

## RESEARCH

# Effect of pre-diabetes on future risk of stroke: meta-analysis

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## Abstract

**Objectives** To assess the association between pre-diabetes and risk of stroke, and to evaluate whether this relation varies by diagnostic criteria for pre-diabetes.

**Design** Systematic review and meta-analysis of prospective studies.

**Data sources** A search of Medline, Embase, and the Cochrane Library (1947 to 16 July 2011) was supplemented by manual searches of bibliographies of key retrieved articles and relevant reviews.

**Selection criteria** Prospective cohort studies that reported multivariate adjusted relative risks and corresponding 95% confidence intervals for stroke with respect to baseline pre-diabetes were included.

**Data extraction** Two independent reviewers extracted data on pre-diabetes status at baseline, risk estimates of stroke, study quality, and methods used to assess pre-diabetes and stroke. Relative risks were pooled using random effects models when appropriate. Associations were tested in subgroups representing different characteristics of participants and studies. Publication bias was evaluated with funnel plots.

**Results** The search yielded 15 prospective cohort studies including 760 925 participants. In 8 studies analysing pre-diabetes defined as fasting glucose 100-125 mg/dL (5.6-6.9 mmol/L), the random effects summary estimate did not show an increased risk of stroke after adjustment for established cardiovascular risk factors (1.08, 95% confidence interval 0.94 to 1.23; P=0.26). In 5 studies analysing pre-diabetes defined as fasting glucose 110-125 mg/dL (6.1-6.9 mmol/L), the random effects summary estimate showed an increased risk of stroke after adjustment for established cardiovascular risk factors (1.21, 1.02 to 1.44; P=0.03). In 8 studies with information about impaired glucose tolerance or combined impaired glucose tolerance and impaired fasting glucose, the random effects summary estimate showed an increased risk of stroke after adjustment for established cardiovascular risk factors (1.26, 1.10 to 1.43; P<0.001). When studies that might have enrolled patients with

undiagnosed diabetes were excluded, only impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance independently raised the future risk of stroke (1.20, 1.07 to 1.35; P=0.002).

**Conclusion** Pre-diabetes, defined as impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance, may be associated with a higher future risk of stroke, but the relative risks are modest and may reflect underlying confounding.

## Introduction

The growing obesity epidemic in the United States has been inextricably linked with a surge in rates of pre-diabetes.<sup>1</sup> Pre-diabetes has been called “America’s largest healthcare epidemic,”<sup>1</sup> and current estimates indicate that about 35% of adults in the United States have pre-diabetes, or approximately 79 million people. This number is more than three times the number of people with frank diabetes (26 million people).<sup>2</sup> Also concerning is that the overwhelming majority of people with pre-diabetes may be unaware of their risk of diabetes.<sup>3</sup>

Pre-diabetes is generally defined as impaired fasting glucose, impaired glucose tolerance, or both.<sup>4</sup> In 1997 the American Diabetes Association defined impaired fasting glucose as a plasma glucose concentration of 110 to 125 mg/dL (6.1-6.9 mmol/L).<sup>5</sup> However, in 2003 the American Diabetes Association redefined impaired fasting glucose as a plasma concentration of 100 to 125 mg/dL (5.6-6.9 mmol/L).<sup>6</sup> The underlying pathophysiological disturbances (insulin resistance and impaired  $\beta$  cell function) responsible for the development of type 2 diabetes are expressed in people with pre-diabetes.<sup>7</sup> People with pre-diabetes harbour the same vascular risk factors (dysglycaemia, hypertension, dyslipidaemia, obesity, physical inactivity, insulin resistance, endothelial dysfunction,

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pro-coagulant state, and inflammation) that place people with type 2 diabetes at high risk of macrovascular complications.<sup>7</sup> Pre-diabetes has been linked to a modest increase in overall cardiovascular events,<sup>8</sup> but the effect of pre-diabetes on risk of future stroke has not been established.

The objective of this study was twofold: to investigate the direction and magnitude of the relation of pre-diabetes with risk of future stroke after accounting for other stroke risk factors, and to evaluate whether this relation varies on the basis of the threshold for impaired fasting glucose or inclusion of impaired glucose tolerance criteria in the diagnosis of pre-diabetes.

## Methods

The search strategy was in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.<sup>9</sup> We searched PubMed (1947 to 16 July 2011), Embase (1947 to 16 July 2011), and the Cochrane Library (1947 to 16 July 2011), using the search terms “prediabetes” or “impaired fasting glucose” or “impaired glucose intolerance” or “borderline diabetes” AND “cardiovascular disease” or “myocardial ischemia” or “myocardial infarct” or “ischemic heart disease” or “coronary heart disease” or “coronary artery disease” or “angina” or “stroke” or “cerebrovascular disease” or “cerebrovascular attack” or “cerebral ischemia” or “brain ischemia” or “intracranial hemorrhage” AND “cohort” or “observational” or “prospective” or “trial.” We restricted the search to studies in humans and applied no language restrictions. We retrieved further information by a manual search of references from recent reviews and relevant published original studies.

## Inclusion and exclusion criteria

We selected studies if they met the following entry criteria: prospectively collected data within cohort studies or clinical trials; blood glucose evaluated at baseline; assessed stroke event as an endpoint during the follow-up period (for example, if a person had a stroke before enrolment, the stroke event during follow-up would be recurrent stroke; if a person did not have a stroke before enrolment, the stroke event during follow-up would be the first stroke event); intended follow-up of at least one year for all participants; and reported quantitative estimates of the multivariate adjusted (that is, age, sex, and one other conventional vascular risk factor as minimum requirements) relative risk and 95% confidence interval or standard error for the log relative risk for future stroke associated with baseline pre-diabetes. Pre-diabetes was defined as impaired fasting glucose (fasting glucose 100-125 mg/dL or 110-125 mg/dL<sup>5 6</sup>) or impaired glucose tolerance (two hour values in the oral glucose tolerance test of 140-199 mg/dL (7.8-11.0 mmol/L)).<sup>4</sup> The reference group (that is, normoglycaemia) included people with fasting glucose less than 100 mg/dL, fasting glucose less than 110 mg/dL, or non-fasting glucose less than 140 mg/dL. Although we preferred studies that measured baseline fasting plasma glucose and oral glucose tolerance test, in the main analysis we did not exclude studies that measured only baseline fasting or non-fasting glucose concentrations. So, for instance, people with a fasting plasma glucose of 126 mg/dL or greater (that is, diabetes mellitus) may have inadvertently been included if only non-fasting glucose was measured; on the other hand, people with a non-fasting glucose of 200 mg/dL or greater (that is, diabetes mellitus) might have been included if a study measured only fasting glucose. We also did a sensitivity analysis that excluded studies that might have inadvertently enrolled people who met the criterion for a diagnosis of diabetes. Finally,

we also excluded studies in which more than 50% of participants were pregnant women.

## Data extraction and quality assessment

Two investigators (ML and KSH) independently abstracted data from eligible studies. Discrepancies were resolved by discussion with a third investigator (BO) and by referencing the original report. Relevant data included the first author's name, study name, year of publication, country of origin, number of participants, age of participants, duration of follow-up, percentage of participants followed to the end of a study, outcome assessment, prevalence of pre-diabetes, multivariate adjusted relative risks or hazard ratios for stroke and corresponding 95% confidence interval, and covariates adjusted for in the statistical analysis.

We assessed studies' quality on the basis of adequate adjustment for potential confounders (at least six of seven factors: age, sex, hypertension or systolic blood pressure or antihypertensive drug, body mass index or other measure of overweight/obesity, physical activity, cholesterol concentration or statin use, and smoking).

## Statistical analysis

We used multivariate adjusted outcome data for our data analysis. We converted these values in every study by using their natural logarithms and calculated the standard errors from these logarithmic numbers and their corresponding 95% confidence intervals. The statistical analysis used the inverse variance approach to combine log relative risks and standard errors. We used a random effect model and assessed heterogeneity by P value of  $\tau^2$  statistics.<sup>10</sup> We used a funnel plot based on the primary outcome to evaluate potential systematic bias in studies, including publication bias. All reported P values were two sided with significance set at less than 0.05.

We calculated summary estimates of relative risk for fasting glucose of 100 to 125 mg/dL, fasting glucose of 110 to 125 mg/dL, and presence of impaired glucose tolerance with or without impaired fasting glucose. We did predefined subgroup analyses according to population type (general population versus established cardiovascular disease at entry), ethnicity (Asians versus non-Asians), sex (men versus women versus both men and women), mean age at entry (<65 years versus  $\geq$ 65 years), possibility of enrolling patients with diabetes (none enrolled versus might be enrolled), and adjustment for confounders (adequate adjustment versus inadequate adjustment). We used the Cochrane Collaboration's Review Manager software package (RevMan 5) for the meta-analysis of observational studies.<sup>11 12</sup>

## Results

The literature review identified 62 full articles for detailed assessment. We excluded 29 studies owing to lack of a multivariate adjusted stroke estimate, seven studies for providing only fatal endpoints; two studies for follow-up duration less than one year; eight studies for lacking proper impaired fasting glucose or impaired glucose tolerance categories at baseline,<sup>13-20</sup> and one study that was retrospective rather than prospective (fig 1). The final analysis included 760 925 participants from 15 prospective cohort studies.<sup>21-35</sup> All studies excluded people with fasting glucose of 126 mg/dL or greater, except one study in which only non-fasting glucose was measured at baseline.<sup>33</sup> In this study, impaired glucose tolerance was defined as non-fasting venous plasma glucose 140 to 199 mg/dL, and a non-fasting glucose below 140 mg/dL was used as a reference; a few patients

with fasting glucose of 126 mg/dL or greater might thus have been enrolled in the impaired glucose tolerance group or reference group.<sup>33</sup> On the other hand, among 15 included studies, seven studies measured only fasting glucose at baseline<sup>24 25 27 29 31 32 34</sup>, so some people with non-fasting glucose of 200 mg/dL or greater might have been included in these studies.

Table 1<sup>1</sup> shows the characteristics of the studies. Among the 15 studies, nine were derived from the general population, one from the aged population, four from populations with a history of coronary artery disease, and one from a population with history of stroke or transient ischemic attack. Ten studies reported any stroke as an endpoint, four reported ischaemic stroke as an endpoint, and one reported ischaemic and haemorrhagic strokes separately as endpoints. Sample sizes ranged from 1032 to 652 901, and follow-up durations ranged from one year to 17 years. One study enrolled only women, and another enrolled only men; the remainder enrolled both men and women.

In eight studies with information about fasting glucose 100 to 125 mg/dL, the random effects summary estimate did not show increased risk of stroke after adjustment for established cardiovascular risk factors (relative risk 1.08, 95% confidence interval 0.94 to 1.23;  $P=0.26$ ) (fig 2<sup>1</sup>). We found evidence of heterogeneity across studies ( $P$  for heterogeneity  $<0.0001$ ) but no major asymmetrical appearance in the funnel plot (supplementary fig A).

In five studies with information about fasting glucose 110 to 125 mg/dL, the random effects summary estimate showed an increased risk of stroke after adjustment for established cardiovascular risk factors (relative risk 1.21, 1.02 to 1.44;  $P=0.03$ ) (fig 3<sup>1</sup>). Although we again found evidence of heterogeneity across studies ( $P$  for heterogeneity 0.003), we saw no substantial asymmetrical appearance in the funnel plot (supplementary fig B).

Eight studies had information about impaired glucose tolerance or combination of impaired fasting glucose and impaired glucose tolerance. The random effects summary estimate for these studies showed an increased risk of stroke after adjustment for established cardiovascular risk factors (relative risk 1.26, 1.10 to 1.43;  $P<0.001$ ) (fig 4<sup>1</sup>). We found no obvious heterogeneity across studies ( $P=0.15$ ) and no major asymmetric appearance in the funnel plot (supplementary fig C).

In a sensitivity analysis excluding the study that might have enrolled people with fasting glucose of 126 mg/dL or above,<sup>33</sup> we saw a smaller, but still significant, effect of impaired glucose tolerance or combination of impaired fasting glucose and impaired glucose tolerance on future stroke (relative risk 1.20, 1.07 to 1.35;  $P=0.002$ ). However, when we excluded studies that might have enrolled people with non-fasting glucose of 200 mg/dL or above, neither fasting glucose 100 to 125 mg/dL nor 110 to 125 mg/dL was significantly associated with increased risk of future stroke (relative risks 0.91, 0.50 to 1.63, and 1.11, 0.77 to 1.61) (table 2<sup>1</sup>).

Table 2<sup>1</sup> shows subgroup analyses. Heterogeneity existed between estimates among participants' ages at entry ( $<65$  years versus  $\geq 65$  years) and degree of adjustment for confounders (adequate adjustment versus inadequate adjustment). In four studies with adequate adjustment of confounders, baseline impaired glucose tolerance or combination of impaired fasting glucose and impaired glucose tolerance was associated with a trend towards higher future risk of stroke (relative risk 1.11, 0.99 to 1.25;  $P=0.08$ ). We further analysed three studies that provided information on participants with fasting glucose of

100 to 109 mg/dL and found no associated increased risk of stroke (relative risk 0.94, 0.73 to 1.20;  $P=0.61$ ).

## Discussion

In this meta-analysis of 15 prospective studies, with more than 760 000 participants, we found that people with baseline pre-diabetes, defined as impaired fasting glucose of 110 to 125 mg/dL (6.1-6.9 mmol/L) or presence of impaired glucose tolerance, were at modestly higher risk of future stroke. The American Diabetes Association's current, less stringent impaired fasting glucose definition (fasting glucose 100-125 mg/dL (5.6-6.9 mmol/L)) of pre-diabetes was not associated with increased risk of stroke. After further exclusion of studies that may have enrolled patients with diabetes, only impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance showed significant relation with risk of stroke. The observed lack of a relation between impaired fasting glucose and risk of future stroke is in accord with results from a recent individual level collaborative meta-analysis.<sup>36</sup> It reinforces the notion that two hour postprandial glucose challenge is probably a stronger predictor of macrovascular complications than is fasting glucose.<sup>37</sup>

The risk of stroke seems to rise progressively across the spectrum of insulin resistance from impaired fasting glucose to impaired glucose tolerance to diabetes,<sup>37</sup> suggesting that hyperglycaemia might be a continuous risk factor for stroke. Nonetheless, people with pre-diabetes can be as insulin resistant as people with diabetes.<sup>38</sup> A common mechanism linking all components of the insulin resistance syndrome is the cellular/molecular cause of the insulin resistance,<sup>38 39</sup> which not only promotes atherogenesis and inflammation but also leads to or aggravates other components of the syndrome, which themselves are major vascular risk factors. Also, people with pre-diabetes develop dyslipidaemia characterised by small, dense, atherogenic low density lipoprotein particles, hypertriglyceridaemia, and reduced high density lipoprotein cholesterol,<sup>40 41</sup> as well as accelerated atherogenesis.<sup>42</sup>

All of the aforementioned notwithstanding, the relation of pre-diabetes with risk of future stroke was relatively modest, so underlying confounding is probably easily able to affect these results. Furthermore, compared with the studies with inadequate adjustment of confounders, the effect size of the association of pre-diabetes with stroke risk was attenuated in those studies that used adequate adjustment.

We found that the definition of pre-diabetes seems to matter with regard to risk of stroke. Even though insulin resistance may be a condition on a continuous scale, when it comes to stroke, the only diagnostic approach for pre-diabetes that is clearly linked to risk seems to be one that includes impairment in glucose tolerance. Of note, the American Diabetes Association recently updated its screening recommendation for pre-diabetes to include haemoglobin A<sub>1c</sub> as another diagnostic testing option.<sup>4</sup> These recommendations state that an haemoglobin A<sub>1c</sub> between 5.7% and 6.4% identifies people at high risk of diabetes and that the label of pre-diabetes can be applied.<sup>4</sup> We did not include haemoglobin A<sub>1c</sub> criteria in the investigation of the association between pre-diabetes and risk of stroke because this recent diagnostic criterion had not yet been proposed when the prospective cohort studies we evaluated were conducted. Ongoing or future prospective cohort studies that include haemoglobin A<sub>1c</sub> among their baseline variables may provide more information on the association between pre-diabetes and risk of stroke.

## Strengths and limitations of study

Our study has several limitations. Firstly, a large amount of heterogeneity was observed in the results of the various studies. Although we did subgroup analyses, heterogeneity persisted in many subgroups, suggesting that other factors might explain some results. Despite these limitations, the results of this systematic review are possibly the most precise estimate available of the nature and strength of the relation between pre-diabetes and future risk of stroke. Secondly, knowing whether strokes occurred before or after diagnosis of diabetes during the study period would have been helpful. Such information might have clarified to what degree pre-diabetes itself is a risk factor or whether it simply reflects the risk associated with development of overt diabetes. Thirdly, 85% of the patients in the 15 included studies were enrolled in one study (which enrolled only Korean men).<sup>31</sup> However, the weight of this study was actually only 17% in the analysis of fasting glucose 100 to 125 mg/dL and 27% in the analysis of fasting glucose 110 to 125 mg/dL. Fourthly, although most studies included in this meta-analysis used all stroke as an endpoint, a few evaluated only ischaemic stroke as an endpoint. Fifthly, some people with diabetes mellitus at baseline might have been included in our analyses owing to the design of some studies in which only fasting or non-fasting glucose was measured, and determining the exact percentage of such patients in the pre-diabetes and reference groups was difficult. However, we still found a modest but increased risk of future stroke among people with impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance when we excluded studies that may have enrolled patients with diabetes.

## Conclusions and policy implications

An immediate implication of our findings is that people with pre-diabetes should be aware that they are at increased risk of future stroke. Also, pre-diabetes is not only a risk factor for stroke but is also frequently associated with the presence of one or more other recognised major cardiovascular risk factors.<sup>7</sup> When pre-diabetes is discovered, the person's overall cardiovascular risk factor profile should be reviewed to ensure that risk factors are being appropriately modified. Given the strong relation between being overweight/obese and pre-diabetes, recommending the maintenance of an ideal weight may improve clinical outcomes in these patients. For people with pre-diabetes, weight loss in conjunction with healthy lifestyle changes is associated with decreased risk of transitioning to frank diabetes and may even reduce future stroke events.<sup>43-44</sup> Our study also underscored a need to evaluate both fasting glucose and two hour postprandial glucose challenge for identifying people with pre-diabetes who may be at risk of stroke. Finally, randomised controlled trials evaluating the effect of glycaemic control on the occurrence of stroke among people with impaired glucose tolerance or a combination of impaired fasting glucose and impaired glucose tolerance are warranted.

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Contributors: ML and BO had the idea for the study. ML, JLS, and BO designed the inclusion and exclusion criteria. ML and KSH participated in the search and the data collection and extraction. ML did the statistical analysis with guidance from JLS and BO. ML wrote the first draft of the report, and JLS, SS, and BO did the major revision and made comments. All other authors commented on the draft and approved the final version. ML and BO are the guarantors.

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**What is already known on this topic**

- Pre-diabetes is a surging epidemic in many developed countries
- Pre-diabetes has been linked to a modest rise in overall cardiovascular risk, but the effect of pre-diabetes on risk of future strokes has not been established
- The definition of pre-diabetes includes presence of impaired fasting glucose, impaired glucose tolerance, or both

**What this study adds**

- People with pre-diabetes on the basis of presence of impaired glucose tolerance had an independent risk of future stroke that was 20% greater than those with a normal glycaemia
- The relation between pre-diabetes and risk of stroke seems to depend on the definition of pre-diabetes
- Pre-diabetes based on a more recent guideline recommended definition of impaired fasting plasma glucose (100 to 125 mg/dL) was not linked to future stroke risk

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## Tables

Table 1 | Characteristics of included studies

Study and publication year	Country	Population characteristics*	Sample size of cohorts (% women)	Average age (range or SD)	Years of follow-up in all participants (% followed up to or died before stated time point)	Prevalence of pre-diabetes	Baseline pre-diabetes category and definition	Endpoint assessed during follow-up	Adjustment variables	Adjustment for confounders†
Doi 2010 <sup>21</sup>	Japan	General, excluded history of CVD (excluded all diabetes)	2421 (57%)	58 (10)	14 (100%)	NA	IFG 100, IFG 110, IGT	Ischaemic stroke	Age, sex, SBP, ECG abnormalities, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise	Adequate
Hyvärinen 2009 <sup>22</sup>	Finland, Sweden	General (excluded all diabetes)	18 360 (54%)	55 (20-90)	12.9 (not reported)	22%	IFG 110, IGT	All stroke	Age, sex, centre, MAP, BMI, total cholesterol, and smoking status	Adequate
Iso 2004 <sup>23</sup>	Japan	General, excluded history of CVD (excluded all diabetes)	10 582 (59%)	53 (40-69)	17 (not reported)	7%	IFG 110, IGT	Ischaemic stroke	Age, sex, community, hypertension status, BMI, TSF, SSF, total and HDL cholesterol, smoking status, alcohol intake, and (for women) menopausal status	Adequate
Janszky 2009 <sup>24</sup>	Sweden	CAD (might include non-fasting glucose $\geq$ 200 mg/dL)	1167 (30%)	59 (45-70)	8 (not reported)	22%	IFG 100	All stroke	Age, sex, obesity, hypertension, physical activity, total cholesterol, triglycerides, apo B:apo A ratio, Q wave infarction, and education	Adequate
Kaarisalo 2006 <sup>26</sup>	Finland	70-year-old people (excluded all diabetes)	1032 (52%)	70	9.6 (not reported)	12%	IGT	Ischaemic stroke	Sex, previous stroke or TIA, atrial fibrillation, history of MI, HF, poorly controlled hypertension (SBP $\geq$ 160 mm Hg or DBP $\geq$ 95 mm Hg), current smoking, acetylsalicylic acid use, normal memory	Not adequate
Kanaya 2005 <sup>25</sup>	USA	Postmenopausal women with CAD (might include non-fasting glucose $\geq$ 200 mg/dL)	2763 (100%)	67 (44-79)	6.8 (93.7%)	25%	IFG 100	All stroke and transient ischaemic attack	Age, current smoking, physical activity, alcoholic drinks/week, BMI, overall health status, use of statins, diuretics, ACEI and hormone therapy, assignment time dependent covariates, race or ethnicity, education, previous PTCA, previous CABG, sign of HF, and >1 previous MI, using baseline covariates;	Adequate

Table 1 (continued)

Study and publication year	Country	Population characteristics*	Sample size of cohorts (% women)	Average age (range or SD)	Years of follow-up in all participants (% followed up to or died before stated time point)	Prevalence of pre-diabetes	Baseline pre-diabetes category and definition	Endpoint assessed during follow-up	Adjustment variables	Adjustment for confounders†
Kokubo 2010 <sup>27</sup>	Japan	General, excluded history of CVD (might include non-fasting glucose $\geq$ 200 mg/dL)	5321 (53%)	55 (30-79)	11.7 (100%)	28%	IFG 100	All stroke	Age, sex, BMI, hypertension, hyperlipidaemia, and smoking and drinking status	Not adequate
Lezen 2006 <sup>28</sup>	Europe	CAD (excluded all diabetes)	4676 (70%)	65 (11)	1 (not reported)	24%	IFG 110, IGT	All stroke	Age, sex, history of MI, HF, PVD, stroke, hyperlipidaemia, diagnosis at admission, and treatment with anti-thrombotic drugs, lipid lowering drugs, and $\beta$ blockers	Not adequate
Liu 2007 <sup>29</sup>	China	General, excluded history of CVD (might include non-fasting glucose $\geq$ 200 mg/dL)	30 378 (47%)	47 (35-64)	10 (94%)	21%	IFG 100	Ischaemic and haemorrhagic stroke separately	Age, sex, smoking, CVD family history, and elevated total cholesterol	Not adequate
Oizumi 2008 <sup>30</sup>	Japan	General, excluded history of stroke	2938 (56%)	57 (> 35)	9.7 (not reported)	15%	IGT	All stroke	Age, sex, hypertension	Not adequate
Sung 2009 <sup>31</sup>	Korea	General, men (might include non-fasting glucose $\geq$ 200 mg/dL)	652 901 (0%)	43 (30-64)	8.8 (not reported)	13%	IFG 100, IFG 110	All stroke	Age, height, smoking, alcohol consumption, regular exercise, level of monthly salary, area of residence, BP, total cholesterol, BMI	Adequate
Tanne 2004 <sup>32</sup>	Israel	CAD (might include non-fasting glucose $\geq$ 200 mg/dL)	13 999 (34%)	60 (45-74)	7 (not reported)	30%	IFG 100, IFG 110	Ischaemic stroke and TIA	Age, sex, BMI, hypertension, triglycerides, % HDL, and use of antiplatelets or antihypertensives.	Adequate
Vermeer 2006 <sup>33</sup>	Netherlands	TIA or minor stroke (might include fasting glucose $\geq$ 126 mg/dL)	3127 (35%)	65 (10)	2.6 (not reported)	5%	IGT	All stroke	Age, sex, smoking, hypertension, and minor ischaemic stroke in history	Not adequate
Yeboah 2011 <sup>34</sup>	USA	General, excluded history of CVD (might include non-fasting glucose $\geq$ 200 mg/dL)	6753 (47%)	62 (45-84)	7.5 (not reported)	14%	IFG 100	All stroke	Age, sex, race/ethnicity, SBP, BMI, cigarette smoking, total cholesterol, HDL-cholesterol, triglycerides, blood pressure drug use, and statin use	Adequate

Table 1 (continued)

Study and publication year	Country	Population characteristics*	Sample size of cohorts (% women)	Average age (range or SD)	Years of follow-up in all participants (% followed up to or died before stated time point)	Prevalence of pre-diabetes	Baseline pre-diabetes category and definition	Endpoint assessed during follow-up	Adjustment variables	Adjustment for confounders†
Zhang 2008 <sup>35</sup>	USA	American Indians, excluded history of stroke (excluded all diabetes)	4507 (56%)	60 (45-74)	13.4 (99.8%)	NA	IFG 110 or IGT	All stroke	Age, sex, SBP, DBP, BMI, waist circumference, LDL and HDL cholesterol, triglycerides, physical activity, smoking, alcohol use, microalbuminuria, and macroalbuminuria	Adequate

ACEI=angiotensin converting enzyme inhibitor; BP=blood pressure; BMI=body mass index; CABG=coronary artery bypass graft; CAD=coronary artery disease; CVD=cardiovascular disease; DBP=diastolic blood pressure; ECG=electrocardiogram; HDL=high density lipoprotein; HF=heart failure; IFG 100=impaired fasting glucose (fasting glucose 100-125 mg/dL); IFG 110=impaired fasting glucose (fasting glucose 110-125 mg/dL); IGT=impaired glucose tolerance (post-challenge glucose 140-199 mg/dL); MAP=mean arterial pressure; MI=myocardial infarction; NA=not available; PTCA=percutaneous transluminal coronary angiography; PVD=peripheral vascular disease; SBP=systolic blood pressure; SSF=subscapular skinfold thickness; TIA=transient ischaemic attack; TSF=triceps skinfold thickness.

\*Including whether patients with diabetes may have been included because only fasting or non-fasting glucose was measured.

†Adequate adjustment denoted adjustment of at least six of seven factors: age, sex, hypertension or systolic blood pressure or antihypertensive drug, body mass index or other measure of overweight/obesity, physical activity, cholesterol concentration or statin use, and smoking.



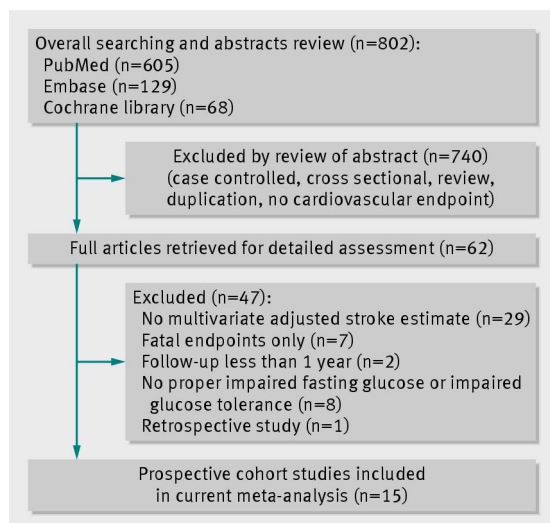
Table 2| Subgroup analyses

Subgroups	Fasting glucose 100-125 mg/dL			Fasting glucose 110-125 mg/dL			IGT or combination of IFG/IGT		
	No of studies	RR (95% CI)	P value*	No of studies	RR (95% CI)	P value*	No of studies	RR (95% CI)	P value*
Population:			0.63			0.59			0.01
Without CVD history at entry	5	1.05 (0.91 to 1.21)		3	1.15 (0.99 to 1.33)		6	1.18 (1.06 to 1.31)	
With CVD history at entry	3	1.17 (0.77 to 1.76)		2	1.36 (0.75 to 2.47)		2	1.77 (1.30 to 2.40)	
Ethnicity:			0.92			0.60			0.98
Asians	4	1.07 (0.93 to 1.24)		2	1.08 (0.77 to 1.52)		4	1.24 (0.99 to 1.55)	
Non-Asians	4	1.09 (0.77 to 1.55)		3	1.21 (0.94 to 1.55)		4	1.23 (1.06 to 1.44)	
Sex:			0.21			0.44			0.09
Male	3	0.91 (0.67 to 1.24)		1	0.94 (0.57 to 1.55)		2	0.95 (0.72 to 1.27)	
Female	3	1.09 (0.79 to 1.49)		1	1.22 (0.78 to 1.90)		2	1.16 (0.86 to 1.56)	
Both	4	1.25 (1.04 to 1.51)		2	1.45 (0.94 to 2.24)		6	1.37 (1.16 to 1.62)	
Mean age at entry:			0.02			—			0.007
<65 years	7	1.12 (0.98 to 1.28)		5	1.21 (1.02 to 1.44)		5	1.15 (1.03 to 1.29)	
≥65 years	1	0.82 (0.65 to 1.03)		0	—		3	1.65 (1.30 to 2.08)	
Possibility of enrolling patients with diabetes:			0.47			0.58			0.05
None enrolled	1	0.91 (0.50 to 1.63)		2	1.11 (0.77 to 1.61)		7	1.20 (1.07 to 1.35)	
Might be enrolled	7	1.13 (0.99 to 1.29)		3	1.27 (0.95 to 1.72)		1	1.80 (1.23 to 2.63)	
Adjustment for confounders:			0.25			—			0.001
Adequate	6	1.04 (0.87 to 1.25)		5	1.21 (1.02 to 1.44)		4	1.11 (0.99 to 1.25)	
Inadequate	2	1.19 (1.05 to 1.36)		0	—		4	1.60 (1.32 to 1.93)	

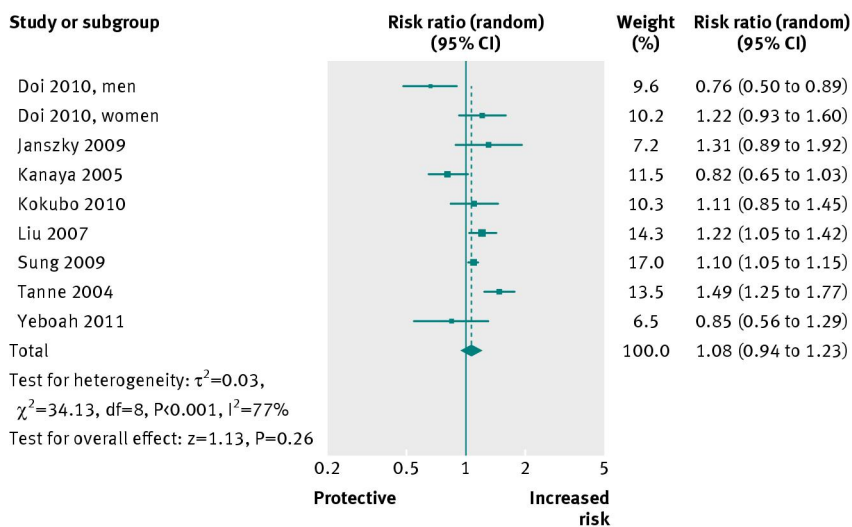
CVD=cardiovascular disease; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; RR=relative risk.

\*For heterogeneity among subgroups.

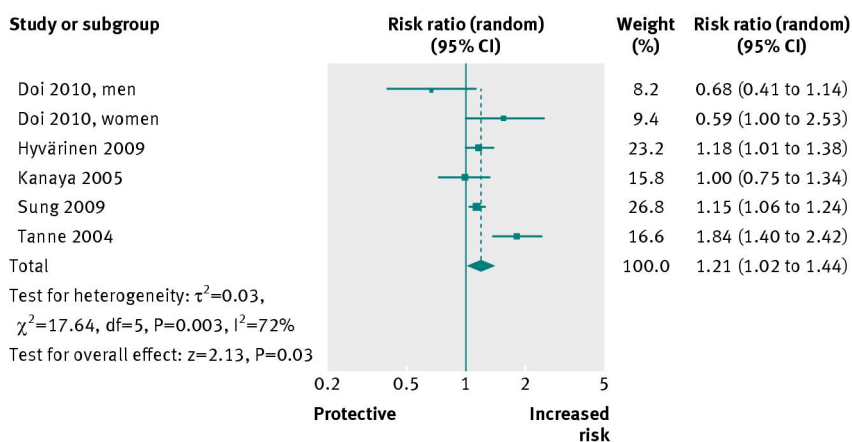
## Figures



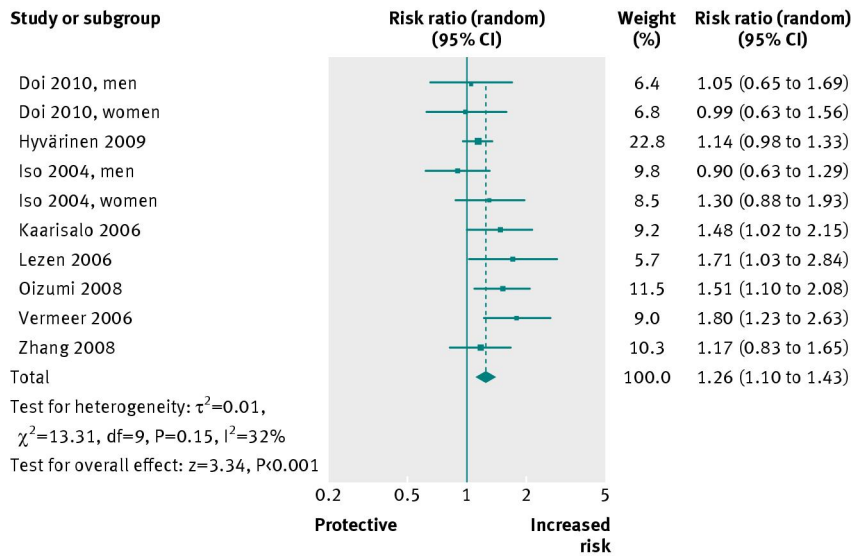
**Fig 1** Study selection



**Fig 2** Baseline fasting glucose 100-125 mg/dL versus risk of stroke



**Fig 3** Baseline fasting glucose 110-125 mg/dL versus risk of stroke



**Fig 4** Baseline impaired glucose tolerance (IGT) or combination of IGT and impaired fasting glucose versus risk of stroke

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