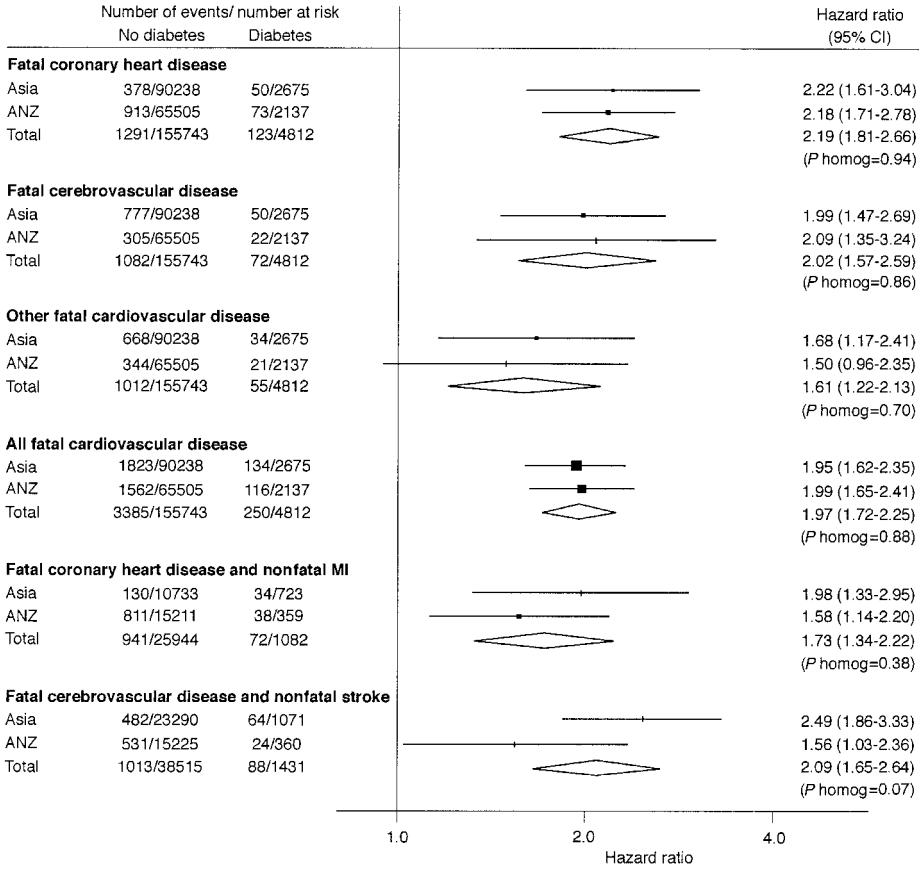

Figure 1—*Sex-, study-, and age-adjusted hazard ratios (on a log scale) for major cardiovascular diseases (diabetic versus nondiabetic), overall and by geographic area. The horizontal lines and (for totals) width of diamonds are 95% confidence limits; the boxes are proportional to the number of events.*

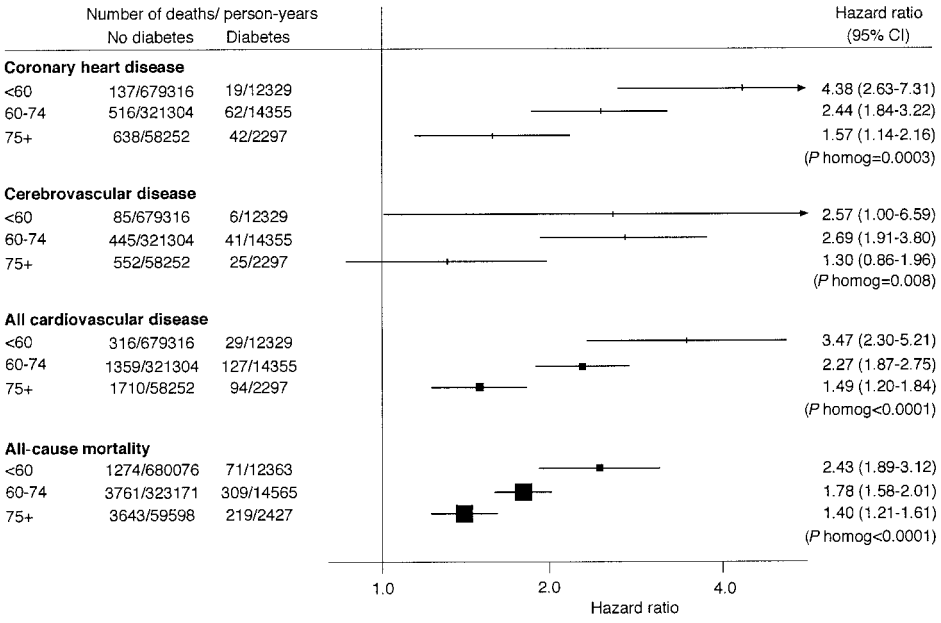

Figure 2—*Sex-, study-, and age-adjusted hazard ratios (on a log scale) for deaths from major cardiovascular diseases and all causes (diabetic versus nondiabetic), by age group. For conventions see Fig. 1.*

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-causes death, each of which decreased with increasing age at risk. All cardiovascular associations were maintained after

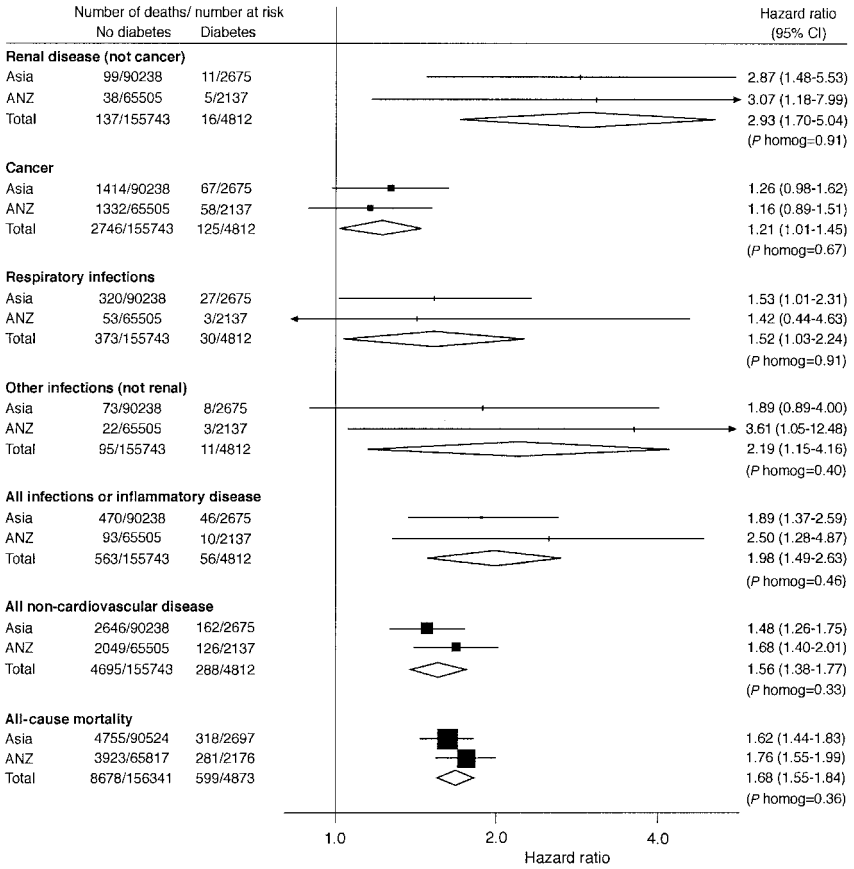

Figure 3—*Sex-, study-, and age-adjusted hazard ratios (on a log scale) for noncardiovascular deaths and deaths from all causes (diabetic versus nondiabetic), overall and by geographic area. For conventions see Fig. 1.*

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 larger 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 blood glucose 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.

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*The studies in *italics* provided the data used in this article.

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