



# Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2016;355:i5953  
<http://dx.doi.org/10.1136/bmj.i5953>

Accepted: 21 October 2016

## ABSTRACT

### OBJECTIVES

To evaluate associations between different definitions of prediabetes and the risk of cardiovascular disease and all cause mortality.

### DESIGN

Meta-analysis of prospective cohort studies.

### DATA SOURCES

Electronic databases (PubMed, Embase, and Google Scholar).

### SELECTION CRITERIA

Prospective cohort studies from general populations were included for meta-analysis if they reported adjusted relative risks with 95% confidence intervals for associations between the risk of composite cardiovascular disease, coronary heart disease, stroke, all cause mortality, and prediabetes.

### REVIEW METHODS

Two authors independently reviewed and selected eligible studies, based on predetermined selection criteria. Prediabetes was defined as impaired fasting glucose according to the criteria of the American Diabetes Association (IFG-ADA; fasting glucose 5.6-6.9 mmol/L), the WHO expert group (IFG-WHO; fasting glucose 6.1-6.9 mmol/L), impaired glucose tolerance (2 hour plasma glucose concentration 7.8-11.0 mmol/L during an oral glucose tolerance test), or raised haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) of 39-47 mmol/mol (5.7-6.4%) according to ADA criteria or 42-47 mmol/mol (6.0-6.4%) according to the National Institute for Health and Care Excellence (NICE) guideline. The relative risks of all cause mortality and cardiovascular events were calculated and reported with 95% confidence intervals.

## RESULTS

53 prospective cohort studies with 1 611 339 individuals were included for analysis. The median follow-up duration was 9.5 years. Compared with normoglycaemia, prediabetes (impaired glucose tolerance or impaired fasting glucose according to IFG-ADA or IFG-WHO criteria) was associated with an increased risk of composite cardiovascular disease (relative risk 1.13, 1.26, and 1.30 for IFG-ADA, IFG-WHO, and impaired glucose tolerance, respectively), coronary heart disease (1.10, 1.18, and 1.20, respectively), stroke (1.06, 1.17, and 1.20, respectively), and all cause mortality (1.13, 1.13 and 1.32, respectively). Increases in HbA<sub>1c</sub> to 39-47 mmol/mol or 42-47 mmol/mol were both associated with an increased risk of composite cardiovascular disease (1.21 and 1.25, respectively) and coronary heart disease (1.15 and 1.28, respectively), but not with an increased risk of stroke and all cause mortality.

## CONCLUSIONS

Prediabetes, defined as impaired glucose tolerance, impaired fasting glucose, or raised HbA<sub>1c</sub>, was associated with an increased risk of cardiovascular disease. The health risk might be increased in people with a fasting glucose concentration as low as 5.6 mmol/L or HbA<sub>1c</sub> of 39 mmol/mol.

## Introduction

Prediabetes is defined as an intermediate metabolic state between normoglycaemia and diabetes and includes those with impaired glucose tolerance and impaired fasting glucose.<sup>1</sup> Although impaired glucose tolerance is consistently defined as a 2 hour plasma glucose concentration of 7.8-11.0 mmol/L during an oral glucose tolerance test, the cut-off point for diagnosis of impaired fasting glucose remains controversial. The World Health Organization (WHO) defines impaired plasma glucose as fasting plasma glucose of 6.1-6.9 mmol/L,<sup>2</sup> while the 2003 American Diabetes Association (ADA) guideline recommended a cut-off point of 5.6-6.9 mmol/L.<sup>3</sup> The ADA's proposal for defining impaired fasting glucose is contentious and has not been adopted by other international guidelines for diabetes management.<sup>4,5</sup> Some researchers opposed to the change believe that it greatly increases the prevalence of what is classified as impaired fasting glucose without any clear association with clinical complications,<sup>6,7</sup> especially for cardiovascular disease and all cause mortality. Although some prospective studies have shown that the 2003 ADA category of impaired fasting glucose with the lower cut-off point is associated with an increased risk of

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Prediabetes, including impaired fasting glucose, impaired glucose tolerance, and mildly raised haemoglobin A<sub>1c</sub>, is a common worldwide condition

The cut points for impaired fasting glucose and haemoglobin A<sub>1c</sub> for defining prediabetes are inconsistent in different guidelines

Reports on the association between prediabetes and all cause mortality and cardiovascular events are inconsistent

## WHAT THIS STUDY ADDS

Prediabetes defined as impaired glucose tolerance or impaired fasting glucose was associated with an increased risk of cardiovascular disease and all cause mortality

The risk increased in people with a fasting glucose concentration as low as 5.55 mmol/L HbA<sub>1c</sub> 39-47 mmol/mol or 42-47 mmol/mol was associated with an increased risk of composite cardiovascular disease and coronary heart disease

Lifestyle modification is the main management for people with prediabetes

cardiovascular disease,<sup>8,9</sup> other studies have not found a similar association.<sup>10-12</sup> Several previous meta-analyses have led to conflicting conclusions,<sup>13-15</sup> which might be because of differences in endpoint assessments and inclusion criteria. Furthermore, the ADA also suggested haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) of 39-47 mmol/mol (5.7-6.4%) could be used as another marker to define prediabetes, while the National Institute for Health and Care Excellence (NICE)<sup>16</sup> and the International Expert Committee<sup>17</sup> suggested using a higher cut point of 42-47 mmol/mol (6.0-6.4%) for prediabetes. It is unclear whether the raised HbA<sub>1c</sub> for defining prediabetes is useful for predicting future cardiovascular disease.

Considering these inconsistencies, we performed a meta-analysis of prospective cohort studies from general populations to evaluate associations between different definitions of prediabetes and the risk of composite cardiovascular events, coronary heart disease, stroke, and all cause mortality.

## Methods

### Search strategy and selection criteria

Following recommendations of the Meta-analysis of Observational Studies in Epidemiology group,<sup>18</sup> we searched electronic databases (PubMed, Embase, and Google Scholar) for prospective cohort studies up to 31 July 2016 using a combined MeSH heading and text search strategy with the following terms: “blood glucose”, “hyperglycaemia”, “impaired fasting glucose”, “impaired glucose intolerance”, “prediabetes”, “prediabetic state”, “borderline diabetes”, “higher risk of diabetes”, “high risk of diabetes”, “hemoglobin A<sub>1c</sub>” or “HbA<sub>1c</sub>” and “cardiovascular disease”, “cardiovascular event”, “cardiocerebrovascular disease”, “cerebrovascular disease”, “cerebrovascular disorder”, “cerebrovascular attack”, “stroke”, “cerebral infarction”, “coronary artery disease”, “coronary heart disease”, “ischemic heart disease”, “myocardial infarction”, “mortality”, or “death” and “risk”. We also manually checked reference lists to identify other potential studies and restricted the search to human studies. Appendix 1 shows the detailed methods used for searching all the databases.

Studies were included for analysis if they were prospective cohort studies with blood glucose and other cardiovascular risk factors measured at baseline; all participants were aged ≥18; and they provided adjusted relative risks and 95% confidence intervals for composite cardiovascular events (combination of coronary heart disease, stroke, or other type of cardiovascular disease together), coronary heart disease, stroke, and all cause mortality associated with prediabetes compared with normoglycaemia.

Prediabetes was defined as impaired fasting glucose according to WHO criteria (IFG-WHO: 6.1-6.9 mmol/L)<sup>2</sup> or the ADA definition (IFG-ADA: 5.6-6.9 mmol/L),<sup>3</sup> impaired glucose tolerance (2 hour plasma glucose 7.8-11.0 mmol/L during an oral glucose tolerance test),<sup>2</sup> or raised HbA<sub>1c</sub> according to ADA criteria (HbA<sub>1c</sub>-ADA: 39-47 mmol/mol)<sup>3</sup> or NICE (HbA<sub>1c</sub>-NICE: 42-47 mmol/mol).<sup>16</sup>

We excluded studies if enrolment was dependent on patients having a particular condition (such as a history of cardiovascular disease) or other cardiovascular risk factors (such as hypertension, chronic kidney disease) and risks for associated events were unadjusted. If multiple articles were derived from the same cohort and reported the same associated events, we included only the latest published data for our primary analysis.

As it has been reported that the potential pathological mechanisms and cardiovascular risk factors are different in those with impaired fasting glucose, impaired glucose tolerance, and raised HbA<sub>1c</sub>,<sup>19,20</sup> we further excluded studies if they reported only data associated with combined impaired fasting glucose or impaired glucose tolerance or combined with either impaired fasting glucose or raised HbA<sub>1c</sub>, but not isolated impaired fasting glucose, impaired glucose tolerance, and HbA<sub>1c</sub> categories. Because the rate of progression to diabetes is higher in people who have both impaired fasting glucose and impaired glucose tolerance,<sup>21</sup> however, we included people with both as a separate category for analysis to explore whether they are at higher risk of cardiovascular disease than those with isolated impaired fasting glucose or isolated impaired glucose tolerance.

### Patient involvement

Patients were not involved in setting the research question, in the outcome measures, in the design, or in the implementation of the study. No patients were asked to advice on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

### Data extraction and quality assessment

Two reviewers (YulH and XC) independently screened the titles and abstracts of the reports, and full copies of potentially suitable studies were obtained. Study information such as ethnicity, participant number, age, sex, follow-up duration, adjusted risk factors, and events assessment was recorded on pretested standard forms.

We used Newcastle-Ottawa quality assessment scale for quality assessment of cohort studies,<sup>22</sup> in which a study is judged based on selection (four items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each). In this meta-analysis we graded quality as good (≥7 stars), fair (4-6 stars), and poor (<4 stars).<sup>23,24</sup> We also evaluated whether the studies had adequately adjusted for potential confounders (at least five of six confounders including sex, age, hypertension or blood pressure or antihypertensive treatment, body mass index (BMI) or other measure of overweight/obesity, cholesterol, and smoking).

### Statistical analysis

Primary outcomes were relative risks for composite cardiovascular events and all cause mortality. Secondary outcomes were relative risks for coronary heart disease and stroke in individuals by using different definitions of prediabetes compared with normoglycaemia.

Subgroup analyses of primary outcomes were conducted according to sex (men *v* women), ethnicity (Asian *v* non-Asian), age (average <55 *v* ≥55), possibility of enrolling patients with diabetes (yes *v* no), duration of follow-up (<10 *v* ≥10 years), exclusion of individuals with baseline cardiovascular disease (yes *v* no), and study quality (adequate adjustment *v* inadequate adjustment). For composite cardiovascular events, we also performed subgroup analysis according to endpoint (incidence *v* mortality). We used  $\chi^2$  to test for subgroup differences—that is, whether the observed differences in the subgroups are compatible with chance alone. A low P value (or a large  $\chi^2$  statistic relative to its degree of freedom) provides evidence of heterogeneity beyond chance.<sup>25</sup>

For meta-analysis we used data on the adjusted outcome in every included study. We logarithmically transformed these data and calculated corresponding standard errors. An inverse variance approach was used to combine the log relative risk and SE. In cases where the odds ratio was described, we converted data to a relative risk for meta-analysis ( $RR=OR/([1-pRef]+[pRef \times OR])$ , where pRef is the prevalence of the outcome in the reference group.<sup>26</sup>

Heterogeneity among studies was assessed with the Q statistic.  $P_{Q\text{ statistic}} \geq 0.10$  was considered to indicate no significant heterogeneity among the included studies. Even when a lack of heterogeneity was indicated, however, we report the results from the DerSimonian and Laird random effects models over the fixed effects model because the included studies differed to some extent, both clinically and methodologically (for example, baseline characteristics of the participants, follow-up duration, and adjustment of confounders). If no heterogeneity exists in the pooled data, results of random and fixed effects models are the same, and if signif-

icant heterogeneity is present, a random effects model is more conservative.<sup>27</sup> To further confirm the results, we have presented the results with both fixed/random effects models in the forest plots.

We evaluated publication bias by inspecting funnel plots for each outcome in which the natural log relative risk was plotted against the SE and further tested with Egger's and Begg's tests. To assess the effect of individual studies on the estimated relative risk, we conducted a sensitivity analysis in which we recalculated the pooled relative risk by omitting one study at a time. Analyses were performed with RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and Stata 12.0 (StataCorp LP, College Station, TX).

## Results

### Studies retrieved and characteristics

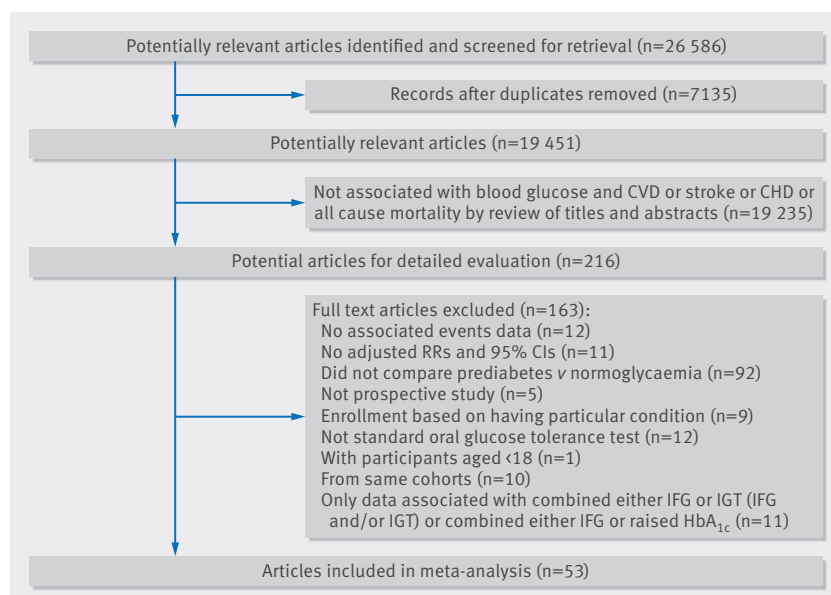
Our initial search returned 26 568 articles. After we screened titles and abstracts, 216 articles qualified for a full review (fig 1). We finally included 53 prospective cohort studies,<sup>8-12 28-75</sup> comprising 1 611 339 individuals for analysis. For the association between prediabetes and risk of all cause mortality, composite cardiovascular disease, coronary heart disease, and stroke, 25, 35, 24, and 18 studies, respectively, provided data.

Table A in appendix 2 provides the key characteristics of the included studies. All were derived from the general population. Nine studies enrolled only men, and all others included both men and women. The duration of follow-up ranged from two to 20 years, with a median duration of 9.5 years. According to quality assessment criteria, 45 studies were graded as good quality and eight as fair (table B in appendix 2). Furthermore, based on adjusted confounders, 33 studies met our criteria for adequate adjustment, while 20 studies did not adequately adjust for potential confounders (table C in appendix 2).

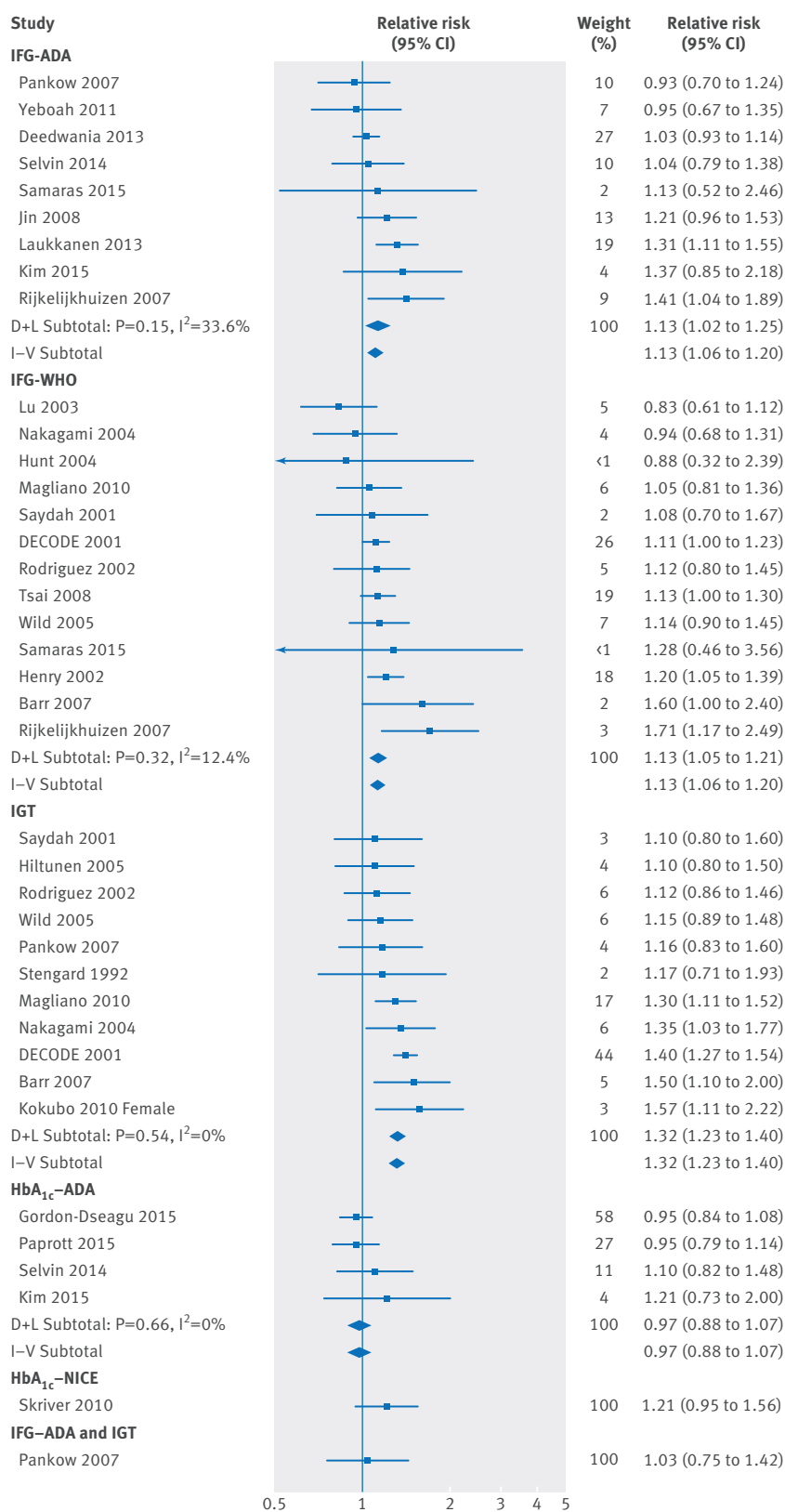
All studies excluded people with fasting plasma glucose concentration ≥7.0 mmol/L, except for one that only measured 2 hour plasma glucose concentration during an oral glucose tolerance test at baseline,<sup>28</sup> with the possibility that a few patients with fasting plasma glucose ≥7.0 mmol/L were enrolled in the impaired glucose tolerance groups. Twenty eight studies measured fasting plasma glucose only at baseline without an oral glucose tolerance test; these studies therefore possibly enrolled patients with 2 hour plasma glucose ≥11.1 mmol/L.

### Prediabetes and all cause mortality

Twenty five studies reported data for the association between prediabetes and risk of all cause mortality. Random effects models analyses show that prediabetes was associated with an increased risk of all cause mortality: IFG-ADA (relative risk 1.13, 95% confidence interval 1.02 to 1.25), IFG-WHO (1.13, 1.05 to 1.21), impaired glucose tolerance (1.32, 1.23 to 1.40). Prediabetes was not associated with an increased risk of all cause mortality when it was defined as HbA<sub>1c</sub> 39-47 mmol/mol (0.97, 0.88 to 1.07) or HbA<sub>1c</sub> 42-47 mmol/mol (1.21, 0.95 to 1.56) (fig 2). Data from a single



**Fig 1** | Flow of papers through review of prediabetes and risk of cardiovascular disease and all cause mortality. CVD=cardiovascular disease, CHD=coronary heart disease, IFG=impaired fasting glucose, IGT=impaired glucose tolerance



**Fig 2 | Association between prediabetes and risk of all cause mortality.** D+L=DerSimonian and Laird random effects models; HbA<sub>1c</sub>-ADA=prediabetes defined as raised HbA<sub>1c</sub> according to American Diabetes Association (ADA) criteria (39-47 mmol/mol); HbA<sub>1c</sub>-NICE=prediabetes defined as raised HbA<sub>1c</sub> according to NICE guidance (42-47 mmol/mol); IFG-ADA=impaired fasting glucose (IFG) according to ADA criteria (fasting plasma glucose of 5.6-6.9 mmol/L); IFG-WHO=IFG according to WHO criteria (6.1-6.9 mmol/L); IGT=impaired glucose tolerance; I-V=inverse variance fixed effects models

study showed that prediabetes defined as IFG-ADA and impaired glucose tolerance was not associated with increased risk of all cause mortality (1.03, 0.75 to 1.42).<sup>48</sup> No studies reported the risk of all cause mortality in patients with both IFG-WHO and impaired glucose tolerance. The increased risk of all cause mortality was significantly higher in the impaired glucose tolerance group than in groups according to other definitions of prediabetes ( $P<0.001$ ).

### Prediabetes and composite cardiovascular events

Thirty five studies reported data for the association between prediabetes and risk of composite cardiovascular disease. Table D in appendix 2 provides detailed definitions of composite cardiovascular disease in every included study. Random effects models analyses showed that prediabetes was associated with increased composite cardiovascular events when it was defined as IFG-ADA (relative risk 1.13, 95% confidence interval 1.05 to 1.21), IFG-WHO (1.26, 1.12 to 1.41), impaired glucose tolerance (1.30, 1.19 to 1.42), HbA<sub>1c</sub> 38.8-46.4 mmol/mol (1.21, 1.01 to 1.44), or HbA<sub>1c</sub> 42.11-46.4 mmol/mol (1.25, 1.01 to 1.55) (fig 3). The difference in risk of cardiovascular disease with different definitions of prediabetes was not significant ( $P=0.16$ ). No studies reported the risk of composite cardiovascular events in patients with both impaired plasma glucose (either IFG-ADA or IFG-WHO) and impaired glucose tolerance.

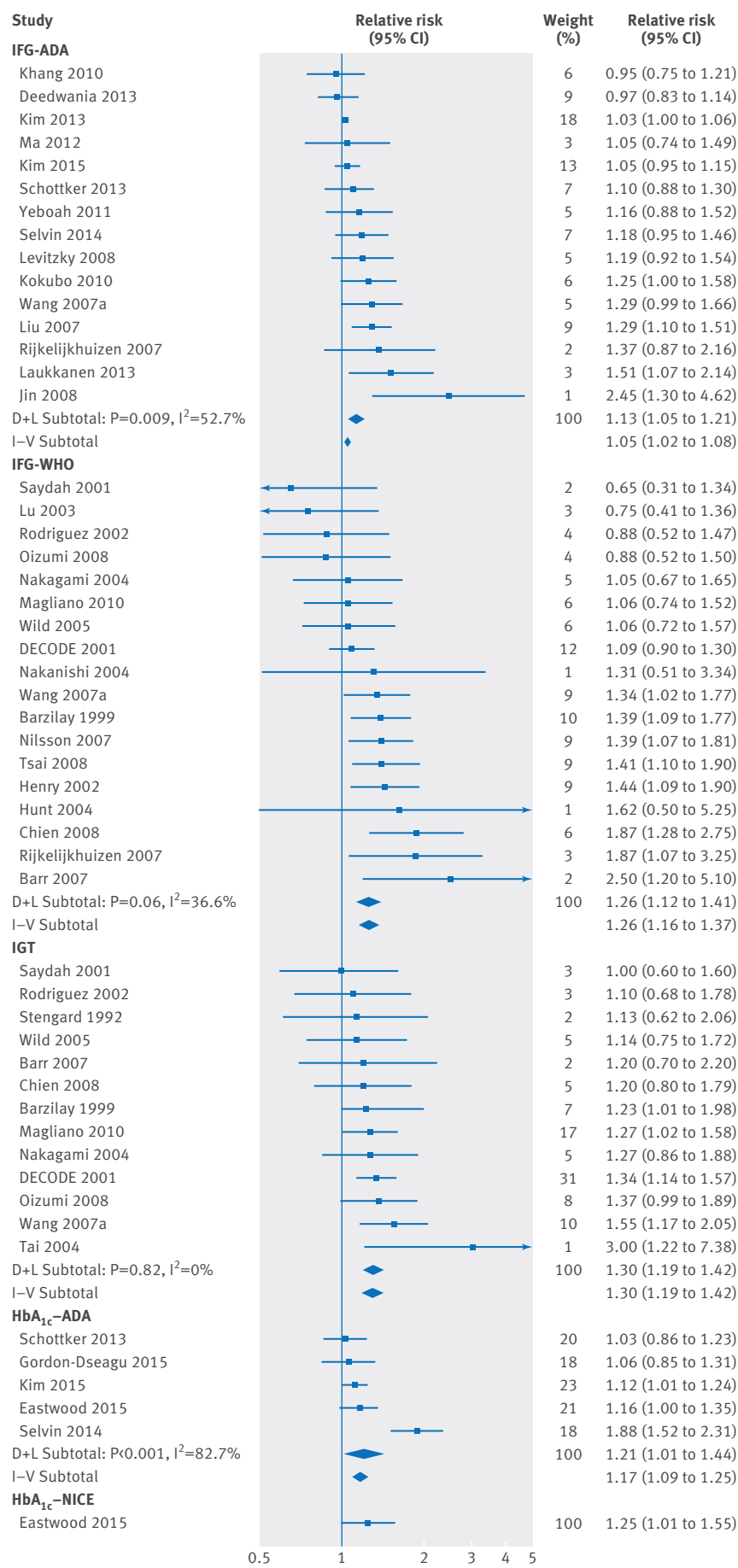
### Prediabetes and risk of coronary heart disease

Twenty four studies reported data for the association between prediabetes and risk of coronary heart disease. Similar to results for composite cardiovascular events, prediabetes was associated with increased risk of coronary heart disease when it was defined as IFG-ADA (relative risk 1.10, 95% confidence interval 1.04 to 1.16), IFG-WHO (1.18, 1.08 to 1.28), impaired glucose tolerance (1.20, 1.0 to 1.44), HbA<sub>1c</sub> 39-47 mmol/mol (1.15, 1.01 to 1.33), or HbA<sub>1c</sub> 42-47 mmol/mol (1.28, 1.03 to 1.59) (fig 4). Combined data from two studies, however, did not show an increased risk of coronary heart disease in people with both IFG-ADA and impaired glucose tolerance (0.93, 0.70 to 1.25). No studies reported the risk of coronary heart disease in people with both IFG-WHO and impaired glucose tolerance. There was no significant difference in risk of coronary heart disease with different definition of prediabetes ( $P=0.36$ ).

### Prediabetes and risk of stroke

Eighteen studies reported data for the association between prediabetes and risk of stroke. Combined data showed that IFG-ADA (relative risk 1.06, 95% confidence interval 1.01 to 1.11), IFG-WHO (1.17, 1.09 to 1.25), or impaired glucose tolerance (1.20, 1.0 to 1.45) were associated with an increased risk of stroke after multivariate adjustment. The risk of stroke, however, was not significant in studies that defined prediabetes as raised HbA<sub>1c</sub>, either according to the ADA (1.05, 0.81 to 1.35) or NICE recommendation (1.33, 0.89 to 1.99) (fig 5). No studies reported data the risk of stroke with prediabetes defined as combined impaired fasting glucose (either





**Fig 3 | Association between prediabetes and composite cardiovascular events.** D+L=DerSimonian and Laird random effects models; HbA<sub>1c</sub>-ADA=prediabetes defined as raised HbA<sub>1c</sub> according to American Diabetes Association (ADA) criteria (39-47 mmol/mol); HbA<sub>1c</sub>-NICE=prediabetes defined as raised HbA<sub>1c</sub> according to NICE guidance (42-47 mmol/mol); IFG-ADA=impaired fasting glucose (IFG) according to ADA criteria (fasting plasma glucose of 5.6-6.9 mmol/L); IFG-WHO=IFG according to WHO criteria (6.1-6.9 mmol/L); IGT=impaired glucose tolerance; I-V=inverse variance fixed effects models

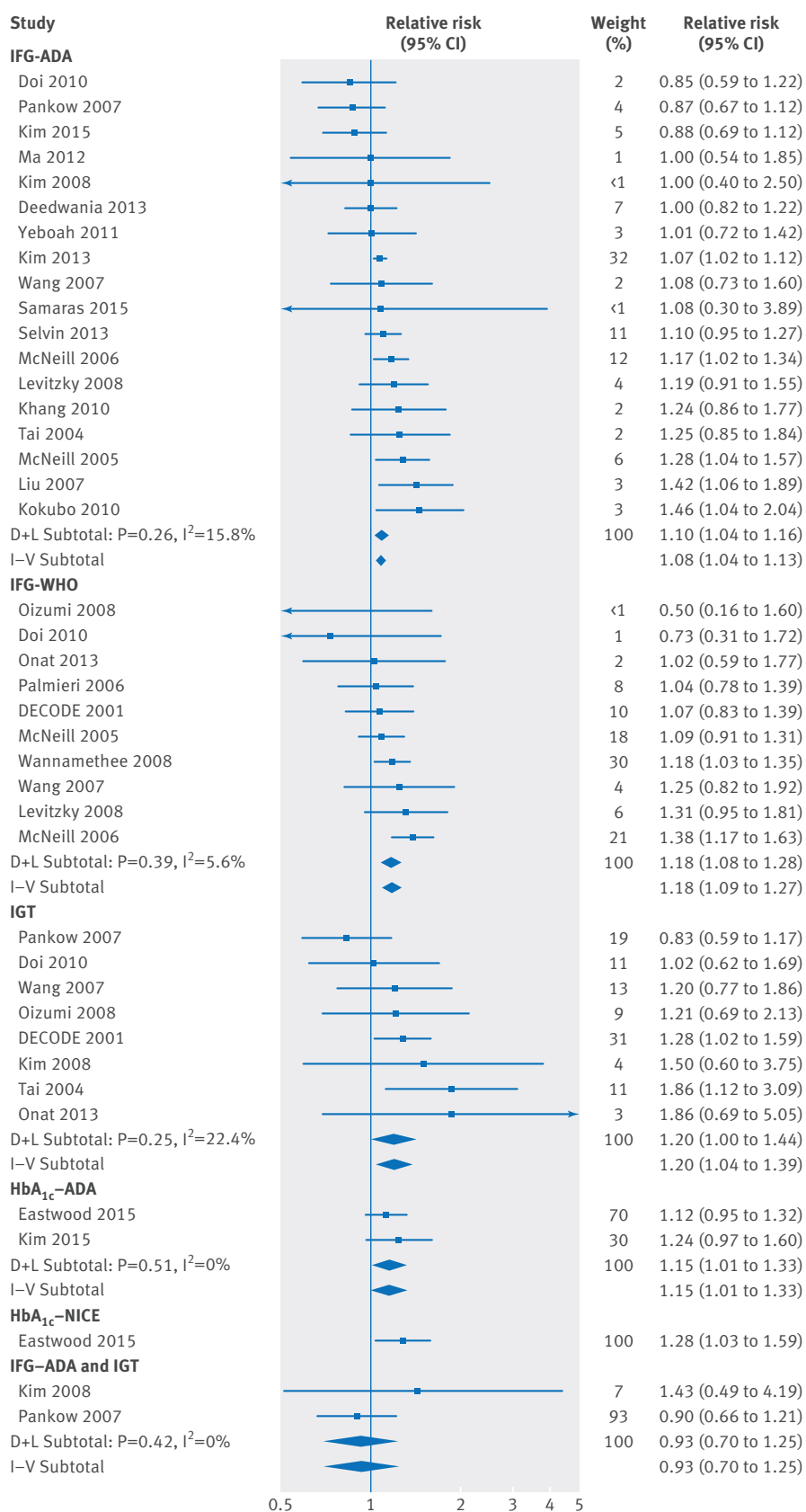


Fig 4 | Association between prediabetes and risk of coronary heart disease. D+L=DerSimonian and Laird random effects models; HbA<sub>1c</sub>-ADA=prediabetes defined as raised HbA<sub>1c</sub> according to American Diabetes Association (ADA) criteria (39-47 mmol/mol); HbA<sub>1c</sub>-NICE=prediabetes defined as raised HbA<sub>1c</sub> according to NICE guidance (42-47 mmol/mol); IFG-ADA=impaired fasting glucose (IFG) according to ADA criteria (fasting plasma glucose of 5.6-6.9 mmol/L); IFG-WHO=IFG according to WHO criteria (6.1-6.9 mmol/L); IGT=impaired glucose tolerance; I-V=inverse variance fixed effects models

IFG-ADA or IFG-WHO) and impaired glucose tolerance. There was no significant difference for increased risk of stroke in different definition of prediabetes ( $P=0.64$ ).

### Sensitivity analyses and subgroup analyses

We found no evidence of publication bias based on visual inspection of funnel plots (appendix 3) or according to Begg's or Egger's tests (all  $P>0.1$ ). Sensitivity analyses confirmed that the association between endpoint events and the different definitions of prediabetes did not change with the use of random effects models or fixed effects models for the meta-analysis. Furthermore, considering smoking is the strongest confounder for cardiovascular disease, we further performed a sensitivity analysis on primary outcomes with data with adjustment for smoking. We found that after controlling for smoking, the presence of prediabetes remained

associated with an increased risk of composite cardiovascular disease when it was defined as IFG-ADA, IFG-WHO, impaired glucose tolerance, or  $\text{HbA}_{1c}$  39-47 mmol/mol or 42-47 mmol/mol (fig A in appendix 4). The risk of all cause mortality associated with IFG-ADA was not significant under random effects models analysis (relative risk 1.09, 95% confidence interval 0.97 to 1.22), though it did reach significance when we used fixed effects models (1.08, 1.0 to 1.17). Furthermore, IFG-WHO or impaired glucose tolerance was still associated with an increased risk of all cause mortality after we excluded data from studies that did not adjust for smoking (fig B in appendix 4).

Tables E and F in appendix 2 show the results of subgroup analyses for the risk of all cause mortality and composite cardiovascular events associated with prediabetes defined as IFG-ADA, IFG-WHO, or impaired glucose tolerance. Briefly, we found no significant heterogeneity among all subgroup comparisons for prediabetes defined as IFG-WHO or impaired glucose tolerance (all  $P\geq 0.05$ ). IFG-ADA, however, was significantly associated with all cause mortality in participants with a mean age  $<55$  at study entry, but not in those aged  $\geq 55$  ( $P=0.009$  for interaction). This was the only significant heterogeneity we observed among all subgroup comparisons in our study. We did not perform subgroup analyses for participants with other definitions of prediabetes because of the limited number of studies.

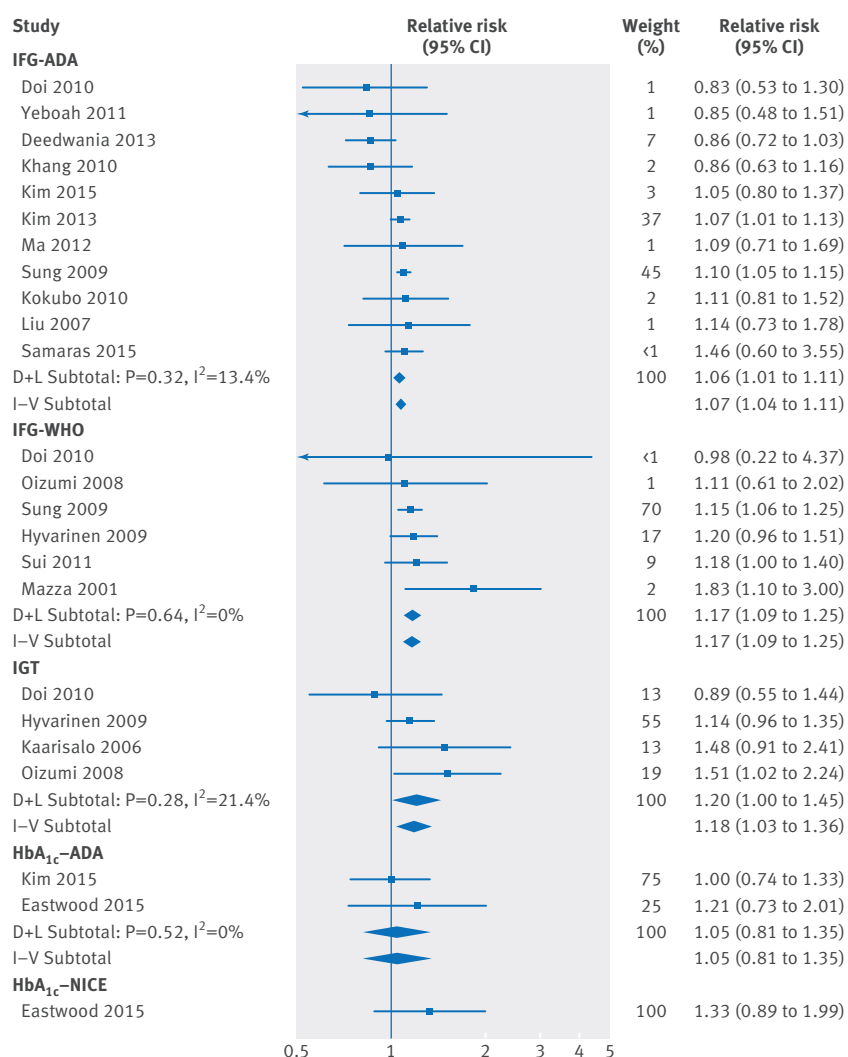
### Discussion

#### Principal findings

In this meta-analysis with a large sample size (comprising 1611339 individuals), we found that prediabetes defined as impaired fasting glucose or impaired glucose tolerance was associated with an increased risk of composite cardiovascular events, coronary heart disease, stroke, and all cause mortality. Importantly, we observed increased risks when fasting plasma glucose was as low as 5.6 mmol/L according to the current ADA definition of impaired fasting glucose (IFG-ADA).<sup>3</sup> We also found that the risks for composite cardiovascular events and coronary heart disease were higher in people with prediabetes defined as raised  $\text{HbA}_{1c}$  of 39-47 mmol/mol (according to ADA criteria)<sup>3</sup> or 42-47 mmol/mol (according to NICE),<sup>16</sup> respectively.

#### Strengths and limitations of study

An important strength of our study is the large sample size. We included only prospective cohort studies with adjusted relative risks from general populations. There were, however, some limitations. Firstly, though individuals with prediabetes are more likely to progress to diabetes than those with normoglycaemia, most of the included studies did not adjust for the future development of diabetes during the follow-up period. Therefore, it is still unclear whether the long term health risk associated with prediabetes is because of a mild increase of blood glucose concentration or because of future progression to diabetes. Nevertheless, the results indicate that, on the basis of a "snapshot" measurement



**Fig 5 | Association between prediabetes and risk of stroke.** D+L=DerSimonian and Laird random effects models;  $\text{HbA}_{1c}$ -ADA=prediabetes defined as raised  $\text{HbA}_{1c}$  according to American Diabetes Association (ADA) criteria (39-47 mmol/mol);  $\text{HbA}_{1c}$ -NICE=prediabetes defined as raised  $\text{HbA}_{1c}$  according to NICE guidance (42-47 mmol/mol); IFG-ADA=impaired fasting glucose (IFG) according to ADA criteria (fasting plasma glucose of 5.6-6.9 mmol/L); IFG-WHO=IFG according to WHO criteria (6.1-6.9 mmol/L); IGT=impaired glucose tolerance; I-V=inverse variance fixed effects models

of blood glucose, prediabetes is associated with an increased risk of cardiovascular disease as well as all cause mortality, and early lifestyle interventions should be implemented in these populations. Secondly, almost half of the included studies measured fasting plasma glucose only at baseline, without performing an oral glucose tolerance test; therefore, these studies possibly enrolled patients with increased 2 hour plasma glucose. The risk of cardiovascular events and all cause mortality associated with impaired fasting glucose could be confounded by the undetected increase in 2 hour plasma glucose (diabetes defined by 2 hour plasma glucose). We found no significant heterogeneity, however, in subgroup comparisons conducted according to the possibility of enrolling patients with diabetes. Thirdly, we found that the risk of composite cardiovascular events and coronary heart disease was higher in people with mild raised HbA<sub>1c</sub> (39-47 mmol/mol or 42-47 mmol/mol), though the risk of stroke did not reach significance. These inconsistent results should be interpreted with caution because of the small numbers of studies included in these analyses. More prospective cohort studies that evaluate the level of HbA<sub>1c</sub> and health risk are needed. Fourthly, there were too few studies to draw a solid conclusions for the risk of cardiovascular disease in people with both impaired fasting glucose and impaired glucose tolerance.

#### Comparison with other studies

Several previous meta-analyses have returned inconsistent results on the different definitions of prediabetes and target organ damage. In 2014, our group reported that prediabetes, defined as IFG-WHO, impaired glucose tolerance, but not IFG-ADA, was associated with increased risk of all cause and cardiovascular mortality.<sup>76</sup> Similarly, another published meta-analysis that included 15 prospective cohort studies (including 760 925 participants) reported that the risk of stroke increased in people with IFG-WHO or impaired glucose tolerance but not in people with IFG-ADA.<sup>14</sup> In the past few years, however, an increasing number of studies have reported on the association between health risks and IFG-ADA. We updated our data and found differences with our previous analysis, with the risks for all cause mortality, composite cardiovascular disease, coronary heart disease, and stroke all significantly increased in people with IFG-ADA.

Ford and colleagues included 18 studies with 175 152 participants in their analysis and found that impaired fasting glucose (defined with either ADA or WHO criteria) and impaired glucose tolerance was associated with a modest increased risk of cardiovascular disease.<sup>15</sup> Endpoint events in the studies included in that meta-analysis, however, were significantly different. For example, some had data only for coronary heart disease,<sup>37 44 45</sup> while others reported the risk of composite cardiovascular disease.<sup>8 35 77</sup> It is suggested that combining data with different events in a meta-analysis could produce misleading results. Contrary to the analysis conducted by Ford and colleagues,<sup>15</sup> the large sample size in our study (53 prospective cohort studies

comprising 1 611 339 participants) allowed us to analyse the risk of composite cardiovascular disease, coronary heart disease, and stroke separately. The strict inclusion criteria in our study were important to avoid heterogeneity among studies and lead to a reliable conclusion. Furthermore, Ford and colleagues did not analyse the risk of cardiovascular disease with prediabetes defined with HbA<sub>1c</sub> criteria.<sup>15</sup>

#### Future research

Our findings strongly support the lower cut-off point for impaired fasting glucose proposed by the 2003 ADA guideline, and they have important public health implications. According to the 2003 ADA definition, the prevalence of prediabetes in adults was up to 36.2% in the US<sup>78</sup> and 50.1% in China.<sup>79</sup> Considering the high prevalence of prediabetes, successful intervention in these large populations could have major impacts on public health. The ADA suggests that lifestyle intervention is the fundamental management approach for prediabetes.<sup>80</sup> For people with impaired glucose tolerance, lifestyle interventions can reduce the risk of progression to diabetes.<sup>81</sup> Recently, Yates and colleagues reported that in patients with impaired glucose tolerance, a change in daily ambulatory activity can significantly decrease the risk of cardiovascular events.<sup>82</sup> Similarly, the Da Qing diabetes prevention study also reported that lifestyle intervention in people with impaired glucose tolerance can reduce the incidence of cardiovascular and all cause mortality.<sup>83</sup> It should be noted, however, that all these studies were performed on people with impaired glucose tolerance. There are few data in terms of interventions for prediabetes defined by impaired fasting glucose and HbA<sub>1c</sub>. Considering the different underlying pathophysiological mechanisms<sup>84 85</sup> and associated cardiovascular risk factors<sup>19 20</sup> between impaired fasting glucose, impaired glucose tolerance, and raised HbA<sub>1c</sub>, future studies are urgently needed to explore effective interventions to decrease the risk of cardiovascular disease in people with prediabetes defined as impaired fasting glucose and raised HbA<sub>1c</sub>. Furthermore, it should be noted that prediabetes is not a disease but rather a risk factor for future diabetes and cardiovascular disease, and the findings in our study do not mean that pharmacological treatment is warranted in everyone with prediabetes. Further studies are needed to determine which phenotype of prediabetes can benefit from pharmacological treatment. Nowadays, the ADA recommended pharmacological intervention can be considered in individuals with both impaired glucose tolerance and impaired fasting glucose and at least one of age <60, BMI ≥35, family history of diabetes mellitus in first degree relative, high concentrations of triglycerides, reduced concentration of high density lipoprotein cholesterol, hypertension, and HbA<sub>1c</sub> >42 mmol/mol.<sup>80</sup> Furthermore, pharmacological treatment should be individualised on the basis of the known efficacy and safety of drugs and accompanied by lifestyle intervention programmes.<sup>85</sup>



Interestingly, we found that the risk of all cause mortality was significantly higher in the impaired glucose tolerance group than in groups with other definition of prediabetes. There were, however, no significant differences in risks of cardiovascular disease, coronary heart disease, and stroke with different definitions of prediabetes. These results suggest that impaired glucose tolerance is a stronger risk factor for all cause mortality, but not for cardiovascular disease, than other definitions of prediabetes, which might be caused by the significant association between impaired glucose tolerance and non-cardiovascular death, especially cancer mortality.<sup>76</sup> It has been reported that the risk of cancer mortality is greater with impaired glucose tolerance than with impaired fasting glucose.<sup>46 86</sup>

### Conclusions and implications

In conclusion, we found that prediabetes defined as impaired fasting glucose or impaired glucose tolerance is associated with an increased risk of composite cardiovascular events, coronary heart disease, stroke, and all cause mortality. There was an increased risk in people with fasting plasma glucose as low as 5.6 mmol/L. Additionally, the risk of composite cardiovascular events and coronary heart disease increased in people with raised HbA<sub>1c</sub>. These results support the lower cut-off point for impaired fasting glucose according to ADA criteria as well as the incorporation of HbA<sub>1c</sub> in defining prediabetes. At present, lifestyle modification is the mainstay management for people with prediabetes. High risk subpopulations with prediabetes, especially combined with other cardiovascular risk factors, should be selected for controlled trials of pharmacological treatment.

We thank Jun Lu (Clinical Research Centre, the First Affiliated Hospital of Xi'an Jiaotong University, China) for help in statistical analysis.

**Contributors:** YH and YunH were responsible for the initial plan, study design, conducting the study, data interpretation. YH, XC, and WM were responsible for data collection, data extraction, statistical analysis, and manuscript drafting. YH, XC, and ML analysed and interpreted the data and critically revised the paper. YH and YunH are guarantors and had full access to all of the data, including statistical reports and tables, and take full responsibility for the integrity of the data and the accuracy of the data analysis.

**Funding:** This study was funded by the National Natural Science Foundation of China (No 81600239).

**Competing interests:** All author have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** Not required.

**Data sharing:** No additional data available.

**Transparency:** The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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**Appendix 1:** Literature search strategy for all the databases

**Appendix 2:** Supplementary tables A-F

**Appendix 3:** Supplementary figures A-D (funnel plots for detection for publication bias)

**Appendix 4:** Supplementary forest plots A-B