Associations of random plasma glucose with risk of cardiovascular disease among 467 000 Chinese adults without known diabetes: a 7-year prospective study

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ABSTRACT

Importance: Diabetes is a known risk factor for cardiovascular disease (CVD). Substantial uncertainty remains, however, about the relevance to CVD risk of blood glucose levels below the diabetes threshold.

Objective: To examine the associations of random plasma glucose (RPG) levels with risks of major CVDs in Chinese adults without known diabetes.

Design: Prospective cohort study.

Setting: 10 (five urban and five rural) diverse localities across China.

Participants: 467 508 men and women aged 30-79 years with no prior history of diabetes, ischaemic heart disease (IHD), stroke or transient ischaemic attack when recruited in 2004-8.

Exposure: Baseline and usual (longer-term average) RPG level.

Main Outcomes and Measures: 6645 cardiovascular deaths, 3270 major coronary events (MCE, fatal IHD and non-fatal myocardial infarction), 19 153 ischaemic strokes (IS), 22 023 major occlusive vascular disease (MOVD, MCE or IS) events and 4326 intracerebral haemorrhages (ICH). Preliminary validation of stroke and IHD events demonstrated positive predictive values of ~90% and ~85%, respectively. Cox regression yielded adjusted hazard ratios (HRs) for CVDs associated with RPG.

Results: There was a significant positive association of baseline RPG with CVD risks that continued down to ~4.0 mmol/L (72 mg/dL). After adjusting for regression dilution bias, each 1 mmol/L (18mg/dL) higher usual RPG above 5.9 mmol/L (106 mg/dL) was associated with an 11% (adjusted HR 1.11, 95% CI 1.10-1.13) higher risk of cardiovascular death. Similarly strong positive associations were seen for MCE (1.10, 1.08-1.13), IS (1.08, 1.07-1.09) and MOVD (1.08, 1.07-1.09). For ICH, the association

was weaker, but also significant (1.05, 1.02-1.07). These associations persisted after excluding participants who developed diabetes during follow-up.

Conclusions and Relevance: Among adult Chinese without diabetes, lower RPG is associated with lower risks of major CVDs, even within the so-called “normal” range of blood glucose levels.

INTRODUCTION

Diabetes is a major cardiovascular disease (CVD) risk factor.[1,2] There is also evidence from Western populations that individuals with pre-diabetes[3] have elevated CVD risks,[4] although the magnitude of risk in different populations and population subgroups is less clear. Below this range, there is uncertainty as to whether lower blood glucose levels are associated with lower CVD risk,[5] and, if so, whether the association is continuous[6] or a threshold exists.[1,7] Furthermore, most studies have focused on fasting blood glucose (FBG)[1,7,8] and few on random blood glucose (RBG), a more practical, and arguably more relevant, measure.[9]

Recent decades have seen a marked increase in diabetes prevalence[10,11] and high pre-diabetes prevalence in China.[11] Despite this, there is little reliable prospective evidence about the relevance to CVD risk of blood glucose levels below the diabetic threshold in China.[12] Previous findings from the China Kadoorie Biobank (CKB) showed a positive association of random plasma glucose (RPG) levels with prevalent CVDs, but these were limited by their cross-sectional design and self-reported disease outcomes.[2] We present 7-year prospective follow-up data from the CKB, examining the associations of RPG levels with risks of incident CVDs in individuals without known diabetes, and assessing whether factors, such as age, sex, adiposity and blood pressure, modify these.

METHODS

Study population

Details of the CKB design, survey methods and population have been described previously.[13,14] Briefly, the baseline survey took place in 2004-2008 involving 10 diverse areas (five urban and five rural) of China (eFigure 1), selected to provide diversity in exposures and diseases as well as taking account of population stability, quality of disease and death registries, capacity and commitment. All permanent residents aged 35-

74 years from 100-150 rural villages or urban committees in each area were invited to participate. Overall, ~30% responded,[13] comparable with other large nationwide prospective studies.[15] 512 891 men and women were enrolled, including a small number just outside the target age range (n=10 168). Local, national and international ethical approval for the study was obtained. All participants provided informed, written consent.

Data collection

At local study assessment clinics, participants completed an interviewer-administered questionnaire collating data on demographics, socioeconomic factors, lifestyle measures (including smoking, alcohol consumption, diet and physical activity) and medical history. Physical measurements were undertaken including blood pressure, height, weight and hip and waist circumferences, by trained health workers using calibrated instruments and standard protocols. A 10ml non-fasting (with the exception of one area—Zhejiang—where participants were asked to fast) blood sample was collected from participants and plasma glucose was measured immediately using Johnson & Johnson SureStep Plus meters (Lifescan, Milpitas, CA, USA),[16] regularly calibrated with manufacturer control solutions. Data were collected on time since last food. Individuals with a plasma glucose level ≥7.8 (140 mg/dL) and <11.1 mmol/L (200 mg/dL) were invited back the following day for a fasting plasma glucose (FPG) test. A resurvey of a 5% randomly selected sample of surviving participants was undertaken during May to October 2008 using the same procedures as in the baseline survey.

Follow-up for morbidity and mortality

Information on vital status of participants was obtained from local death registries based at China's Disease Surveillance Points (DSPs), checked annually against local residential records and health insurance records, and by active confirmation through street committees or village administrators. Information on cause of death was supplemented by

review of available medical records. In deaths without recent medical attention (~5%), verbal autopsies determined probable causes. Information on hospitalised events was collected through linkage to established disease registries (for cancer, IHD, stroke and diabetes) and, via unique national ID, to the health insurance system, which has almost universal coverage in the study areas. All events were ICD-10 coded[17] by trained staff, blinded to baseline information.

The primary outcomes examined were cardiovascular death (I00-25, I27-88, I95-99), myocardial infarction (MI, I21-23), major coronary event (MCE: non-fatal MI or fatal IHD [I20-25]), ischaemic stroke (IS, I63), intracerebral haemorrhage (ICH, I61), total stroke (TS, I60, I61, I63, I64), and major occlusive vascular disease (MOVD: IS, non-fatal MI or fatal IHD) (eTable 1). By January 1 2014, 2411 (0.5%) participants were lost to follow-up.

Statistical analyses

The present study excluded individuals with self-reported, doctor-diagnosed diabetes (n=16 162), IHD (n=15 472) or stroke/transient ischaemic attack (n=8884) at baseline and those with missing RPG data (n=8160) (mainly recruited prior to formal commencement of blood glucose testing). Within-study area comparisons of participants with and without RPG data showed no consistent, clinically significant differences. 1017 participants with missing, implausible or extreme values for body mass index (BMI), systolic (SBP) or diastolic blood pressure, height, waist circumference, hip circumference or waist-to-hip ratio were excluded; 467 508 participants (191 555 men, 275 953 women) remained for inclusion in the analyses.

The prevalence and mean values of baseline characteristics were calculated across RPG categories, with cut-points of 4.3 (77), 5.3 (95), 5.8 (105), 6.8 (123), 7.8 (140) and 11.1 (200) mmol/L (mg/dL), standardised by 5-year age groups, sex and study area. RPG cut-points were chosen to include oral glucose tolerance test 2-hour post-load thresholds for

diabetes and impaired glucose tolerance,[3] and to ensure reasonable participant numbers in all groups.

Cox proportional hazards models were used to estimate hazard ratios (HRs) for the associations of baseline RPG levels with incident CVDs, stratified by age-at-risk, sex (where appropriate) and study area, and adjusted for education (no formal education, primary school, middle school, high school, college/university), smoking (never, occasional, ex-regular, current regular), alcohol (never, occasional intake, ex-regular, reduced intake, weekly intake), SBP (<100, 100-109, 110-119,120-129, 130-139, 140-149, 150-159, 160-169, ≥170 mmHg) and physical activity (<10, 10-19.9, 20-29.9, 30-39.9, ≥40 metabolic equivalent of task [MET] hours/day). Confounding variables were selected based on a priori knowledge of underlying biological mechanisms and demonstrated associations with RPG and CVD outcomes. The floating absolute risk method was used; this does not alter the value of the HRs, but provides confidence intervals for all RPG categories enabling comparisons between any two categories, and not only with the reference group.[18] Discrimination of the models was examined using Harrell's C-statistic.[19]

Single RPG measurements may not accurately reflect an individual's usual, or longer-term average, RPG level due to random measurement error and more systematic changes over time, resulting in "regression dilution" bias when assessing the associations with disease risks.[20] To correct for this, data on repeat RPG levels measured at resurvey (on average, 2.6 years after the baseline survey) in 17 863 participants were used to estimate usual (mean resurvey) RPG levels for individuals in each baseline RPG category. Usual RPG levels for the lowest three RPG categories were similar; these categories were therefore combined when investigating associations of usual RPG levels. Departure from linearity was assessed using the likelihood ratio test.[21] If the shape was log-linear,

baseline RPG was also investigated as a continuous variable. As sensitivity analyses, we conducted fractional polynomial analyses of baseline RPG that allow a continuous variable to be modelled using a non-linear relationship.[22] Examination of HRs for the first four and subsequent years of follow-up showed no strong evidence of departure from the proportional hazards assumption. The overall regression dilution ratio was calculated as the ratio of the range of the mean resurvey RPG levels, between top and bottom RPG categories, to the range of the mean baseline RPG levels.[23] Log HR estimates for baseline RPG examined as a continuous variable were multiplied by the reciprocal of the regression dilution ratio to obtain regression dilution bias-corrected estimates.[23] Adjusted HRs were compared across strata of other CVD risk factors and fasting time, and chi-squared tests for trend and heterogeneity (ie, effect modification or statistical interaction) were applied to the log HRs and their standard errors.[24]

Separate analyses were done excluding individuals with a baseline plasma glucose level suggestive of diabetes,[2] individuals from Zhejiang (where 72.5% reported not having consumed food for ≥8 hours) or individuals diagnosed with diabetes during follow-up, identified from diagnoses in mortality, disease surveillance or health insurance data. Sensitivity analyses examined the association of RPG with all-cause mortality.[19] All analyses used SAS version 9.3. Figures were produced using R version 2.13.1.

RESULTS

Among the 467 508 participants without known diabetes or CVD at baseline, the mean (SD) age was 51 (11) years, and 59% were women (Table 1). Mean (SD) baseline RPG was 5.9 (1.9) mmol/L (106 [34] mg/dL), slightly higher in women than men (6.0 vs. 5.8 mmol/L [108 vs. 105 mg/dL]). Baseline RPG was associated positively with age, education, SBP and adiposity, and inversely with physical activity. There was no clear trend in fasting time across baseline RPG categories.

During ~3.3 million person-years of follow-up (mean 7 years) there were 19 214 deaths, 6645 cardiovascular deaths, 3270 MCE, 19 153 IS, 22 023 MOVD events and 4326 ICH. For all CVDs, the risk increased progressively with higher baseline RPG levels, with no evidence of a threshold in the association (Table 2). Multivariable-adjusted fractional polynomial models examining the association of RPG with cardiovascular death, MCE, IS and MOVD, consistently indicated that models using the linear form of RPG best fitted the data (eFigure 2). There was a strongly significant, positive association of baseline RPG with cardiovascular death, MCE, IS and MOVD (p for trend <0.001), and a weaker association with ICH (p for trend=0.10). The incremental changes in Harrell's C-statistic (Δc) for comparing the base-model (ie, a Cox model including education, smoking, alcohol, SBP and physical activity stratified by age-at-risk, sex and study area) with the model that additionally included baseline RPG were very modest (Δc: 0.0050, 0.0053, 0.0036,0.0033 for cardiovascular death, MCE, IS and MOVD, respectively). The overall values of the Harrell's C-statistic for the multivariable adjusted Cox models for cardiovascular death, MCE, IS and MOVD were 0.68, 0.63, 0.61 and 0.61, respectively.

Based on resurvey data from 17 863 randomly selected participants we estimated usual RPG in each baseline RPG category. Figure 1a shows the relationship between usual RPG and risk of cardiovascular death. There was a positive, log-linear, relationship between usual RPG and cardiovascular death continuing down to at least 5.9 mmol/L (106 mg/dL); each 1 mmol/L (18 mg/dL) higher usual RPG was associated with an adjusted HR of 1.11 (95% CI 1.10-1.13), applying the calculated regression dilution ratio of 0.56. The positive association appeared stronger in men than women (p=0.005), and in individuals with lower SBP (p for trend=0.002) or higher levels of education (p=0.009) (Figure 2).

A positive, log-linear, association was also found between usual RPG and risk of ischaemic CVDs, with no evidence of a threshold (Figure 1). For MCE, each 1 mmol/L (18 mg/dL) higher usual RPG was associated with an adjusted HR of 1.10 (1.08-1.13), while for IS it was 1.08 (1.07-1.09). For MI and IS, the HRs were somewhat greater for fatal than non-fatal events (MI: 1.13 vs. 1.05; IS: 1.15 vs. 1.08) (eTable 5). For MOVD, each 1 mmol/L (18 mg/dL) higher usual RPG was associated with an 8% (1.08, 1.07-1.09) greater risk, with some suggestion of a stronger association at younger ages (p for trend=0.003) (Figure 3).

The associations with ischaemic CVDs and cardiovascular death did not appear to differ across fasting periods (eFigure 3). There was no clear difference in the strength of association per 1 SD higher non-fasting (fasting period <8 hours, 2.0 mmol/L [36 mg/dl]) and fasting (fasting period ≥8 hours, 1.1 mmol/L [20 mg/dL]) baseline plasma glucose with cardiovascular death or ischaemic CVDs (eFigure 4).

The association of usual RPG with ICH was more modest, with each 1 mmol/L (18 mg/dL) higher usual RPG associated with an adjusted HR of 1.05 (95% CI 1.02-1.07), driven mainly by fatal (1.10, 1.07-1.13), rather than non-fatal (0.98, 0.95-1.02), ICH (eTable 2). For ICH there was an apparently stronger association with non-fasting, than with fasting, baseline plasma glucose (p for heterogeneity=0.004) (eFigure 4).

Additional adjustment for waist-to-hip ratio did not materially alter the associations of usual RPG with disease risk (eTable 2). The associations also persisted after excluding participants diagnosed with diabetes during follow-up (n=12 048) (eTable 3) or those with a baseline plasma glucose level suggestive of diabetes (n=13 050) (eTable 4). Exclusion of individuals from Zhejiang (n=51 656) did not materially alter risk estimates. In sensitivity analyses, the association of usual RPG with all-cause mortality was similar to that with cardiovascular death (1.11 [1.10-1.12] per 1 mmol/L [18 mg/dL] higher usual RPG).

DISCUSSION

The present study is the largest prospective investigation in China of the association of plasma glucose levels with risks of CVDs in individuals without known diabetes, and the only study to-date with power to investigate the associations of RPG with CVDs. It showed positive, log-linear associations between usual RPG and the risk of cardiovascular death and major ischaemic CVDs continuing down to at least a usual RPG of 5.9 mmol/L (106 mg/dL), with no evidence of a threshold. Each 1 mmol/L (18 mg/dL) higher usual RPG was associated with ~10% increased CVD risk.

Prospective studies of mostly Western populations have investigated the association of blood glucose—mainly FBG—with CVD risks, relatively consistently showing a greater CVD risk in the pre-diabetes range, when compared with lower blood glucose levels.[1,6,7] Below this range, however, evidence is conflicting. In the Asia Pacific Cohort Studies Collaboration of ~240 000 participants from 13 cohorts, there was a positive, log-linear association between usual FBG and incident IHD (n=816) and cardiovascular death (n=1661), continuing down to at least 4.9 mmol/L (88 mg/dL).[6] In contrast, in a study of ~1.2 million Koreans, with ~60 000 IHD and >45 000 IS events, there was a J-shaped association with baseline FPG, with the lowest risks at ~5.0 mmol/L (90 mg/dL).[7] In the Emerging Risk Factors Collaboration, including ~260 000 participants from 51 studies with ~11 000 IHD and ~1500 IS events, there was no significant association of FPG with IS, but a J-shaped association with IHD, with the lowest risk at 3.9-5.6 mmol/L (70-101 mg/dL).[1] No prospective studies in mainland China have reported on the association, and two small Taiwanese studies have produced conflicting findings.[25,26]

There is limited evidence about the association of RBG with CVD. A published data meta-analysis, including seven cohort studies, found no convincing evidence of an association of RBG with cardiac (n=314; HR=1.02, 95% CI 0.98-1.07 per 1 mmol/L [18 mg/dL] higher

RBG), stroke (n=544; 1.11, 0.95-1.31) or cardiovascular (n=1782; 1.11, 1.00-1.24) mortality, and only weak evidence of a positive association with total CVD (n=2087; 1.12, 1.01-1.25).[27] Our study provides the first convincing evidence of a positive association of RBG with CVDs.

Fasting and post-load blood glucose are arguably more robust glycaemic measures than RBG, which may be subject to greater inter- and intra-individual variation. However, non-fasting glucose may be more relevant to CVD risks, as people spend most time in a non-fasting state.[9] Furthermore, we found fasting time explained only a small proportion of variation in plasma glucose levels in the CKB (<8 hours r^2=0.01; ≥8 hours r^2=0.001), with no consistent difference in associations with CVD risks across fasting time strata. In addition, use of fasting time-adjusted plasma glucose (eFigure 5), or additional adjustment for fasting time, did not materially alter risk estimates. Thus, despite recognised limitations,[28] in large-scale population-based epidemiological studies, RPG appears to be a reliable and practical glycaemic indicator.[29]

The large number of well-characterised stroke events (~90% of validated stroke events had been confirmed on CT/MRI) is a strength of this study and partly reflects frequent use of CT/MR scans in China. Medical record review for all stroke cases is underway; findings to-date have shown a positive predictive value of ~90% for stroke (~85% for IHD). Frequent use of scans detects a relatively high proportion of lacunar infarcts without major, or any, apparent focal neurological deficit,[30] likely contributing to the relatively low IS case fatality in the CKB. Stroke, particularly haemorrhagic stroke (HS),[31] rates are characteristically high in Chinese populations, as reflected in the CKB. Due to lower HS rates in Western populations, and limited availability of scanning technology in earlier studies, evidence of the association of plasma glucose levels with HS has been limited. The Korean Cancer Prevention Study included ~19 000 HS and showed a more modest

association than was seen for other CVDs, with clearly elevated risks only in the highest FPG categories.[7] The stronger association for fatal than non-fatal ICH and, to a lesser extent, MI and IS events in the CKB may reflect a survival effect or more severe disease in fatal cases, although this has not been reported previously.[6,7] The models using baseline RPG showed moderate ability to discriminate between participants developing and not developing CVDs. The discriminatory ability of our models appears to be somewhat lower than that reported in previous Chinese studies.[32] This may reflect our exclusion of individuals with known diabetes and the current lack of lipids data. Importantly, however, our study included much larger numbers of well-characterised CVD endpoints, so our results are more statistically robust. This discriminatory ability is, however, of limited relevance to disease aetiology, which is the main focus of our analyses.

Increased CVD risks at higher glucose levels could reflect undiagnosed or future diabetes.[1,2] However, persistence of the associations after excluding individuals with plasma glucose levels suggestive of diabetes, or who developed new diabetes during follow-up, supports the existence of independent log-linear associations of RPG with CVD risks. Loss to follow-up in the study was low, and any resulting bias would be negligible. Residual confounding could not be excluded, especially given our current inability to adjust for lipids (known CVD risk factors associated with plasma glucose[1]). Lack of renal function data prevented investigation of its influence on RPG-associated CVD risks, but would not bias risk estimates. Randomised trials of glucose lowering agents in pre-diabetes have, so far, been inconclusive in their effects on CVD risk.[33-36] However, evidence from Mendelian randomisation studies is generally compatible with a causal association between higher blood glucose levels and CVD throughout the glycaemic range.[9,37,38]

311 The present analyses provide clear evidence of an independent, continuous relationship
312 of RPG with risk of CVDs in Chinese adults without known diabetes. They support
313 consideration of blood glucose as a continuous variable (rather than simply the presence
314 or absence of diabetes[39,40]) in cardiovascular risk prediction models, and suggest the
315 need to consider CVD primary prevention at glucose levels below the diabetes threshold.
316 Our findings, supported by Mendelian randomisation[9,37,38] and some trial[33] evidence,
317 suggest interventions to reduce plasma glucose levels may reduce CVD risk in individuals
318 without diabetes, but further data are required.

Contributors: ZC, FB and LL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in study design, conduct, long-term follow-up, analysis of data, interpretation, or writing the report.

Conflicts of interest: We declare that we have no conflict of interest.

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FIGURE LEGENDS

Figure 1: Adjusted hazard ratios for cardiovascular diseases by usual random plasma glucose

Stratified by age, sex and study area and adjusted for education, smoking, alcohol, systolic blood pressure and physical activity. HRs are plotted against mean usual random plasma glucose level in each category. Squares represent the HR with area inversely proportional to the variance of the log HR. Vertical lines represent the corresponding 95% CIs. HR, hazard ratio. To convert plasma glucose to mg/dL multiply by 18.

Figure 2: Adjusted hazard ratios for cardiovascular death per 1 mmol/L (18 mg/dL) higher usual random plasma glucose

Stratified by age, sex and study area and adjusted (except where it is the variable of interest) for education, smoking, alcohol consumption, physical activity and systolic blood pressure. Shaded squares represent the HR with area inversely proportional to the variance of the log HR. Horizontal lines represent the corresponding 99% CI. The dotted line represents the overall HR. The open diamond represents the overall HR and its 95% CI. BMI, body mass index; HR, hazard ratio; MET, metabolic equivalent of task; SBP, systolic blood pressure. To convert plasma glucose to mg/dL multiply by 18.

Figure 3: Adjusted hazard ratios for MOVD per 1 mmol/L (18 mg/dL) higher usual random plasma glucose

Conventions as Figure 2.

Table 1: Baseline characteristics of participants by random plasma glucose

Characteristic	Baseline RPG level (mmol/L)							
	<4.3	**4.3-5.2**	**5.3-5.7**	**5.8-6.7**	**6.8-7.7**	**7.8-11.1**	**≥11.1**	**Total**
No. of participants	27535	152635	94359	112760	48368	23707	8144	467508
RPG (mmol/L), *mean*	*3.9*	*4.8*	*5.5*	*6.2*	*7.2*	*8.8*	*15.8*	*5.9*
Men[a], %	56.7	45.2	38.3	35.9	36.7	40.1	42.7	41.0
Age (years)[b], %								
30-49	62.0	54.9	48.6	42.7	36.2	31.4	28.4	47.4
50-59	24.7	28.2	30.2	32.2	34.1	35.4	36.6	30.6
60-69	10.3	12.7	15.8	18.4	21.5	24.1	25.9	16.3
70-79	2.9	4.1	5.3	6.7	8.1	9.2	9.1	5.7
Mean	*47.4*	*49.1*	*50.6*	*52.0*	*53.6*	*54.7*	*55.5*	*50.9*
Living in urban area, %	25.3	39.7	46.9	46.6	44.4	50.4	49.4	43.3
≥6 years' education, %	49.9	49.8	50.2	51.0	51.3	51.6	52.6	49.6
Smoking history, %								
Never regular	66.0	67.3	68.3	68.3	68.1	67.4	67.1	67.8
Ex-regular	4.6	5.2	5.6	5.6	5.6	5.6	6.1	5.4
Current regular	29.4	27.5	26.1	26.1	26.3	27.0	26.8	26.8
Alcohol consumption, %								
Never regular	45.1	44.8	45.2	45.6	46.2	46.6	48.3	45.4
Occasional	39.0	38.6	37.9	37.6	37.3	35.9	34.1	37.9
Ex regular	1.6	1.5	1.5	1.5	1.7	1.8	1.8	1.5
Regular	14.4	15.0	15.4	15.3	15.0	15.9	15.7	15.1
Physical activity (MET hours/day), %								
<13	33.1	33.2	33.0	32.9	33.4	33.1	37.2	33.2
13-25.9	33.6	33.3	33.3	33.4	33.0	33.1	32.9	33.2
≥26	33.3	33.6	33.7	33.7	33.6	33.8	29.9	33.6
Mean	*21.6*	*21.6*	*21.7*	*21.7*	*21.6*	*21.7*	*20.3*	*21.6*
SBP (mmHg), %								
<120	36.4	35.2	33.8	31.8	29.0	24.6	17.6	32.8
120-139	38.9	39.2	39.9	40.3	40.9	39.6	39.1	39.7
≥140	24.7	25.6	26.3	27.9	30.1	35.8	43.3	27.5
Mean	*128.6*	*129.3*	*129.8*	*130.6*	*131.9*	*134.9*	*139.1*	*130.4*
BMI (kg/m^2), %								
<22.0	40.3	36.1	34.0	31.9	30.1	27.0	19.2	33.6
22.0 to <25.0	34.8	35.1	34.8	34.5	32.6	31.6	29.7	34.4
≥25.0	24.9	28.7	31.2	33.5	37.3	41.4	51.1	32.0
Mean	*23.0*	*23.3*	*23.5*	*23.7*	*24.0*	*24.4*	*25.1*	*23.6*
Waist-to-hip ratio, %								
<0.85	39.5	35.4	32.4	29.7	25.9	22.9	13.0	31.8
0.85 to <0.90	27.2	27.9	28.1	27.6	26.7	25.8	20.7	27.5
≥0.90	33.4	36.6	39.4	42.7	47.5	51.3	66.4	40.8
Mean	*0.87*	*0.87*	*0.88*	*0.88*	*0.89*	*0.90*	*0.92*	*0.88*
Fasting time (hours), *mean*	*4.4*	*5.7*	*5.4*	*4.4*	*3.2*	*3.0*	*3.5*	*4.9*
Family history of diabetes[c,d], %	5.7	6.3	6.5	7.0	7.7	9.7	14.2	6.5

Standardised to the age, sex and study area structure of the study population. [a]standardised to age and study area structure only; [b]standardised to sex and study area structure only; [c]first degree relatives; [d]data missing for 22 336 participants. BMI, body mass index; MET, metabolic equivalent of task; RPG, random plasma glucose; SBP, systolic blood pressure. P-value for trend across random plasma glucose categories: all <0.001. To convert plasma glucose to mg/dL multiply by 18.

Table 2: Adjusted hazard ratios for major cardiovascular diseases by baseline random plasma glucose

Baseline RPG (mmol/L) (Mean)	**Cardiovascular death**		**Major occlusive vascular disease**		**Major coronary event**		**Ischaemic stroke**		**Intracerebral haemorrhage**	
	No. of events	**HR (95% CI)**	**No. of events**	**HR (95% CI)**	**No. of events**	**HR (95% CI)**	**No. of events**	**HR (95% CI)**	**No. of events**	**HR (95% CI)**
<4.3 (4.0) (Ref)	355	1.00 (0.90-1.11)	996	1.00 (0.94-1.07)	180	1.00 (0.86-1.16)	837	1.00 (0.93-1.07)	272	1.00 (0.89-1.13)
4.3-5.2 (4.8)	1727	1.01 (0.96-1.06)	5952	1.07 (1.04-1.10)	883	1.00 (0.94-1.07)	5184	1.08 (1.05-1.11)	1242	1.01 (0.95-1.07)
5.3-5.7 (5.5)	1132	1.05 (0.99-1.12)	4113	1.11 (1.08-1.14)	530	0.95 (0.87-1.03)	3637	1.13 (1.10-1.17)	772	1.04 (0.97-1.11)
5.8-6.7 (6.2)	1643	1.10 (1.05-1.16)	5456	1.14 (1.11-1.17)	806	1.06 (0.99-1.14)	4750	1.15 (1.12-1.18)	1073	1.06 (1.00-1.13)
6.8-7.7 (7.2)	887	1.16 (1.08-1.24)	2893	1.24 (1.19-1.28)	437	1.14 (1.04-1.25)	2509	1.25 (1.20-1.30)	507	1.02 (0.93-1.11)
7.8-11.0 (8.8)	568	1.29 (1.19-1.41)	1718	1.30 (1.24-1.37)	288	1.30 (1.16-1.46)	1462	1.30 (1.23-1.37)	320	1.10 (0.98-1.22)
≥11.1 (15.8)	333	2.03 (1.82-2.26)	895	1.77 (1.66-1.89)	146	1.74 (1.47-2.04)	774	1.79 (1.66-1.92)	140	1.32 (1.11-1.56)
p for trend		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*0.10*
HR per 1 mmol/L[a]		*1.06 (1.05-1.07)*		*1.04 (1.04-1.05)*		*1.06 (1.04-1.07)*		*1.04 (1.04-1.05)*		*1.03 (1.01-1.04)*

Stratified by age, sex and study area and adjusted for education, smoking, alcohol, physical activity and systolic blood pressure. [a]HRs for first and second halves of follow-up: cardiovascular disease death 1.06 vs. 1.07, p=0.2; major occlusive vascular disease 1.04 vs. 1.04, p=0.6; major coronary event 1.05 vs. 1.06, p=0.3; ischaemic stroke 1.04 vs. 1.04, p=0.6; intracerebral haemorrhage 1.02 vs. 1.04, p=0.2. CI, confidence interval; HR, hazard ratio; Ref, reference group; RPG, random plasma glucose. To convert plasma glucose to mg/dL multiply by 18.

Figure 1: Adjusted hazard ratios for cardiovascular diseases by usual random plasma glucose

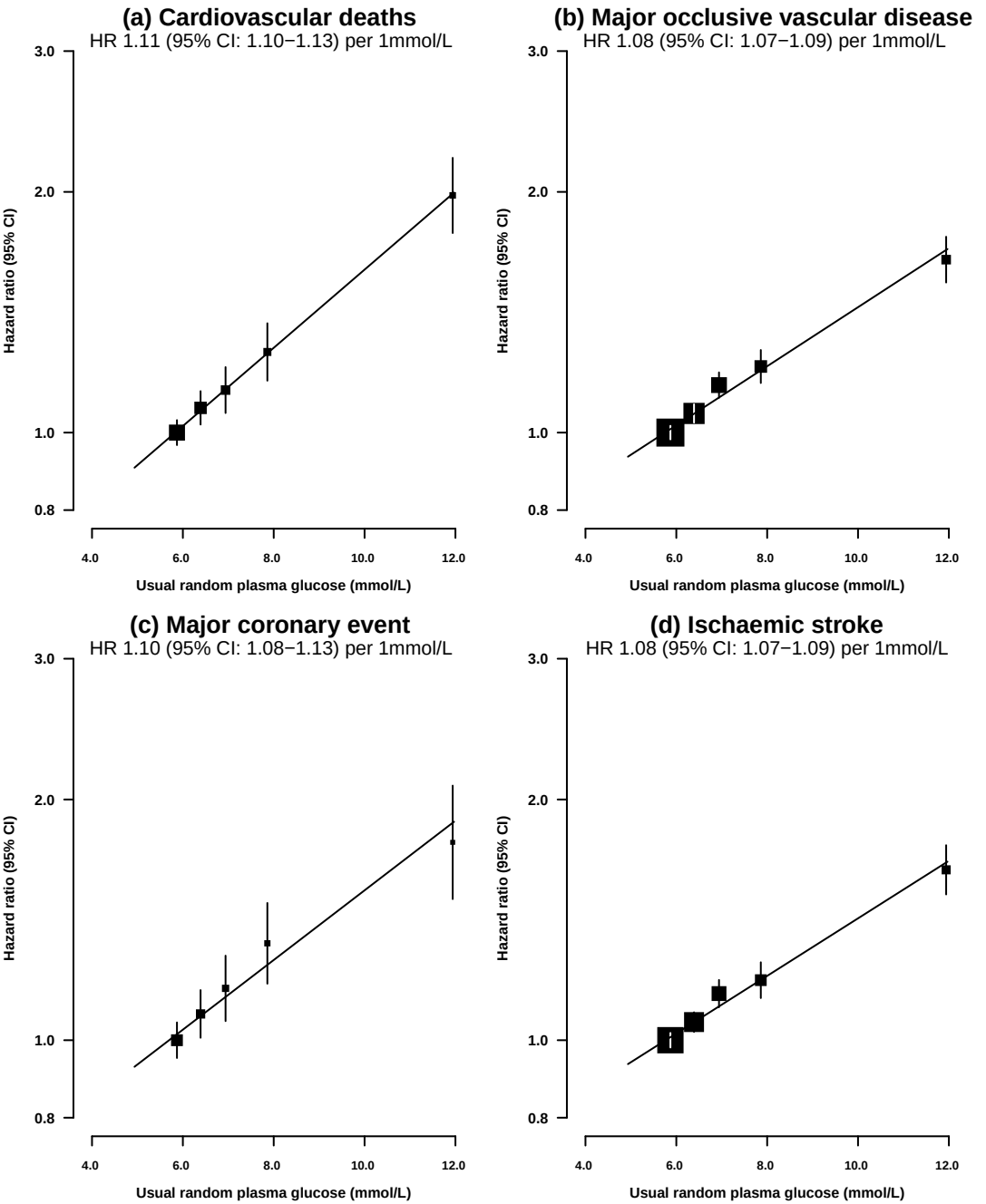

Figure 2: Adjusted HRs for cardiovascular death per 1mmol/L (18 mg/dL) higher usual random plasma glucose

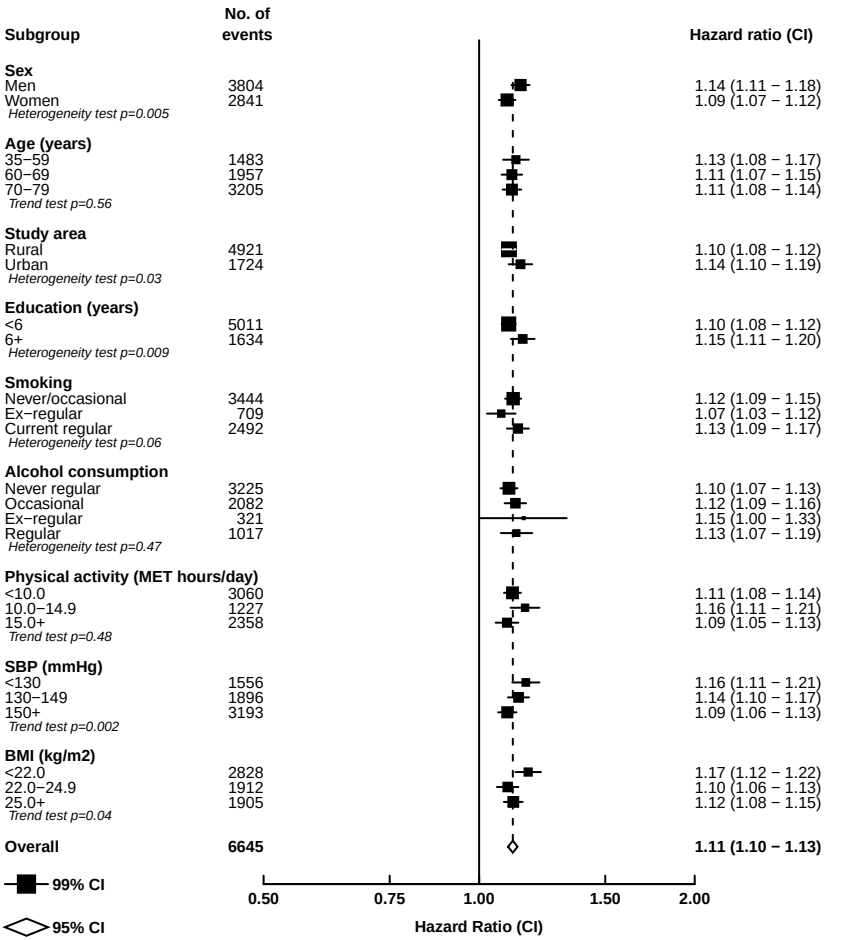

Figure 3: Adjusted HRs for MOVD per 1mmol/L (18 mg/dL) higher usual random plasma glucose