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Low fasting glucose and future risks of major adverse outcomes in people without baseline diabetes or cardiovascular disease: a systematic review and meta-analysis

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ABSTRACT

Objective To investigate the link between low fasting blood glucose levels and all-cause mortality and cardiovascular outcomes among people without baseline diabetes or cardiovascular disease.

Design Systematic review and meta-analysis.

Data sources PubMed and Embase (1966–February 2019).

Selection criteria Prospective cohort studies were included for meta-analysis if they reported adjusted HRs with 95% CIs for associations between risk of all-cause mortality, stroke, major cardiovascular events, coronary heart disease and low fasting glucose levels (<4.6 mmol/L and/or 4.0 mmol/L, respectively) versus normal fasting glucose levels.

Data extraction and statistical analysis Two independent reviewers extracted data from eligible studies. Heterogeneity was assessed by p value of χ^2 tests and I^2. We assessed four characteristics for each included study based on items developed by the US Preventive Task Force, as well as the modified checklist used in previous studies.

Results Eleven articles (consisting of 129 prospective cohort studies) with 2 674 882 participants without diabetes and cardiovascular disease at baseline were included in this meta-analysis. Pooled results from the random effects model showed increased risks of all-cause mortality (HR: 1.56; 95% CI 1.09 to 2.23), total stroke (HR: 1.08, 95% CI 1.03 to 1.13) and ischaemic stroke (HR: 1.06, 95% CI 1.01 to 1.10), and major cardiovascular events (HR: 1.05, 95% CI 1.03 to 1.07) among people with a fasting glucose <4.0 mmol/L, as compared with people with normal fasting glucose. The less stringent low fasting glucose level, <4.6 mmol/L, was not associated with increased risk of any endpoints.

Discussion and conclusions Among people without baseline diabetes or cardiovascular disease, a fasting blood glucose level of <4.0 mmol/L is associated with increased risk of all-cause mortality, major cardiovascular events and stroke.

Strengths and limitations of this study

- The size of this study and inclusion of only prospectively collected data strengthened the robustness of our findings.
- Although individuals in our meta-analysis were not diabetic patients with iatrogenic hypoglycaemia, the reason for the low concentrations of glucose in the low fasting blood glucose population was not established.
- About 5% of people without diabetes and cardiovascular disease at baseline have fasting glucose levels of <4.0 mmol/L and these individuals harbour a 56% greater hazard of long-term all-cause mortality, as compared with individuals with a normal glucose level.

INTRODUCTION

Elevated fasting blood glucose level is associated with higher risk of cardiovascular disease and mortality.[1] Presence of diabetes mellitus or prediabetes have been related to greater risks of major adverse cardiac events, stroke and death.[2–4] Since glucose is a necessary body nutrient, and blood glucose concentration is regulated by various hormones within a narrow range in the body,[5] theoretically fasting blood glucose lower than a certain level may be also associated with harmful effects. In patients with diabetes, intensive glycaemic control increased mortality.[6] In people without diabetes and cardiovascular disease at baseline, whether low fasting blood glucose levels affects outcomes is not well established. A link between low fasting blood glucose concentrations and higher risk of all-cause death was first observed in a long-term follow-up study, the Paris Prospective Study,[7] which enrolled participants from 1967 to 1970. Moreover, people with low fasting blood glucose concentrations had higher occurrences of cardiovascular and all-cause mortality than normal

reference groups.[8] However, other studies have suggested that low fasting blood glucose is not associated with increased risks of major cardiovascular events.[9] A major discrepancy between these various studies has been the definition of low fasting blood glucose, which ranged from <3.9 mmol/L (70 mg/dL)[8] to <4.9 mmol/L (88 mg/dL).[10]

Although blood glucose level ≤3.9 mmol/L (70 mg/dL) has been proposed as hypoglycaemia in patients with diabetes receiving medical therapy,[11] there has not been a consistent definition for low fasting blood glucose levels in people without diabetes, and the cut-off level has varied across studies.

Given the aforementioned issues and discrepancies, we set out to analyse low fasting blood glucose thresholds of <4.6 mmol/L (83 mg/dL) and 4.0 mmol/L (72 mg/dL), respectively, according to cut-off levels of endogenous adjustment to maintain glucose homeostasis.[12–14] We then conducted a systematic review and meta-analysis to determine whether a link exists between low fasting blood glucose and future risks of all-cause mortality, major cardiovascular events, stroke and coronary heart disease in people without diabetes and cardiovascular disease at baseline and to quantify the magnitude of any existing relation.

METHODS

This meta-analysis was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15]

Patient and public involvement

Patients were not involved in the design and conception of this study.

Search strategy

We systematically searched PubMed and Embase for the period up to 20 February 2019 by using Medical Subject Headings (MeSH) terms and free text with detailed search strategy presented in online supplementary table 1. We restricted the search to studies in humans with filters provided by PubMed and Embase. There was no language restriction. We also reviewed the Introduction and Discussion sections of retrieved studies and of prior reviews to identify additional studies.

Study selection and data abstraction

We selected studies that met the following entry criteria: prospectively collected data within cohort studies or clinical trials; blood glucose evaluated at baseline; assessed all-cause mortality, stroke, major cardiovascular events, coronary heart disease or cardiovascular mortality as an endpoint during the follow-up period; intended follow-up of at least 1 year for all participants; and reported quantitative estimates of the multivariate adjusted HR and 95% CI or SE for the log HR for future endpoints associated with baseline low fasting blood glucose. Low fasting blood glucose levels was defined as fasting glucose <4.0 mmol/L and/or <4.6 mmol/L. The reference group (ie, normoglycaemia) included people with fasting blood glucose levels between 4.7 mmol/L and 5.6 mmol/L. We excluded studies that used cross-sectional, case–control or retrospective cohort study approaches, that consisted mostly of participants diagnosed with major diseases such as cardiovascular disease, end-stage renal disease or cancer; that only reported unadjusted HR; that did not report 95% CIs; that the low fasting blood glucose was caused by an antidiabetic drug; that the cut-off level of low fasting blood glucose was higher than the stringent level (ie, 4.6 mmol/L) used in this meta-analysis; or that were duplicated. One investigator (ML) developed selection criteria and conducted the literature search. Two investigators (H-WL and C-HSC) assessed these criteria and abstracted data independently from eligible studies. Discrepancies were resolved by discussion with a third investigator (BO) and by referencing the original report.

Assessment of study quality

We assessed the quality of eligible studies. Assessment was based on guidelines developed by the US Preventive Task Force as well as the modified checklist used in previous studies.[16–18] We assessed four characteristics for each included study and presented it in online supplementary table 2.

Statistical analysis

The primary outcome was HR of all-cause mortality in people with low fasting blood glucose levels versus normoglycaemia. Secondary outcomes were incidences of stroke (including ischaemic or haemorrhage stroke), coronary heart disease, major adverse cardiovascular events and cardiovascular mortality.

We used multivariate-adjusted outcome data (expressed as HRs and 95% CIs) for data analysis. In every study, we converted these values by using their natural logarithms and calculated SEs from these logarithmic numbers and their corresponding 95% CIs. For the statistical analysis, we combined log HRs and SEs using the inverse variance approach. We used a random effect model and assessed heterogeneity by p value of χ^2 tests.[19] A fixed effect model was also used for comparison with the random effects model on the overall risk estimate. We conducted a trim and fill analysis for the primary outcome to evaluate potential systematic bias in studies, including publication bias. A sensitivity analysis was performed to explore the robustness of our results. We removed each study from the meta-analysis one at a time to identify any possible disproportionate influence on results. Reported p values were two sided, with significance set at less than 0.05. Heterogeneity was assessed by p value of χ^2 statistics and I^2, which described the percentage of variability in the effect estimates due to heterogeneity rather than to chance.[20 21] Based on the suggestion of the Cochrane Collaboration, we regarded heterogeneity as possibly unimportant when

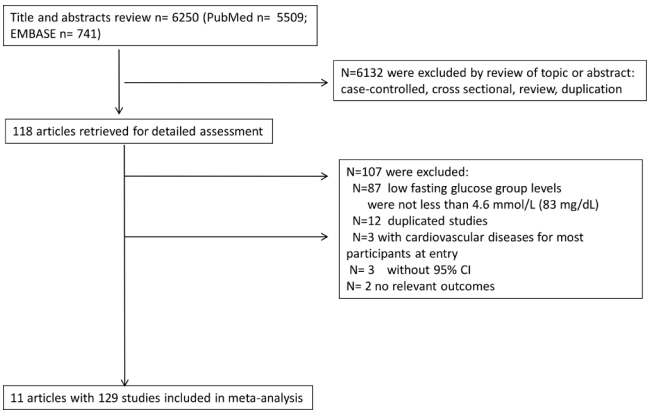


Figure 1 Flow chart of study selection.

the I^2 value was less than 40% and considerable when more than 75%.[22] RevMan 5 was used for the meta-analysis of observational studies.[3 17]

RESULTS

The preliminary literature search identified 6250 articles, and after reviewing the abstracts and contents, 6132 articles were excluded, and the remaining 118 articles went through further detailed assessment. We used fasting blood glucose level <4.6 mmol/L as cut-off to define low fasting glucose for retracting articles. Collaborative studies[1 23–25] that analysed datasets from previous cohort studies were used, while the studies of those individual cohort were excluded in the current meta-analysis to avoid duplications. Finally, 11 articles with 129 studies were included for further analysis (figure 1).[1 8 9 23–30] A total of 2 674 882 individuals without diabetes mellitus and cardiovascular disease at baseline were enrolled in this meta-analysis. The mean age was 48 years and 32% were women. About 5.2% and 21.6% of individuals with their fasting glucose concentration of <4.0 mmol/L and <4.6 mmol/L, respectively. The baseline characteristics of the included studies are summarised in table 1. The number of participants in the included studies ranged from 2429[29] to 1 197 384.[28] The average follow-up duration was 14.3 years, ranging from 1 year to 20 years. In this meta-analysis, we used cut-off fasting glucose levels <4.6 and <4.0 mmol/L, respectively, for analysis. Seven articles reported cut-off fasting glucose level <4.6 mmol/L[18 9 24–26 29] and eight articles reported cut-off level of <4.0 mmol/L.[1 8 23–25 27–29] In Korean Cancer Prevention Study (KCPS) 2013 study, men and women data were separately analysed.[28] Therefore, we analysed the data of men and women in KCPS 2013 study as independent data.

Low fasting glucose and all-cause mortality

In four articles using fasting glucose <4.6 mmol/L as cut-off, the random effects summary estimate did not show increased risk of all-cause mortality after adjustment (HR: 1.17, 95% CI 0.97 to 1.41; p=0.10) (figure 2).[1 8 9 25] We found evidence of heterogeneity across studies (p for heterogeneity=0.0004, I^2=77%) but no major asymmetrical appearance in the funnel plot (online supplementary figure 1A). The estimate from a fixed-effects model (HR: 1.06, 95% CI 1.00 to 1.13; p=0.06) was similar to the estimate from a random-effects model.

In four articles using fasting glucose <4.0 mmol/L as cut-off, the random effects summary estimate showed an increased risk of all-cause mortality after adjustment (HR: 1.56, 95% CI 1.09 to 2.23; p=0.02) (figure 2).[1 8 25 27] We found evidence of heterogeneity across studies (p for heterogeneity=0.03, I^2=67%) and publication bias, with under-representation of small studies showing protective effects (online supplementary figure 1B). The estimate from a fixed-effects model (HR: 1.21, 95% CI 1.09 to 1.34; p=0.0003) was smaller than the estimate from a random-effects model but still significant.

Sensitivity analyses excluding individual trials yielded pooled results that were not significantly different from the overall pooled estimates.

Low fasting glucose and stroke

In articles using fasting glucose <4.6 mmol/L as cut-off, the random effects summary estimate did not show increased risks of total stroke (two articles; HR: 0.90, 95% CI 0.64 to 1.28; p=0.56), ischaemic stroke (two articles; HR: 1.03, 95% CI 0.94 to 1.12, p=0.55) or haemorrhagic stroke (one article; HR: 0.98, 95% CI 0.88 to 1.09, p=0.71).

In articles using fasting glucose <4.0 mmol/L as cut-off, the random effects summary estimate showed increased risks of total stroke (one article with men and women reported separately; HR: 1.08, 95% CI 1.03 to 1.13; p=0.0006) and ischaemic stroke (one article with men and women reported separately; HR: 1.06, 95% CI 1.01 to 1.10; p=0.02). Risk of haemorrhagic stroke was not significantly increased (two articles; HR: 1.16, 95% CI 0.96 to 1.40; p=0.11) (figure 3).

Heterogeneity was difficult to assess for this pooled analysis involving three or fewer studies.

Low fasting glucose and major cardiovascular adverse events, coronary heart disease, and cardiovascular mortality

In articles using fasting glucose <4.6 mmol/L as cut-off, the random effects summary estimate did not show increased risk of major adverse cardiovascular events (one article; HR: 0.96, 95% CI 0.77 to 1.20; p=0.72), coronary heart disease (four articles; HR: 1.07, 95% CI 0.94 to 1.21; p=0.31) or cardiovascular mortality (three articles; HR: 1.26, 95% CI 0.87 to 1.83; p=0.23).

In articles using fasting glucose <4.0 mmol/L as cut-off, the random effects summary estimate showed increased risks of major adverse cardiovascular events (two articles; HR: 1.05, 95% CI 1.03 to 1.07, p<0.0001). Risks of coronary heart disease (three articles; HR: 1.02, 95% CI 0.95 to 1.10; p=0.61) or cardiovascular mortality (three articles; HR: 1.47, 95% CI 0.88 to 2.44; p=0.14) were not significantly increased (figure 4).

Heterogeneity was difficult to assess for this pooled analysis involving three or fewer studies.

Table 1 Baseline characteristics and quality assessment of included studies

Study, country	Population	Sample size (% of women)	Age, years	Definition of low fasting glucose	Definition of normal fasting glucose	Follow-up years	Outcomes	Adjustment variables
ACLS and SAHS 2000, USA[8]	People free of diabetes and CVD at baseline; ACLS: 97% white. SAHS: 62% Mexican-American.	40 069 (ACLS: 22; SAHS: 57)	20–80 (mean 43).	<70 and 70–79 mg/dL	80–109 mg/dL	8	All- cause, cardiovascular mortality.	Age, sex, population, ethnicity, BMI, triglycerides, hypertension, total cholesterol, parental CVD, history of CVD and cancer, current smoking status and examination years.
DECODE 2003, Europe[25]	People free of diabetes and CVD at baseline; 22 cohort studies in Europe.	29 714 (35)	30–89.	<4.5 mmol/L	4.5–6.0 mmol/L	Mean: 11	All- cause, cardiovascular mortality.	Age, sex, cohorts, BMI, SBP, cholesterol and smoking.
ERFC 2010, 96% in Europe, North America and Australia, others in Japan or Caribbean[24]	People free of diabetes and CVD at baseline; 102 prospective studies; not known previous CAD history.	279 290 (43)	52±13	<4.0 and 4.0–4.5 mmol/L	5.0–5.5 mmol/L	≥1	CHD and ischaemic stroke.	Age, smoking status, BMI, SBP and total cholesterol.
ERFC 2011, 58% in Europe and 36% in North America[1]	People free of diabetes and CVD at baseline; 97 prospective studies.	715 061 (48)	55±9	<4.0 and 4.0–4.5 mmol/L	5.0–5.5 mmol/L	≥1	All-cause, cardiovascular death.	Age, sex, smoking status (current vs other) and BMI.
ERFC 2014, 86% in Europe or North America[23]	People free of diabetes and CVD at baseline; 73 prospective studies.	150 617 (49)	58±9	<76 and 76–90 mg/dL	90–105 mg/dL	9.9	CVD	Age, smoking status, systolic blood pressure, total cholesterol and HDL-C.
KCPS 2013, Korea[28]	Government employees, public and private school teachers and their dependents; free of diabetes and CVD at baseline.	1 197 384 (36)	30–95	<70 mg/dL	85–99 mg/dL	18	CVD, CHD, stroke, haemorrhagic stroke and ischaemic stroke.	Age, smoking status, alcohol drinking, exercise, BMI and SBP. The different genders were analysed separately.

Continued

Table 1 Continued

Study, country	Population	Sample size (% of women)	Age, years	Definition of low fasting glucose	Definition of normal fasting glucose	Follow-up years	Outcomes	Adjustment variables
KIHD 2014, Finland[29]	People free of diabetes and CVD at baseline.	2429 (0)	42–61 (mean: 53).	3.2–4.2 and 4.2–4.5 mmol/L	4.5–4.8 mmol/L	20	CHD mortality.	Age, prevalent CHD, cigarette smoking, BMI, SBP, serum LDL-C, plasma fibrinogen, blood leucocytes and alcohol consumption.
Sung 2009, Korea[26]	Male public servants free of diabetes and CVD at baseline.	570 453 (0)	≥30	<4.6 mmol/L	4.6–5.0 mmol/L	8.8	Myocardial infarction, all stroke, haemorrhagic stroke and ischaemic stroke.	Age, height, smoking, alcohol consumption, regular exercise, level of monthly salary, area of residence, BP level, serum total cholesterol level and BMI.
Wen 2005, Taiwan[27]	Governmental employees and school teachers free of diabetes and CVD at baseline.	23 755 (0)	40–69	50–75 mg/dL	90–109 mg/dL	11	All-cause mortality.	Age, SBP, smoking, total serum cholesterol and BMI.
WHI 2010, USA[9]	Post menopause, free of CVD and diabetes; 52% Caucasian, 24% African-American, 8% Asian and 12% Hispanic.	17 287 (100)	50–79 (mean 61).	<80 mg/dL	80–99 mg/dL	13.6	Heart failure, all CVD and all-cause mortality.	Age, race, income and education, total cholesterol, BP, BMI and smoking.

Continued

Table 1 Continued

Study, country	Population	Sample size (% of women)	Age, years	Definition of low fasting glucose	Definition of normal fasting glucose	Follow-up years	Outcomes	Adjustment variables
Jin 2018, China[30]	Chinese free of CVD and fasting glucose <5.6 mmol/L at baseline.	66 099 (21)	56	<4.0 mmol/L	4.0–5.59 mmol/L	9	Intracerebral haemorrhage.	Age, sex, smoking, alcohol intake, education, physical activity, sodium intake and family income; use of antihypertensive, aspirin and lipid-lowering medications, SBP, DBP, BMI, eGFR, HDL-C, LDL-C, triglycerides and hs-CRP.

ACLS and SAHS, Aerobics Centre Longitudinal Study and San Antonio Heart Study; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DECODE, Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe; ERFC, Emerging Risk Factors Collaboration; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitive C reactive protein; LDL-C, low-density lipoprotein cholesterol; KCPS, Korean Cancer Prevention Study; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; SBP, systolic blood pressure; WHI, Women's Health Initiative.

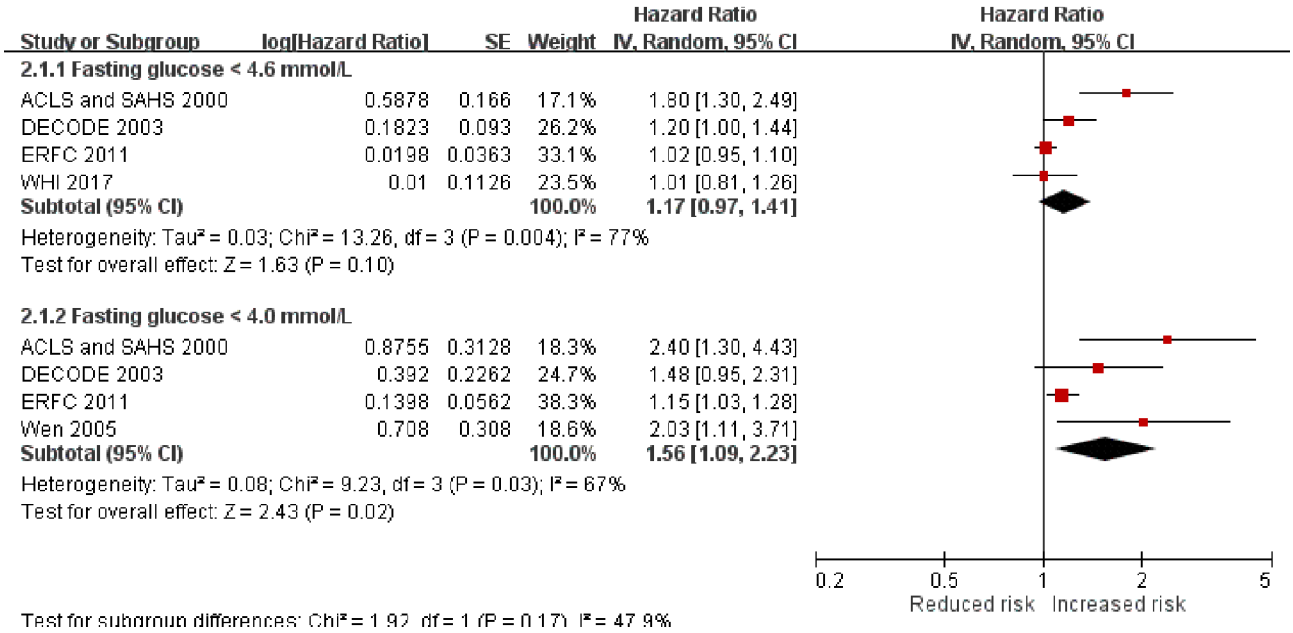


Figure 2 Association of baseline low fasting glucose (<4.6 mmol/L and <4.0 mmol/L, respectively) and risk of all-cause mortality.

DISCUSSION

In this meta-analysis of 11 articles that included 129 prospective studies of generally good quality, consisting of over 2.6 million individuals without diabetes mellitus and cardiovascular disease at baseline, we found that people with a baseline fasting glucose <4.0 mmol/L had an increased risk of all-cause mortality 56% greater than those with a normal baseline fasting glucose. We also found that the risks for major adverse cardiovascular events, stroke and ischaemic stroke were higher in people with baseline fasting glucose <4.0 mmol/L. The less stringent definition of low fasting glucose using <4.6 mmol/L as cut-off was not associated with increased risk of any endpoints. The size of this study and inclusion of only prospectively collected data strengthened the robustness of our findings. In addition, all studies included in our meta-analysis reported a multivariate adjusted HR, which potentially mitigated the possibility of known confounding influencing our results. Still, a meta-analysis based on observational studies cannot prove causality.

During our literature search, there was not a consistent definition of low fasting glucose level among articles. Although some articles described the outcomes of major adverse cardiovascular events, stroke or mortality at low fasting glucose levels, the definition of low fasting glucose concentration was higher than the stringent cut-off levels (<4.6 mmol) used in the current meta-analysis, and we excluded those studies from our analyses.[10 31 32] Fallen blood glucose levels trigger a sequence of physiological effects to maintain glucose homeostasis in healthy individuals. When blood glucose level decreases to a glycaemic threshold of 4.6 mmol/L, insulin secretion starts to decrease and utilisation of glucose reduced.[12 14] When blood glucose concentration falls below the threshold of 4.0 mmol/L, various counter-regulatory hormones, such as catecholamine, glucagon, cortisol and growth hormone, are secreted to compromise hypoglycaemia.[13] Therefore, we used <4.6 mmol/L and <4.0 mmol/L, respectively, as cut-off levels to analyse the influence of low fasting blood glucose in the general population.

The mechanism for low fasting glucose level conferring harmful effects may be related to the activation of counter-regulatory hormones, especially epinephrine.[33] Such a hormone stimulates glucose production and inhibits glucose clearance when hypoglycaemia occurs and could provide enough energy to various organs, especially the brain, under stress. However, Q wave to T wave (QT) interval prolongation also occurs, caused mainly by sympathoadrenal stimulation due to higher epinephrine levels during hypoglycaemia.[34 35] For instance, a previous study on insulin-induced hypoglycaemia in healthy individuals showed that changes in R and T waves were associated with counter-regulatory adrenergic activation, with elevations in norepinephrine and epinephrine.[34] This acquired long QT interval syndrome and T wave abnormality would affect ventricular repolarisation and increase risk of ventricular arrhythmia,[36] as shown in a study of non-diabetic men with a median follow-up of 23.3 years, in which fasting glucose concentration was inversely related to incident risk of ventricular arrhythmias.[37] As such, an increased risk of sudden cardiac death related to ventricular arrhythmias[36] due to low fasting blood glucose levels could explain increased all-cause mortality in our meta-analysis. Although mortality related to cancer could be a concern, studies that analysed the relationship between glucose level and cancer incidence did not show low fasting blood glucose level to be related to increased risk of cancer.[1 8 38]

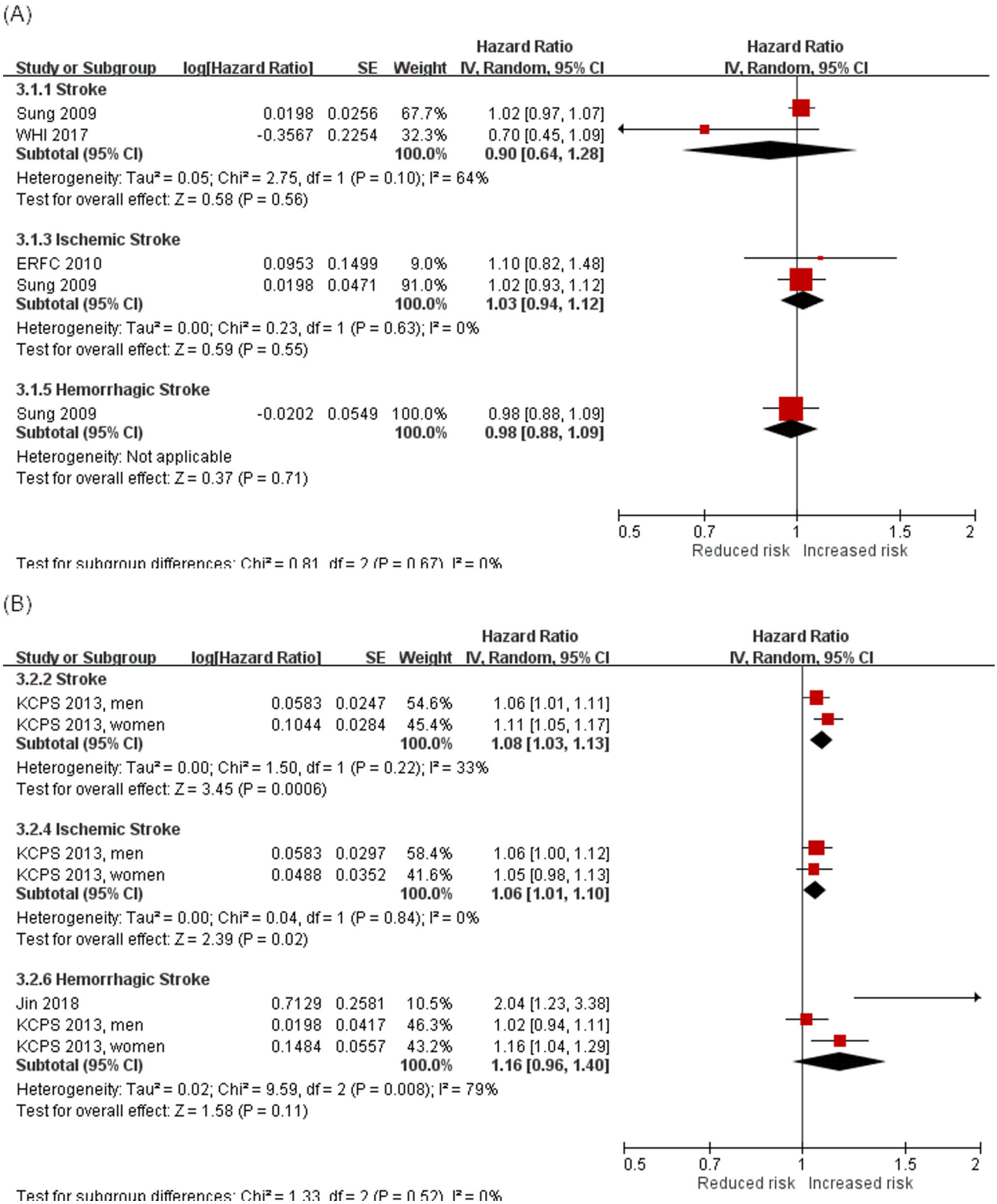
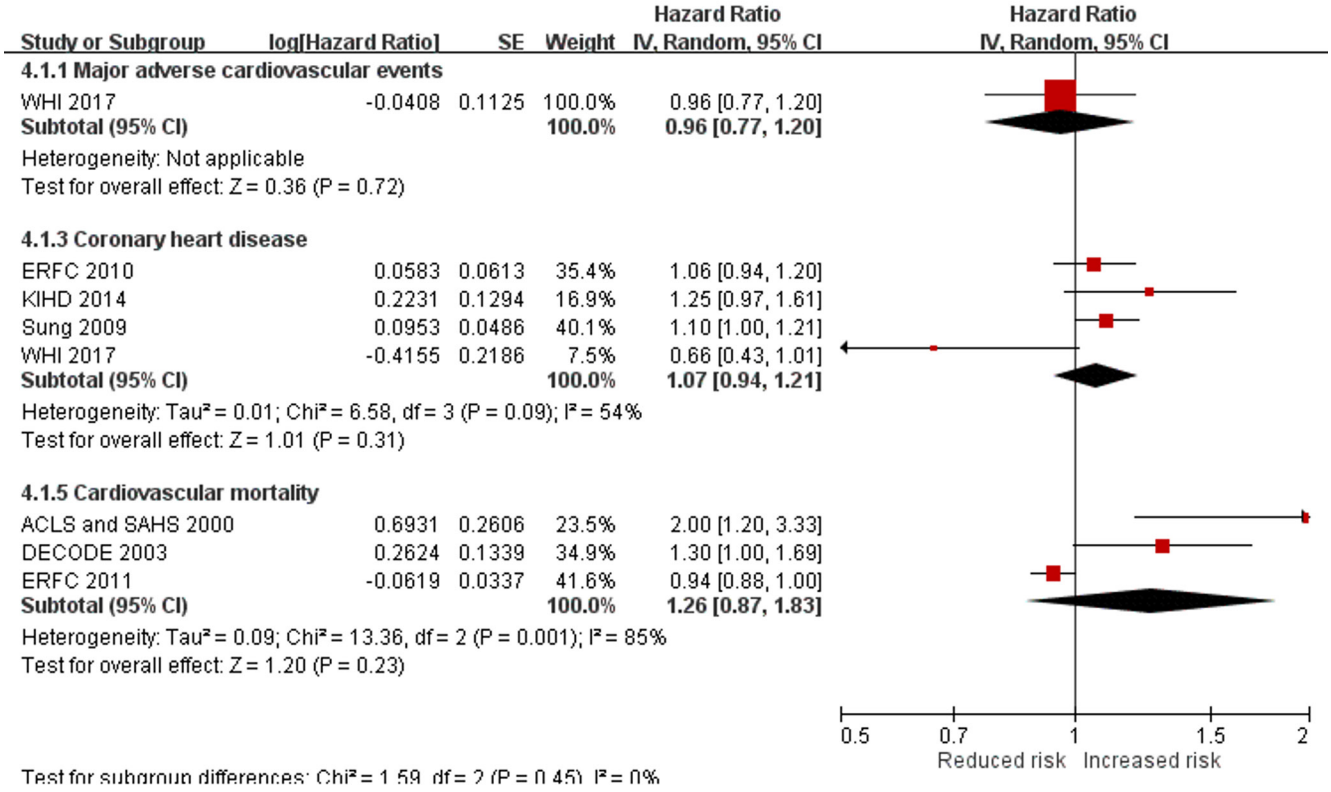


Figure 3 Association of baseline low fasting glucose (<4.6 mmol/L and <4.0 mmol/L, respectively) and risk of stroke, ischaemic stroke and haemorrhagic stroke.

Brain glucose concentration has a linear relationship with blood glucose concentration.[39] Since the major energy source of the brain is glucose, hypoglycaemia may damage the brain and cause stroke-like symptoms.[40] Brain imaging changes could be observed if severe long-term hypoglycaemia occurs.[40 41] Also, arrhythmia caused by hypoglycaemia may increase stroke risk.[36]

There have been some systematic reviews and meta-analyses exploring the association of hypoglycaemia and mortality/cardiovascular disease.[18 42] Goto

(A)



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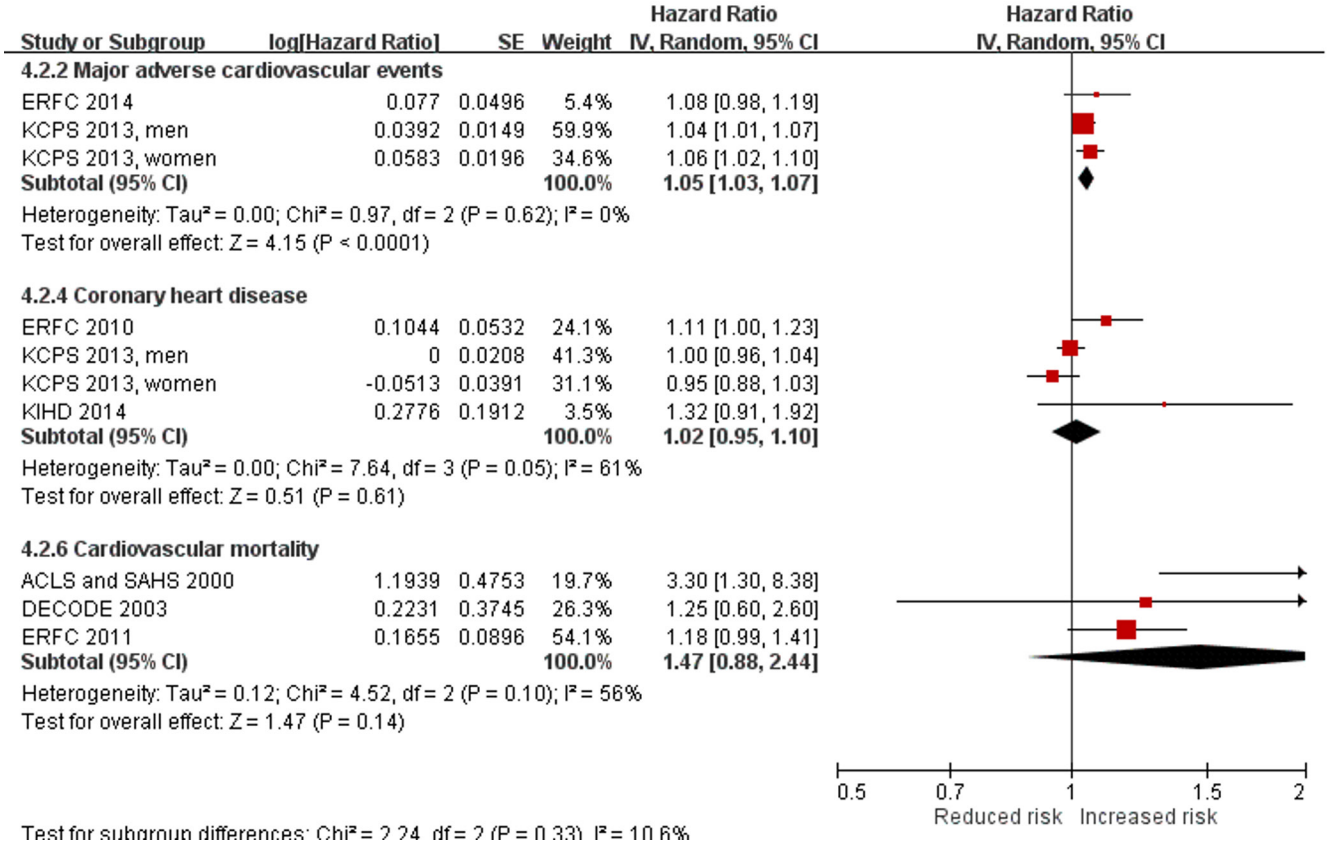

Figure 4 Association of baseline low fasting glucose (<4.6 mmol/L and <4.0 mmol/L, respectively) and risk of major adverse cardiovascular events, coronary heart disease and cardiovascular mortality.

et al[42] found that hypoglycaemia was associated with a higher risk of cardiovascular disease in patients with diabetes, and Yeh *et al* found that hypoglycaemia was a risk factor for adverse vascular events and mortality across different populations.[18] The novelty of the current meta-analysis we conducted is we only included studies enrolling people without diabetes and cardiovascular disease at baseline, and therefore, the majority of studies included in our meta-analysis were not included in the previously published two meta-analyses mentioned above.[18 42] Although the detrimental effects of hypoglycaemia are well established in people with diabetes or critical illness,[18 42] this is the first met-analysis, to our knowledge, to show that low fasting glucose (ie, <4.0 mmol/L) is associated with increased risks of all-cause mortality and stroke in people without baseline diabetes or cardiovascular disease. Low fasting glucose concentration found in people without diabetes and cardiovascular disease is not typically regarded as a marker of potential danger for future mortality and cardiovascular disease. However, the current meta-analysis suggests that non-diabetic people with a fasting glucose <4.0 mmol/L may be at future higher risk of mortality and stroke, and therefore might merit a more comprehensive evaluation and regular follow-up.

Our study has several limitations. First, all included articles used baseline glucose levels at the time of study enrolment. Whether individuals with low fasting glucose level at the time of enrolment had persistently low fasting plasma glucose values is not known. Second, although individuals in our meta-analysis were not diabetic patients with iatrogenic hypoglycaemia, the reason for the low concentrations of glucose in the low fasting blood glucose population was not established. Whether these individuals had hyperinsulinaemia, insulin resistance, poor nutrition or liver dysfunction[43] leading to hypoglycaemia could not be determined in most of the included articles. Potential confounders adjusted in one study did not change its results.[8] Third, the definition of low fasting blood glucose varied across enrolled studies. We used cut-off values of fasting glucose according to the threshold physiological responses of endogenous adjustment to maintain glucose homeostasis. Since studies were excluded if their cut-off level of low fasting glucose was higher than the stringent level (ie, 4.6 mmol/L) used in this meta-analysis, only limited studies were included for the pooled analysis of each endpoint.

Conclusions and implications

Our study suggests that about 5.2% of people without diabetes and cardiovascular disease at baseline have fasting glucose levels of <4.0 mmol/L, and these individuals, over a 14-year period, harbour a 56% greater hazard of all-cause mortality, as compared with individuals with a normal glucose level. While hypoglycaemia typically manifests with symptoms, and a low fasting glucose level in the general population is usually asymptomatic, when a low fasting glucose is observed during a routine medical examination for people without diabetes and cardiovascular disease, it may be worthwhile to mention to those with a fasting glucose <4.0 mmol/L that they might be at increased long-term risks for all-cause mortality, stroke and cardiovascular events. When fasting glucose <4.0 mmol/L is discovered, a comprehensive survey of potential underlying causes, periodic blood glucose level evaluation and cardiac rhythm follow-up might be prudent.

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