Blood Glucose and Risk of Cardiovascular Disease in the Asia Pacific Region

ASIA PACIFIC COHORT STUDIES COLLABORATION*

OBJECTIVE — To assess the shape and strength of the association between usual blood glucose and cardiovascular disease (CVD) in Asian and Australasian cohorts and to determine the impact of adjusting for other determinants of CVD risk and excluding people with diabetes.

RESEARCH DESIGN AND METHODS — Relative risk estimates and 95% CIs were calculated from Cox models, stratified by sex and cohort, and adjusted for age at risk on individual participant data from 17 cohort studies. Repeat measurements of blood glucose were used to adjust for regression dilution bias.

RESULTS — Fasting blood glucose data were available for 237,468 participants, and during ~1.2 million person-years of follow-up, there were 1,661 stroke and 816 ischemic heart disease (IHD) events. Data were also available on 27,996 participants with nonfasting glucose measurements. Continuous positive associations were demonstrated between usual fasting glucose and the risks of CVD down to at least 4.9 mmol/l. Overall, each 1 mmol/l lower usual fasting glucose was associated with a 21% (95% CI 18–24%) lower risk of total stroke and a 23% (19–27%) lower risk of total IHD. The associations were similar in men and women, across age-groups, and in Asian compared with Australasian (Australia and New Zealand) populations. Adjusting for potential confounders or removing those with diabetes as baseline did not substantially affect the associations. Associations for nonfasting glucose were weaker than those with fasting glucose.

CONCLUSIONS — Fasting blood glucose is an important determinant of CVD burden, with considerable potential benefit of usual blood glucose lowering down to levels of at least 4.9 mmol/l.

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The risk of cardiovascular disease (CVD) in type 2 diabetic subjects is about two- to fourfold greater than in people without diabetes (1–3) and appears to be independent of other risk factors including age, smoking, raised serum cholesterol, and blood pressure (4). Much of the research has been conducted in Western populations, but recent evidence demonstrated similarly increased risks in Asian populations (5).

Glucose cutoffs for defining diabetes are based on what has been interpreted as a threshold for microvascular disease such as retinopathy (6). However, there is uncertainty about the relationship between blood glucose and macrovascular complications such as CVD, which account for much of the diabetic morbidity and mortality. There has been some indication of a continuous association for CVD risk (7–9) as is seen for many other CVD determinants such as blood pressure, cholesterol, and BMI (10–15).

Large cohort studies with data across a range of blood glucose levels are necessary to reliably assess the shape and strength of the relationship between blood glucose and CVD risk. One recent overview observed a continuous association between glucose and CVD in nondiabetic subjects that was maintained when those with the highest glucose levels were removed from the analysis and extended below the usual "diabetic threshold" (8). Many smaller prospective studies concur that there is an increased risk of CVD at the upper end of the fasting blood glucose distribution, but the stated threshold levels range between 5.3 to >7.0 mmol/l (16).

Establishing the shape of associations between risk determinants and disease is important to gauge the potential for prevention (10,17). Review of the glucose-CVD association has particular relevance to non-Western parts of the world where there is an increasing burden of noncommunicable diseases such as diabetes and CVD. Data from the Asia Pacific Cohort Studies Collaboration (APCSC) presents an ideal opportunity to explore the shape and strength of this association, to assess the impact of adjusting for other determinants of CVD risk, and to determine whether the patterns differ between populations from Asia and those from Australasia (Australia and New Zealand).

RESEARCH DESIGN AND METHODS

— APCSC is an individual participant data overview (meta-analysis) of prospective cohort studies. The methods have been reported in detail elsewhere (18). In brief, prospective cohort studies were eligible for inclusion if they contained study populations from the Asia Pacific region and had at least 5,000 person-years of follow-up recorded or planned. At a minimum, they had to have

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*A complete list of the writing committee and collaboration members is available in the APPENDIX.

Abbreviations: APCSC, Asia Pacific Cohort Studies Collaboration; CVD, cardiovascular disease; IHD, ischemic heart disease; OGTT, oral glucose tolerance test.

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

recorded data on date of birth or age, sex, blood pressure at baseline, and date or age at death. Additional data sought included date of baseline survey, glucose, fasting status, blood cholesterol, height, weight, smoking, and any data on repeat measures of risk factors. Outcome data included nonfatal stroke and ischemic heart disease (IHD) and cause of death (18).

Statistical methods

Associations between glucose and disease. All analyses are restricted to participants aged ≥20 years who had blood glucose and fasting status recorded at baseline. Analyses reported here excluded individuals with a baseline glucose value of ≥20 mmol/l. Data on fasting and nonfasting glucose were analyzed separately. Stratified Cox proportional-hazards analyses (19) were used to regress time until first event against baseline glucose with individual participant data collected on all cohorts. All analyses were stratified by sex and cohort to control for confounding and reduce statistical heterogeneity. Age was treated as an external time-dependent covariate (20) to assess change in hazards as an individual's age increases. These "age at risk" analyses account for the fact that cohorts had different start and follow-up times.

Age-specific analyses included age at risk categories of <60, 60–69, and ≥70 years (analyses were also conducted by sex) and region (Asia vs. Australasia and comparison of regions within Asia). Where possible, analyses were undertaken for total (fatal and nonfatal) and fatal (death occurring within 28 days of event) CVD outcomes. Further sensitivity analyses included restricting analyses to those participants who had no diagnosis of diabetes at baseline and/or adjusting for other potential confounders, such as systolic blood pressure (mmHg), serum total cholesterol (mmol/l), smoking (current vs. not current), and BMI (kg/m^2), for those cohorts who had recorded these variables at baseline. Insufficient data were available for ethnic-specific analysis. Effect modification was assessed with the use of statistical interaction terms for sex and region in the Cox model.

Estimation of usual glucose. A single baseline measure is subject to random fluctuations of fasting glucose, due partly to the measurement process and partly to any real but temporary deviations at the baseline visit from the usual blood glucose level (21). The distribution of single baseline glucose measures is therefore wider than the distribution of true usual glucose values due to regression to the mean. The term for the resulting underestimation of an exposure with an end point that occurs with one-off baseline measures is "regression dilution bias" (21). Usual glucose values are estimates that have been corrected for regression dilution bias and are therefore closer to true glucose values. These usual estimates were made using repeated glucose measurement data from three cohort studies. A mixed-model approach was used to calculate the regression dilution ratio (λ) that took into account the varying time intervals between the glucose measurements. Several other methods of correction (22), including the method of MacMahon et al. (21), have been used in previous analyses of APCSC data, and each yielded very similar regression dilution ratios (11). To adjust for regression dilution bias, the regression coefficient (β^*) was calculated by multiplying the uncorrected regression coefficient (β) by λ^{-1} (where $\lambda^{-1} = 1.6$). A similar approach was used to adjust the standard errors.

The hazard ratios and corresponding 95% CIs were estimated for a 1-mmol/l reduction in usual glucose. In the nonparametric analyses, participants were divided into quartiles according to baseline glucose (<5, 5–5.9, 6–6.9, and ≥7 mmol/l), and the hazard ratios were plotted against "usual" glucose rather than baseline glucose. The 95% CIs for each exposure group were estimated by treating the hazard ratios as "floating variances." This approach does not affect the hazard ratios but enables the comparison between pairs of exposure groups rather than the comparison of a single exposure group with an arbitrary reference group (23,24).

RESULTS

Data availability and study population characteristics

Baseline glucose data were available in 17 of the 43 cohort studies (Table 1). Of these cohorts, fasting glucose measurements were recorded in 13 studies, including 237,468 participants with 1,194,320 person-years of follow-up, and nonfasting glucose measurements were recorded in 6 studies, including 27,996 participants with 185,324 person-years of follow-up (the Melbourne and Akabane cohorts included a mixture of fasting and nonfasting glucose data). During a mean follow-up of 5 years, there were 1,661 stroke and 816 IHD events in the fasting glucose studies, and during a mean follow-up of 6.5 years, there were 144 stroke and 240 IHD events in the nonfasting glucose studies.

Levels of other risk factors (with the exception of smoking prevalence) tended to be lower in the lowest two quartiles (<5 and 5.0–5.9 mmol/l) compared with the top two glucose quartiles (6.0–6.9 and ≥7mmol/l). For example, in those studies with fasting glucose data, the mean systolic blood pressure levels were 120–127 vs. 135 mmHg, mean total cholesterol was 4.9–5.2 vs. 5.4–5.5 mmol/l, and mean BMI was 22.8–24.1 vs. 25.0–25.5 kg/m^2.

Glucose and risk of cardiovascular end points

There was a positive log-linear association between usual fasting glucose and the risk of total stroke and IHD (Fig. 1). For both end points, this association was continuous down to at least 4.9 mmol/l, with no evidence of a threshold level. Overall, a 1 mmol/l lower usual fasting glucose level was associated with a 21% (95% CI 18–24%) lower risk of total stroke and a 23% (19–27%) lower risk of total IHD. Associations were of similar magnitude for both stroke and IHD mortality (fatal events) and incidence (total events).

There was a strong continuous relationship between usual fasting glucose and the risk of CVD death (Fig. 1); a 1 mmol/l lower usual fasting glucose level was associated with a 19% (15–22%) lower risk of CVD death.

Consistency of associations in population subgroups

Figure 2 illustrates that while the 95% CIs became wider, the strength of the associations for usual fasting glucose and either CVD end point were not substantially changed when adjusting for confounders, excluding individuals with a diagnosis of diabetes or excluding those with a diagnosis of diabetes and adjusting for confounders. Overall, the associations for usual nonfasting glucose were weaker and less precise than those for usual fasting glucose. This was particularly evident for stroke.

Table 1—*Characteristics of study populations*

Fasting status and study name	Country	Sample size	Start year	Follow-up (years)	Diagnosis of diabetes (%)	Female (%)	Baseline glucose (mmol/l)	Baseline age (years)	Total stroke events	Total IHD events
Fasting glucose										
Busselton*	Australia	1,566	1975	16.7	1.0	55	5.1 ± 0.8	44 (20–91)	88	135
Melbourne*	Australia	28,015	1990	8.9	3.7	59	5.7 ± 1.1	55 (27–75)	76	227
Anzhen02	China	4,144	1992	2.8	—	51	5.4 ± 1.0	47 (34–65)	16	1
Beijing Ageing*	China	1,694	1992	4.4	3.8	50	5.7 ± 2.0	69 (55–93)	67	0
Fangshan	China	820	1992	2.7	—	68	5.0 ± 1.4	47 (34–71)	8	2
Guangzhou Occupational	China	5,814	1987	7.9	—	34	5.1 ± 1.3	44 (31–75)	7	5
Huashan*	China	1,810	1992	2.5	0	52	5.2 ± 1.3	53 (35–75)	16	3
Akabane	Japan	1,044	1985	11.2	1.2	56	4.9 ± 0.8	54 (40–69)	26	16
Konan*	Japan	1,223	1987	6.3	3.1	55	5.3 ± 1.1	52 (20–96)	12	2
Tanno/Soubetsu	Japan	1,980	1977	15.3	6.1	53	5.2 ± 1.2	51 (39–65)	33	20
Singapore Heart*	Singapore	2,293	1982	12.3	9.7	49	5.3 ± 1.6	41 (20–89)	74	62
KMIC	South Korea	183,573	1992	4.0	—	37	5.0 ± 1.1	44 (35–59)	1,222	315
EGAT	Thailand	3,492	1985	10.0	1.5	23	5.0 ± 1.0	43 (35–54)	16	2
Total/average†		237,468		5.0	3.7	43	5.2 ± 1.1	47 (20–96)	1,661	816
Nonfasting glucose										
Melbourne*	Australia	13,312	1990	7.9	3.7	58	5.7 ± 1.4	54 (34–73)	25	100
Akabane	Japan	769	1985	11.1	1.6	56	5.0 ± 1.0	55 (40–67)	12	11
Miyama*	Japan	414	1988	6.6	2.2	62	5.2 ± 0.8	59 (41–80)	0	0
Ohasama*	Japan	1,930	1992	4.2	10.9	65	6.4 ± 1.7	59 (35–91)	40	5
Shigaraki Town*	Japan	3,742	1991	3.9	5.2	60	6.0 ± 1.7	57 (29–95)	13	3
Fletcher Challenge*	New Zealand	7,829	1992	5.9	1.7	21	4.6 ± 1.3	39 (20–89)	54	121
Total/average†		27,996		6.5	3.6	49	5.5 ± 1.4	51 (20–95)	144	240

Data are means ± SD and means (range) unless otherwise indicated. Follow-up years are mean values. —, the study did not record this information. *Studies that contributed to all three age-groups provided baseline data on diagnosis of diabetes and potential confounders (systolic blood pressure, total cholesterol, smoking, and BMI). †Weighting by person-years of follow-up (total person-years of follow-up was 1,194,320 for fasting glucose and 185,324 for nonfasting glucose).

There was a suggestion of a slightly stronger association between usual fasting glucose for both total stroke and IHD in the youngest age-group, but the 95% CIs overlapped with those of older age-groups. There was no significant difference between the associations for males and females (e.g., a 1 mmol/l lower usual fasting glucose was associated with 21% [14–29%] and 23% [11–34%] lower risk of total IHD in males and females, respectively). The hazard ratio for stroke in Australasia appeared stronger than in Asia; however, the CIs of the hazard ratios overlapped, and Australasia estimates were only based on two Australian cohorts. Sensitivity analyses that excluded those with diabetes (at baseline) and adjusted for potential confounders diminished the regional differences. No significant differences were found between regions within Asia. Limited data were available by stroke subtype, but analyses indicated that a 1 mmol/l lower usual fasting glucose level was associated with a 20% (0–36%) lower risk of total hemorrhagic stroke (excluding subarachnoid hemorrhage) and a 17% (−1 to 32%) lower risk of total ischemic stroke.

Associations in individuals with and without diagnosed diabetes

Nine cohort studies included data on fasting glucose and diagnosis of diabetes at baseline. Figure 3 demonstrates that the continuous log-linear association was maintained, regardless of diabetes status at baseline. Overall, a 1 mmol/l lower usual fasting glucose was associated with a 20% (13–25%) reduction in total stroke risk and a 23% (18–29%) reduction in total IHD risk.

CONCLUSIONS— This analysis of cohorts from the Asia Pacific region clearly indicates a positive continuous association between usual blood glucose and CVD risk. This association extends down to about 4.9 mmol/l, well below the usual fasting glucose cutoff levels for diagnosis of diabetes and impaired glucose tolerance. The positive association was maintained when individuals with diabetes at baseline were excluded and with adjustment for potential confounders. The associations were very similar for males and females and across age subgroups. There was no strong evidence of regional differences, but small numbers limited subgroup analysis. The overall as-

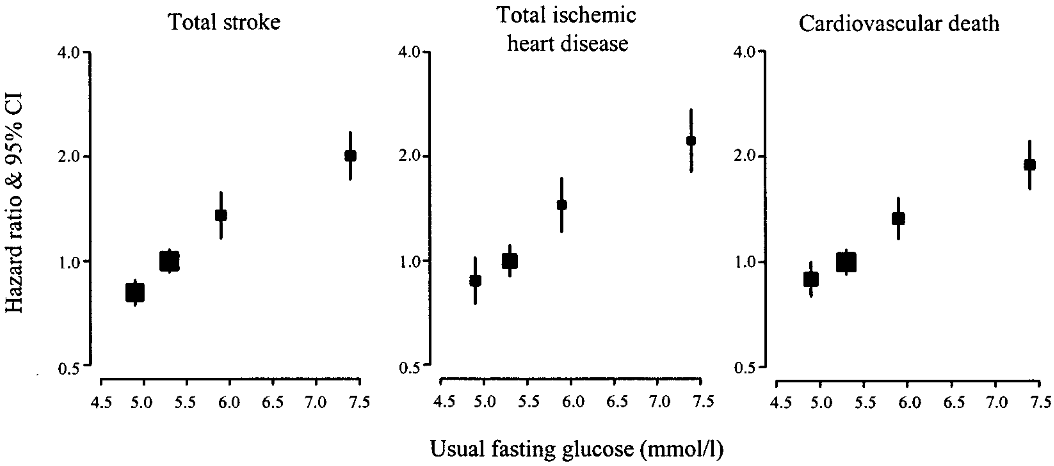

Figure 1—*Usual fasting glucose and risk of cardiovascular end points. The hazard ratios for total (fatal and nonfatal) stroke and IHD and cardiovascular death events adjusted for age, sex, and cohort are plotted on a log scale against usual fasting glucose for each of the four groups defined by baseline fasting glucose (<5, 5–5.9, 6–6.9, ≥7 mmol/l). The* x-*axis coordinate for each group is the mean follow-up usual fasting glucose (not the mean baseline fasting glucose [see* RESEARCH DESIGN AND METHODS*]). For studies without follow-up measurements, weighted average* x-*axis values were calculated from other cohorts. The 95% CIs for the* y-*axis coordinate (hazard ratios) are calculated as floating variances, with the glucose group 5–5.9 mmol/l as the reference. The solid squares are larger where there are more events because their size is proportional to the inverse variance, and the vertical lines represent 95% CIs.*

sociations for usual nonfasting glucose were weaker than those for usual fasting glucose; however, nonfasting measures are less robust because they are affected by the postprandial state.

This study has several advantages over previous studies, such as the substantial size of the database, the availability of individual participant data across a range of glucose levels, and the ability to correct for regression dilution bias, exclude those with diabetes at baseline, and control for potential confounders. Unlike most other analyses, it also enabled the shape and strength of the dose-response relationship to be assessed in non-Western cohorts.

No data were available for oral glucose tolerance tests (OGTTs). Previous comparisons have concluded that 2-h post-load glucose from an OGTT is a superior test to fasting glucose for diabetes (25,26) and predicting cardiovascular and/or all-cause mortality (27,28). However, the OGTT is more difficult and expensive to perform than simpler fasting blood glucose measures (8,29). Fasting

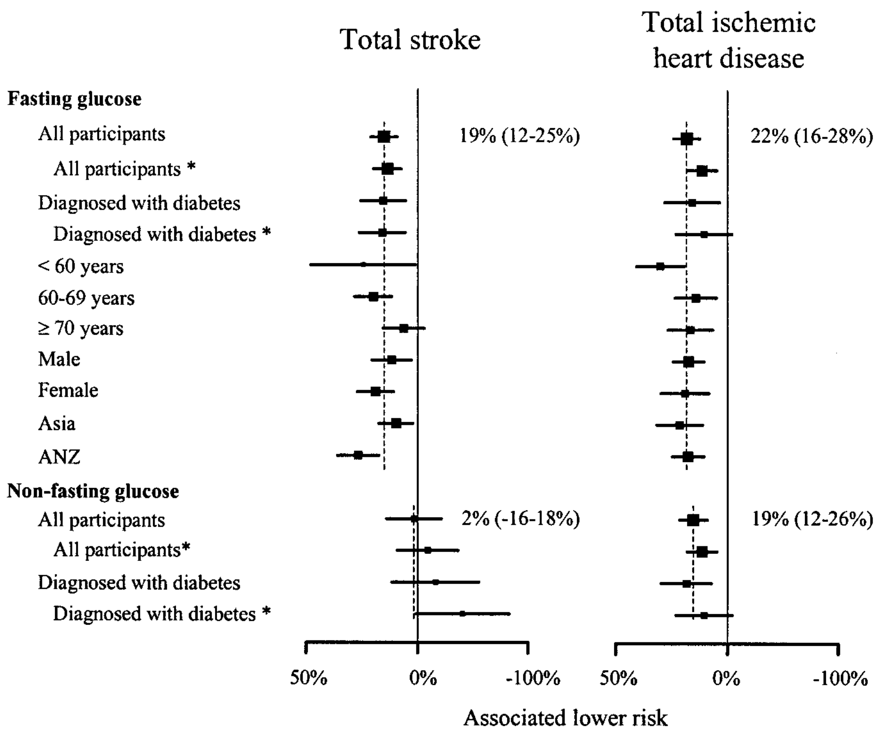

Figure 2—*Associations of 1 mmol/l reduction in usual glucose and risk of total stroke and IHD by subgroups. The hazard ratios and 95% CIs for fasting and nonfasting glucose are plotted separately for different subgroups. Analysis was restricted to cohort studies that contributed to all three age-groups and provided baseline variables on diagnosis of diabetes, systolic blood pressure, serum total cholesterol, smoking, and BMI (Table 1). Other conventions are as in Fig. 1. *Additionally adjusted for systolic blood pressure, total cholesterol, smoking, and BMI.*

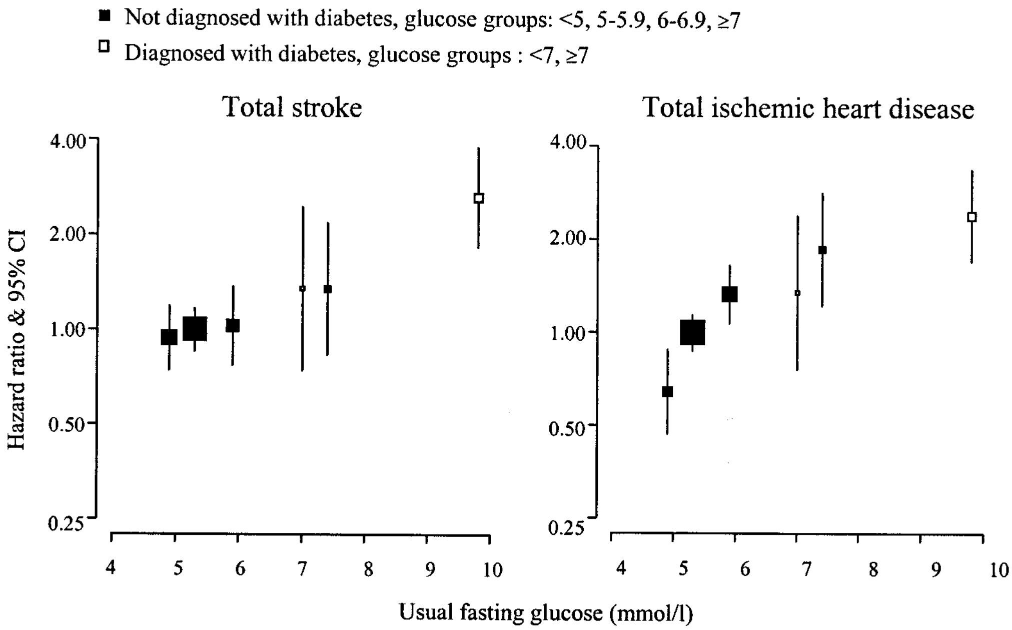

Figure 3—*Usual fasting glucose and risk of total stroke and IHD by baseline diabetic status. The hazard ratios for total stroke and IHD events for those without diagnosed diabetes at baseline (glucose categories <5, 5–5.9, 6–6.9, ≥7 mmol/l) and those with diabetes at baseline (glucose categories <7, ≥7 mmol/l) are plotted on the same log scale against usual fasting glucose. Other conventions are as in Fig. 1.*

blood glucose measures are still useful (29) and are likely to be more reliable than the OGTT across several studies (8).

Many studies and overviews dating back to the 1970s and 1980s investigated whether a threshold relationship existed between glycemia and IHD risk (30) and investigated the effect of adjusting for classic risk factors (31). The overall results of the early studies were inconclusive and conflicting (30,31), and it was unclear whether glucose was a risk factor in the absence of diabetes (32,33). Subsequent analyses have found a positive association between the highest and lowest glucose centiles and CVD. The shape of the association has often been reported as nonlinear (e.g., J-shaped) (34–40). However, the categorization of glucose and small study size substantially limited the ability to explore the shape of the dose-response relationship across the whole range of glucose levels.

A recent overview of 20 studies concluded that there was a significant exponential association between glucose and CVD in nondiabetic individuals that extended below the usual "diabetic threshold" (8). Another prospective study demonstrated that HbA_{1c} was continuously related to subsequent CVD and all-cause mortality through the whole population distribution, with lowest rates in individuals with HbA_{1c} concentrations <5% (~4.5–5.0 mmol/l fasting glucose) (41).

Randomized controlled trials indicate to what extent the "epidemiologically expected" reductions in disease are realized. Trials have examined the effect of blood glucose lowering in type 2 diabetes (42–48), but several have had small sample size, less glycemic control than planned, and relatively short follow-up periods (49,50). Overall, the trials did demonstrate decreased microvascular complications and a nonsignificant trend toward decreasing macrovascular complications. The modest size of the effect on macrovascular outcomes is consistent with the predicted effects from this analysis and the relatively small change in achieved glucose differences. Further analysis showed a continuous association between glycemia and the risk of macrovascular complications below diabetic thresholds (45,49,50).

There are several implications for clinical and public health practice from this study. The continuous association suggests that a wider group of individuals may benefit from glucose lowering, not just those with diabetes or impaired glucose tolerance, but further trial evidence would confirm this. Risk prediction tools could be improved by including fasting glucose as a continuous risk factor, rather than diagnosis of diabetes. Finally, and perhaps most importantly, there are potential benefits from population-wide lowering of determinants of CVD risk. The most appropriate approach to cardiovascular prevention is often a coordinated effort to lower the risk profiles of entire populations coupled with a targeted approach to those at highest absolute risk of CVD. Previous analyses have demonstrated continuous associations between risk factors such as blood pressure, cholesterol, and BMI and CVD risk (11–15). Results from the current study support the view that this is also the case for blood glucose, and the blood glucose levels may be an important risk factor in the Asia Pacific region in individuals with and without diagnosed diabetes.

APPENDIX

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