



33 **ABSTRACT**

34 **Importance:** Diabetes is a known risk factor for cardiovascular disease (CVD).

35 Substantial uncertainty remains, however, about the relevance to CVD risk of blood  
36 glucose levels below the diabetes threshold.

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

39 **Design:** Prospective cohort study.

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

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

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

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

51 **Results:** There was a significant positive association of baseline RPG with CVD risks that  
52 continued down to ~4.0 mmol/L (72 mg/dL). After adjusting for regression dilution bias,  
53 each 1 mmol/L (18mg/dL) higher usual RPG above 5.9 mmol/L (106 mg/dL) was  
54 associated with an 11% (adjusted HR 1.11, 95% CI 1.10-1.13) higher risk of  
55 cardiovascular death. Similarly strong positive associations were seen for MCE (1.10,  
56 1.08-1.13), IS (1.08, 1.07-1.09) and MOVD (1.08, 1.07-1.09). For ICH, the association

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

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

## 62 INTRODUCTION

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

71 Recent decades have seen a marked increase in diabetes prevalence<sup>10,11</sup> and high pre-  
72 diabetes prevalence in China.<sup>11</sup> Despite this, there is little reliable prospective evidence  
73 about the relevance to CVD risk of blood glucose levels below the diabetic threshold in  
74 China.<sup>12</sup> Previous findings from the China Kadoorie Biobank (CKB) showed a positive  
75 association of random plasma glucose (RPG) levels with prevalent CVDs, but these were  
76 limited by their cross-sectional design and self-reported disease outcomes.<sup>2</sup> We present  
77 7-year prospective follow-up data from the CKB, examining the associations of RPG  
78 levels with risks of incident CVDs in individuals without known diabetes, and assessing  
79 whether factors, such as age, sex, adiposity and blood pressure, modify these.

## 80 METHODS

### 81 *Study population*

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

87 74 years from 100-150 rural villages or urban committees in each area were invited to  
88 participate. Overall, ~30% responded,<sup>13</sup> comparable with other large nationwide  
89 prospective studies.<sup>15</sup> 512 891 men and women were enrolled, including a small number  
90 just outside the target age range (n=10 168). Local, national and international ethical  
91 approval for the study was obtained. All participants provided informed, written consent.

## 92 *Data collection*

93 At local study assessment clinics, participants completed an interviewer-administered  
94 questionnaire collating data on demographics, socioeconomic factors, lifestyle measures  
95 (including smoking, alcohol consumption, diet and physical activity) and medical history.  
96 Physical measurements were undertaken including blood pressure, height, weight and hip  
97 and waist circumferences, by trained health workers using calibrated instruments and  
98 standard protocols. A 10ml non-fasting (with the exception of one area—Zhejiang—where  
99 participants were asked to fast) blood sample was collected from participants and plasma  
100 glucose was measured immediately using Johnson & Johnson SureStep Plus meters  
101 (Lifescan, Milpitas, CA, USA),<sup>16</sup> regularly calibrated with manufacturer control solutions.  
102 Data were collected on time since last food. Individuals with a plasma glucose level  $\geq 7.8$   
103 (140 mg/dL) and  $< 11.1$  mmol/L (200 mg/dL) were invited back the following day for a  
104 fasting plasma glucose (FPG) test. A resurvey of a 5% randomly selected sample of  
105 surviving participants was undertaken during May to October 2008 using the same  
106 procedures as in the baseline survey.

## 107 *Follow-up for morbidity and mortality*

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

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

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

### 123 *Statistical analyses*

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

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

137 diabetes and impaired glucose tolerance,<sup>3</sup> and to ensure reasonable participant numbers  
138 in all groups.

139 Cox proportional hazards models were used to estimate hazard ratios (HRs) for the  
140 associations of baseline RPG levels with incident CVDs, stratified by age-at-risk, sex  
141 (where appropriate) and study area, and adjusted for education (no formal education,  
142 primary school, middle school, high school, college/university), smoking (never,  
143 occasional, ex-regular, current regular), alcohol (never, occasional intake, ex-regular,  
144 reduced intake, weekly intake), SBP (<100, 100-109, 110-119, 120-129, 130-139, 140-  
145 149, 150-159, 160-169, ≥170 mmHg) and physical activity (<10, 10-19.9, 20-29.9, 30-  
146 39.9, ≥40 metabolic equivalent of task [MET] hours/day). Confounding variables were  
147 selected based on a priori knowledge of underlying biological mechanisms and  
148 demonstrated associations with RPG and CVD outcomes. The floating absolute risk  
149 method was used; this does not alter the value of the HRs, but provides confidence  
150 intervals for all RPG categories enabling comparisons between any two categories, and  
151 not only with the reference group.<sup>18</sup> Discrimination of the models was examined using  
152 Harrell's C-statistic.<sup>19</sup>

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

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

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

## 180 **RESULTS**

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

187 During ~3.3 million person-years of follow-up (mean 7 years) there were 19 214 deaths,  
188 6645 cardiovascular deaths, 3270 MCE, 19 153 IS, 22 023 MOVD events and 4326 ICH.  
189 For all CVDs, the risk increased progressively with higher baseline RPG levels, with no  
190 evidence of a threshold in the association (Table 2). Multivariable-adjusted fractional  
191 polynomial models examining the association of RPG with cardiovascular death, MCE, IS  
192 and MOVD, consistently indicated that models using the linear form of RPG best fitted the  
193 data (eFigure 2). There was a strongly significant, positive association of baseline RPG  
194 with cardiovascular death, MCE, IS and MOVD (p for trend <0.001), and a weaker  
195 association with ICH (p for trend=0.10). The incremental changes in Harrell's C-statistic  
196 ( $\Delta c$ ) for comparing the base-model (ie, a Cox model including education, smoking,  
197 alcohol, SBP and physical activity stratified by age-at-risk, sex and study area) with the  
198 model that additionally included baseline RPG were very modest ( $\Delta c$ : 0.0050, 0.0053,  
199 0.0036, 0.0033 for cardiovascular death, MCE, IS and MOVD, respectively). The overall  
200 values of the Harrell's C-statistic for the multivariable adjusted Cox models for  
201 cardiovascular death, MCE, IS and MOVD were 0.68, 0.63, 0.61 and 0.61, respectively.

202 Based on resurvey data from 17 863 randomly selected participants we estimated usual  
203 RPG in each baseline RPG category. Figure 1a shows the relationship between usual  
204 RPG and risk of cardiovascular death. There was a positive, log-linear, relationship  
205 between usual RPG and cardiovascular death continuing down to at least 5.9 mmol/L  
206 (106 mg/dL); each 1 mmol/L (18 mg/dL) higher usual RPG was associated with an  
207 adjusted HR of 1.11 (95% CI 1.10-1.13), applying the calculated regression dilution ratio  
208 of 0.56. The positive association appeared stronger in men than women (p=0.005), and in  
209 individuals with lower SBP (p for trend=0.002) or higher levels of education (p=0.009)  
210 (Figure 2).

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

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

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

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

236 **DISCUSSION**

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

244 Prospective studies of mostly Western populations have investigated the association of  
245 blood glucose—mainly FBG—with CVD risks, relatively consistently showing a greater  
246 CVD risk in the pre-diabetes range, when compared with lower blood glucose levels.<sup>1,6,7</sup>  
247 Below this range, however, evidence is conflicting. In the Asia Pacific Cohort Studies  
248 Collaboration of ~240 000 participants from 13 cohorts, there was a positive, log-linear  
249 association between usual FBG and incident IHD (n=816) and cardiovascular death  
250 (n=1661), continuing down to at least 4.9 mmol/L (88 mg/dL).<sup>6</sup> In contrast, in a study of  
251 ~1.2 million Koreans, with ~60 000 IHD and >45 000 IS events, there was a J-shaped  
252 association with baseline FPG, with the lowest risks at ~5.0 mmol/L (90 mg/dL).<sup>7</sup> In the  
253 Emerging Risk Factors Collaboration, including ~260 000 participants from 51 studies with  
254 ~11 000 IHD and ~1500 IS events, there was no significant association of FPG with IS,  
255 but a J-shaped association with IHD, with the lowest risk at 3.9-5.6 mmol/L (70-101  
256 mg/dL).<sup>1</sup> No prospective studies in mainland China have reported on the association, and  
257 two small Taiwanese studies have produced conflicting findings.<sup>25,26</sup>

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

261 RBG), stroke (n=544; 1.11, 0.95-1.31) or cardiovascular (n=1782; 1.11, 1.00-1.24)  
262 mortality, and only weak evidence of a positive association with total CVD (n=2087; 1.12,  
263 1.01-1.25).<sup>27</sup> Our study provides the first convincing evidence of a positive association of  
264 RBG with CVDs.

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

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

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

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

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<sup>39,40</sup>) 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<sup>9,37,38</sup> and some trial<sup>33</sup> evidence,  
317 suggest interventions to reduce plasma glucose levels may reduce CVD risk in individuals  
318 without diabetes, but further data are required.

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

323

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

325

326 **Acknowledgments and Funding:** The chief acknowledgment is to the participants, the  
327 project staff, and the China National Centre for Disease Control and Prevention (CDC)  
328 and its regional offices for access to death and disease registries. The Chinese National  
329 Health Insurance scheme provides electronic linkage to all hospital treatment. The  
330 baseline survey and the first re-survey were supported by the Kadoorie Charitable  
331 Foundation, Hong Kong. The long-term follow-up is supported by the UK Wellcome Trust  
332 (088158/Z/09/Z, 104085/Z/14/Z), Chinese Ministry of Science and Technology  
333 (2011BAI09B01, 2012-14), Chinese National Natural Science Foundation (81390541).  
334 The British Heart Foundation, UK Medical Research Council and Cancer Research UK  
335 provide core funding to the Oxford CTSU. Fiona Bragg acknowledges support from the  
336 BHF Centre of Research Excellence, Oxford. The funding bodies had no role in the design  
337 and conduct of the study; collection, management, analysis, and interpretation of the data;  
338 preparation, review, or approval of the manuscript; or decision to submit the manuscript  
339 for publication.

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- 486

487 **FIGURE LEGENDS**

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

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

495

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

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

505

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

508 Conventions as Figure 2.

509

510 **Table 1: Baseline characteristics of participants by random plasma glucose**

Characteristic	Baseline RPG level (mmol/L)							Total
	<4.3	4.3-5.2	5.3-5.7	5.8-6.7	6.8-7.7	7.8-11.1	≥11.1	
<b>No. of participants</b>	27535	152635	94359	112760	48368	23707	8144	467508
<b>RPG (mmol/L), mean</b>	3.9	4.8	5.5	6.2	7.2	8.8	15.8	5.9
<b>Men<sup>a</sup>, %</b>	56.7	45.2	38.3	35.9	36.7	40.1	42.7	41.0
<b>Age (years)<sup>b</sup>, %</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
<i>Mean</i>	47.4	49.1	50.6	52.0	53.6	54.7	55.5	50.9
<b>Living in urban area, %</b>	25.3	39.7	46.9	46.6	44.4	50.4	49.4	43.3
<b>≥6 years' education, %</b>	49.9	49.8	50.2	51.0	51.3	51.6	52.6	49.6
<b>Smoking history, %</b>								
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
<b>Alcohol consumption, %</b>								
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
<b>Physical activity (MET hours/day), %</b>								
<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
<i>Mean</i>	21.6	21.6	21.7	21.7	21.6	21.7	20.3	21.6
<b>SBP (mmHg), %</b>								
<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
<i>Mean</i>	128.6	129.3	129.8	130.6	131.9	134.9	139.1	130.4
<b>BMI (kg/m<sup>2</sup>), %</b>								
<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
<i>Mean</i>	23.0	23.3	23.5	23.7	24.0	24.4	25.1	23.6
<b>Waist-to-hip ratio, %</b>								
<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
<i>Mean</i>	0.87	0.87	0.88	0.88	0.89	0.90	0.92	0.88
<b>Fasting time (hours), mean</b>	4.4	5.7	5.4	4.4	3.2	3.0	3.5	4.9
<b>Family history of diabetes<sup>c,d</sup>, %</b>	5.7	6.3	6.5	7.0	7.7	9.7	14.2	6.5

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

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

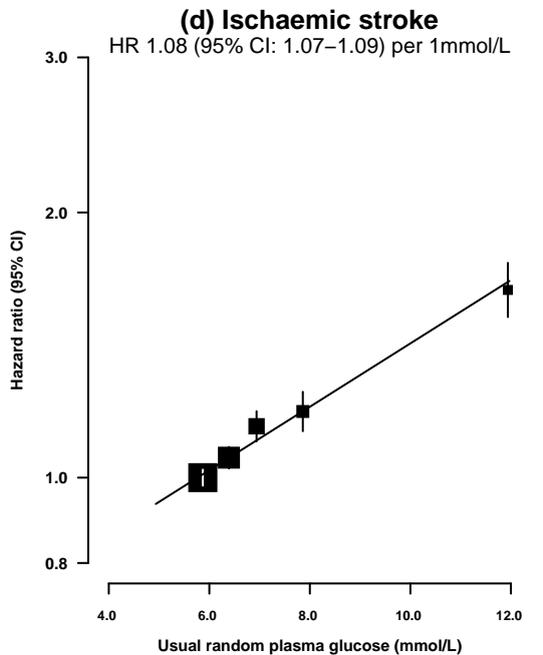
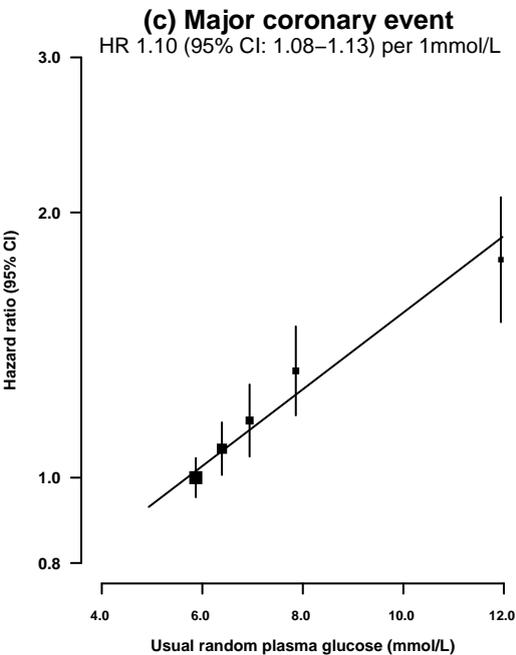
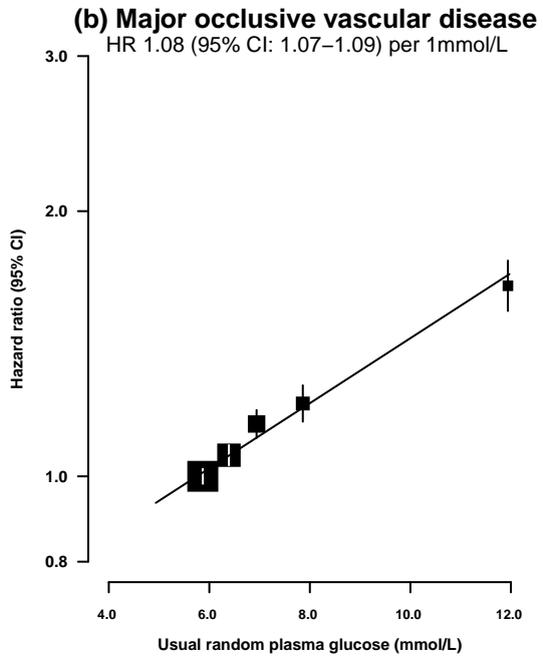
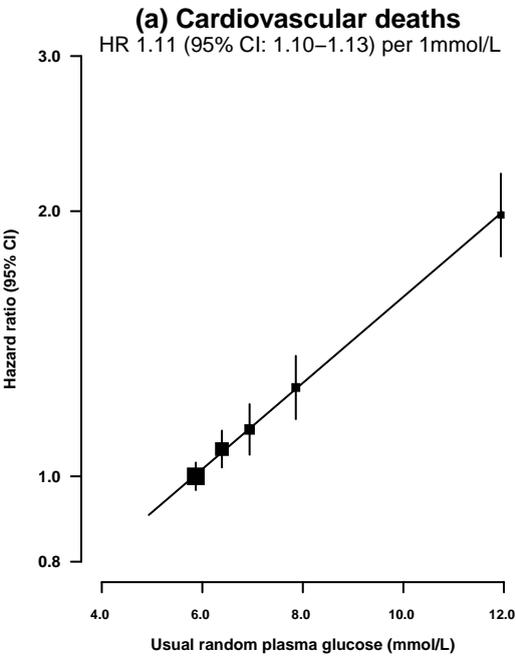
Baseline RPG (mmol/L) (Mean)	Cardiovascular death			Major occlusive vascular disease			Major coronary event			Ischaemic stroke			Intracerebral haemorrhage			
	No. of events	HR	(95% CI)	No. of events	HR	(95% CI)	No. of events	HR	(95% CI)	No. of events	HR	(95% CI)	No. of events	HR	(95% CI)	
<b>&lt;4.3</b> (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)	
<b>4.3-5.2</b> (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)	
<b>5.3-5.7</b> (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)	
<b>5.8-6.7</b> (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)	
<b>6.8-7.7</b> (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)	
<b>7.8-11.0</b> (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)	
<b>≥11.1</b> (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)	
<i>p for trend</i>		<0.001			<0.001			<0.001			<0.001			0.10		
<i>HR per 1 mmol/L<sup>a</sup></i>		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)		

517 Stratified by age, sex and study area and adjusted for education, smoking, alcohol, physical activity and systolic blood pressure. <sup>a</sup>HRs for first and second halves of follow-up:  
518 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,  
519 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  
520 mg/dL multiply by 18.  
521

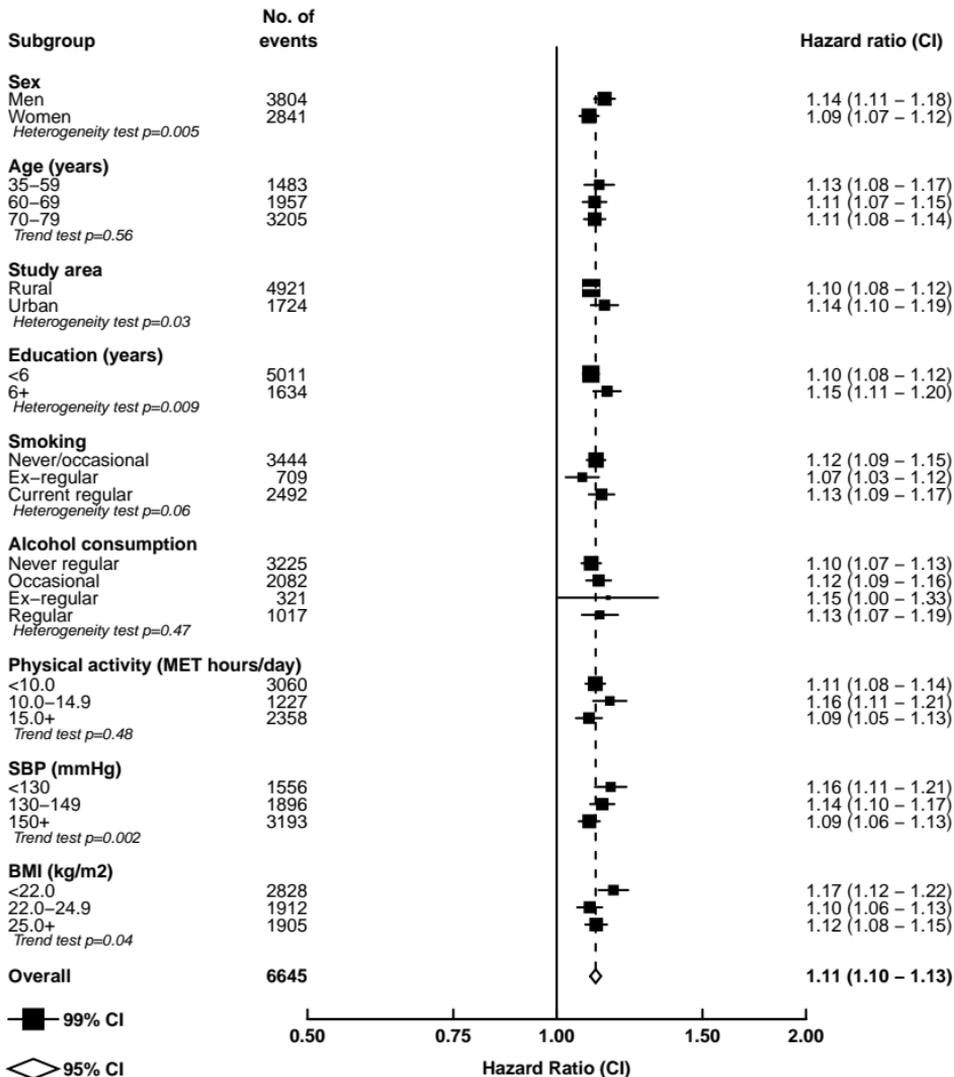
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**Figure 1: Adjusted hazard ratios for cardiovascular diseases by usual random plasma glucose**



**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**

