

## QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

## Cardiovascular Risk

# Pre-Diabetes and the Risk for Cardiovascular Disease

## A Systematic Review of the Evidence

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**Objectives**

Our objective was to estimate the magnitude of the relative risk (RR) for cardiovascular disease associated with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) from published prospective observational studies.

**Background**

Hyperglycemia is a known risk factor for cardiovascular disease. However, the magnitude of the RR for cardiovascular disease associated with IFG and IGT is unclear.

**Methods**

We searched PubMed from 1997 through 2008 for relevant publications and performed a meta-analysis.

**Results**

In 18 publications with information about IFG (110 to 125 mg/dl) (IFG 110), estimates of RR ranged from 0.65 to 2.50. The fixed-effects summary estimate of RR was 1.20 (95% confidence interval [CI]: 1.12 to 1.28). In 8 publications with information about IFG (100 to 125 mg/dl) (IFG 100), estimates of RR ranged from 0.87 to 1.40. The fixed-effects summary estimate of RR was 1.18 (95% CI: 1.09 to 1.28). In 8 publications with information about IGT, estimates of RR ranged from 0.83 to 1.34. The fixed-effects summary estimate of RR was 1.20 (95% CI: 1.07 to 1.34). Five studies combined IFG and IGT, yielding a fixed-effects summary estimate of RR of 1.10 (95% CI: 0.99 to 1.23). No significant difference between the summary estimates for men and women were detected (IFG 110: men: 1.17 [95% CI: 1.05 to 1.31], women: 1.30 [95% CI: 1.10 to 1.54]; IFG 100: men: 1.23 [95% CI: 1.06 to 1.42], women: 1.16 [95% CI: 0.99 to 1.36]).

**Conclusions**

Impaired fasting glucose and IGT are associated with modest increases in the risk for cardiovascular disease. (J Am Coll Cardiol 2010;55:1310–7) © 2010 by the American College of Cardiology Foundation

Hyperglycemia is a well-established risk factor for cardiovascular disease (1–3). Although the shape of the relationship between 2-h post-load concentrations of glucose is linearly related to the risk of cardiovascular disease, the shape of the relationship between fasting concentrations of glucose and the risk of cardiovascular disease might be nonlinear (2,4). Several meta-analyses have shown that diabetes imparts a 2- to 3-fold increase in the risk of developing coronary heart disease (5–8). Furthermore, in 2 of these meta-analyses the summary estimate of relative risk (RR) in women significantly exceeded that in men (5,8). However, it remains unknown whether the risk between pre-diabetes, generally defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), and cardiovascular disease differs according to sex.

Although a continuum of risk extends into and below the pre-diabetic glucose range, the risk associated with IFG and IGT is not well-established. In 1997, the concept of IFG was introduced, and IFG was defined as a plasma glucose concentration of 110 to <126 mg/dl (9). In 2003, IFG was redefined as a plasma glucose concentration of 100 to <126 mg/dl (10). Several revisions of the glucose criteria for defining various categories of dysglycemia by the World Health Organization (WHO) and American Diabetes Association (ADA) necessitate re-examining the risk between pre-diabetes and cardiovascular disease with the most recent definitions of IFG and IGT (9–12). Understanding such risk estimates is important, given the increases in the prevalence of IFG and IGT that have occurred in many populations characterized by increases in the prevalence of obesity, including the U.S. (13). Therefore, the objectives of this study included: 1) performing a quantitative review of prospective studies that reported on the risks of developing cardiovascular disease among study participants with IFG, IGT, or both to estimate the magnitude of the RR for pre-diabetes and cardiovascular disease; and 2) estimating whether the RR between pre-diabetes and cardiovascular disease differed between men and women.

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Manuscript received April 10, 2009; revised manuscript received October 15, 2009, accepted October 26, 2009.

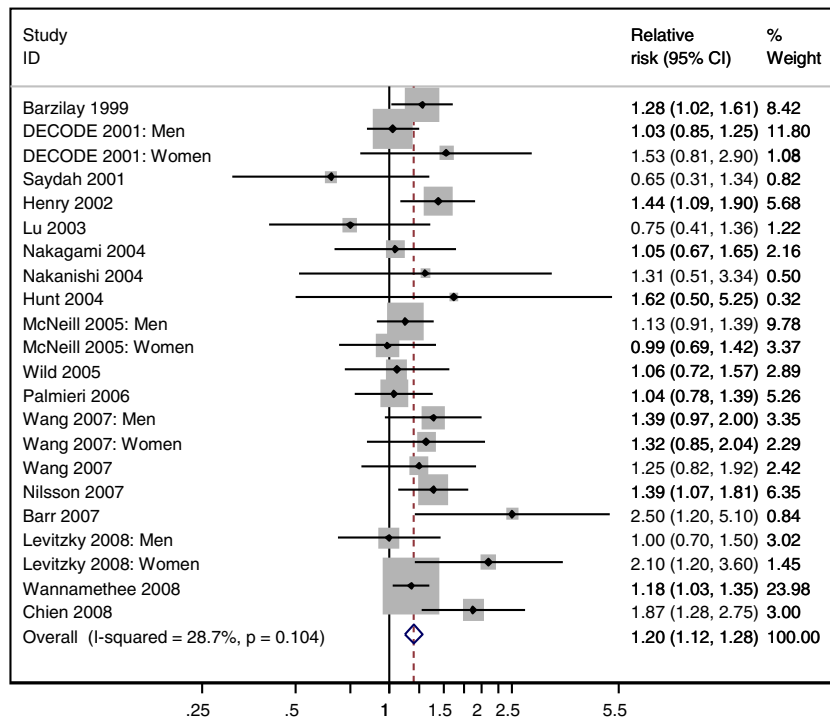
**Methods**

With PubMed, we searched with the terms “impaired fasting glucose’ OR IFG OR ‘impaired glucose tolerance’ OR IGT OR pre-diabetes OR hyperglycemia” as well as “heart OR cardiovascular OR stroke OR cerebrovascular” and “incidence OR incident OR follow-up OR prospective OR longitudinal OR mortality OR death” from 1997 through the end of September 2008. We included prospective observational studies published in English that reported estimated RRs and confidence intervals (CIs) for coronary heart disease or cardiovascular disease and excluded studies that were limited to patients with pre-existing conditions or to patients undergoing medical procedures. Furthermore, classification of IFG or IGT had to be based on 1997 ADA criteria, 2003 ADA criteria, or WHO 1999 criteria (9,10,12). Our search yielded 1,070 citations. After reviewing the abstracts of these publications, we retrieved and reviewed copies of 52. Thirty-two publications did not have relevant information (lack of outcome of interest, no IFG or IGT, duplicate analyses, no estimate of RR or CIs). The remaining 20 publications were augmented with 2 publications that were identified through reviewing bibliographies and 5 publications that were identified after reviewing publications on the metabolic syndrome and cardiovascular disease. Abstracted information included author, year of pub-

lication, study name, study location, numbers of male and female participants, mean age or range, follow-up time, cardiovascular disease end point, number of events, IFG or IGT criteria, estimate of RR and CI, and adjustment variables. Information was abstracted by 2 independent reviewers.

We calculated summary estimates of RR for IFG 110 (6.1 to <7.0 mmol/l or 110 to 125 mg/dl), IFG 100 (5.6 to <7.0 mmol/l or 100 to 125 mg/dl), IGT, and combined IFG 110 and IGT (IFG 110, IGT, or both). Authors defined IGT inconsistently, although all referred to the WHO or ADA criteria. Some used only the 2-h glucose concentration (140 to <200 mg/dl) regardless of fasting concentrations. Others applied the 2-h glucose concentration criteria only to participants with nondiabetic fasting concentrations. All studies that we included in analyses of IGT used a 75-g oral glucose tolerance test (OGTT). Standard errors (SE) for the estimates of RR were estimated from the CIs. For each study,

Abbreviations and Acronyms	
<b>ADA</b>	American Diabetes Association
<b>CI</b>	confidence interval
<b>IFG</b>	impaired fasting glucose
<b>IGT</b>	impaired glucose tolerance
<b>OGTT</b>	oral glucose tolerance test
<b>RR</b>	relative risk
<b>SE</b>	standard error
<b>WHO</b>	World Health Organization



**Figure 1. Measures of Association Between Impaired Fasting Glucose (110 to 125 mg/dl) and Cardiovascular Outcomes**

Moving from left to right, each row of information shows the first author and year of publication, a graphical portrayal of the estimate of relative risk (RR) (represented by the diamond) and confidence interval (CI) (the square box portrays graphically the weight each estimate contributed to the analysis), the estimate of RR and CI, and the weight that each data point contributed to the analysis. The overall summary estimate of RR is shown on the last row of the graph. Impaired fasting glucose of 110 to 125 mg/dl is associated with a small increase in risk for cardiovascular disease. DECODE = Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe.

a weight was calculated as the inverse of the variance ( $1/SE^2$ ). Heterogeneity among studies was assessed with the  $Q$  statistic (14). If no heterogeneity was present ( $p$   $Q$  statistic  $\geq 0.10$ ), fixed-effects estimates of RR were calculated according to the inverse variance method (15). If heterogeneity was present ( $p$   $Q$  statistic  $< 0.10$ ), random-effects estimates of RR were calculated with the approach by DerSimonian and Laird (14). We also considered, in addition to the statistical approach to testing for the presence of heterogeneity, how various study characteristics such as follow-up time might influence the analyses. The influence of single studies on the summary estimates was examined graphically by checking how the elimination of each study affected the resulting summary estimate of RR (16). The Egger's test was used to look for possible publication bias (17). Analyses were conducted in Stata version 10 (StataCorp, College Station, Texas).

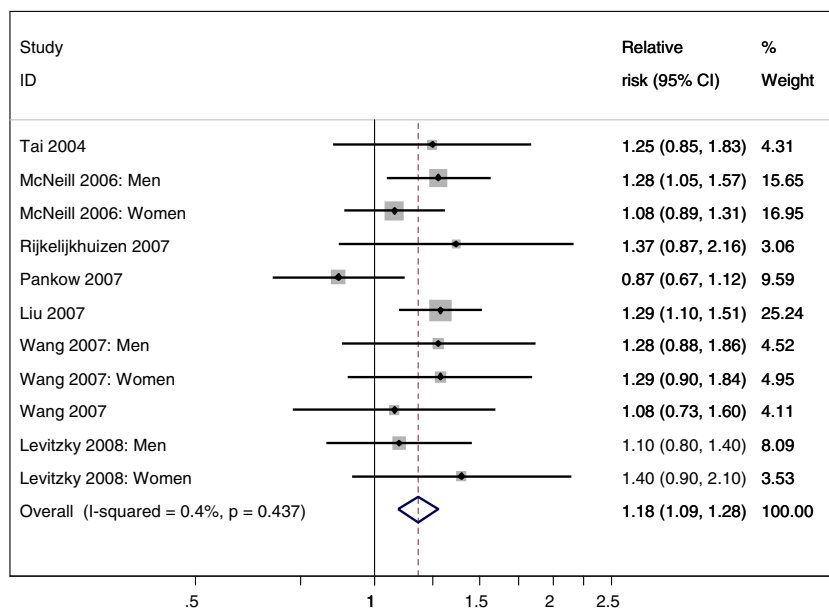
### Results

Selected characteristics of studies that were included in our analyses are shown in the Online Supplement (18–42). Eighteen publications that included 175,152 participants provided estimates of RR associated with IFG 110 (18,19,21,22,25,26,28–30,32,36–43): the DECODE study (Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe) was based on data from 10 European cohorts (19), and the DECODA (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia) study

included data from 5 cohorts (25). Sixteen publications included men and women, and 2 publications included only men. Fourteen publications emanated from Australia, Europe, and the U.S., and 4 publications included Asian participants. Estimates of RR of coronary heart disease or cardiovascular disease ranged from 0.65 (21) to 2.50 (39) (Fig. 1). No significant heterogeneity existed among the studies ( $p = 0.104$ ,  $I^2 = 28.7\%$ ), and the fixed-effects summary estimate of RR was 1.20 (95% CI: 1.12 to 1.28). When we used 2003 DECODE data (23) instead of 2001 DECODE data (19), the fixed-effects summary estimate of RR was 1.19 (95% CI: 1.12 to 1.27).

When we separated the 18 publications into 2 groups—1 that adjusted for age, smoking status, blood pressure, and lipids (18,19,21,25,26,30,40,43); and 1 that did not adjust for all these variables (22,28,29,32,36–39,41,42)—the fixed-effects summary estimate of RR for the 8 studies that did adjust for the risk factors was 1.12 (95% CI: 1.00 to 1.25), and the fixed-effects summary estimate of RR for the 9 studies that did not adjust for the all the risk factors was 1.24 (95% CI: 1.15 to 1.35). Although the estimate of RR for the group of studies that incorporated the adjustment was lower than the estimate for the other group, the 2 estimates did not differ significantly ( $p = 0.129$ ).

The 8 publications with information about the estimated RR associated with IFG 100 included 52,994 participants (27,33–35,37,38,40,44). All publications included men and women, and 3 were from Asia, 3 from the U.S., and 2 from



**Figure 2** Measures of Association Between Impaired Fasting Glucose (100 to 125 mg/dl) and Cardiovascular Outcomes

Moving from left to right, each row of information shows the first author and year of publication, a graphical portrayal of the estimate of relative risk (RR) (represented by the diamond) and confidence interval (CI) (the square box portrays graphically the weight each estimate contributed to the analysis), the estimate of RR and CI, and the weight that each data point contributed to the analysis. The overall summary estimate of RR is shown on the last row of the graph. Impaired fasting glucose of 100 to 125 mg/dl is associated with a small increase in risk for cardiovascular disease.

Europe. Estimates of RR ranged from 0.87 (44) to 1.40 (40) (Fig. 2). There was no statistical evidence for heterogeneity among the studies ( $p = 0.437$ ,  $I^2 = 0.4\%$ ), and the fixed-effects summary estimate of RR was 1.18 (95% CI: 1.09 to 1.28). All of the studies of IFG 100 adjusted for age, smoking status, blood pressure, and lipids.

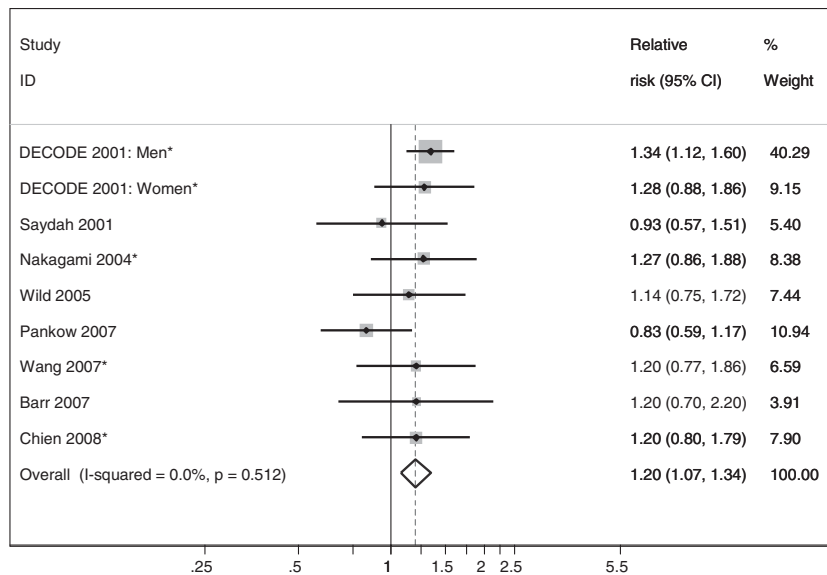
The 8 publications with information about the estimated RR associated with IGT included 53,512 participants (19,21,25,30,38,39,42,44). All publications included men and women, and 3 were from Asia, 2 from Europe, 2 from the U.S., and 1 from Australia. Estimates of RR ranged from 0.83 (44) to 1.34 (19) (Fig. 3). There was no statistical evidence for heterogeneity among the studies ( $p = 0.512$ ,  $I^2 = 0.0\%$ ), and the fixed-effects summary estimate of RR was 1.20 (95% CI: 1.07 to 1.34). One additional study contained information about the RR for ischemic heart disease among participants with IGT stratified by level of fasting glucose (27). After estimating a single overall RR for IGT and combining this information with that from the other studies, the fixed-effects summary estimate of RR was 1.24 (95% CI: 1.11 to 1.38). Six of the 8 studies adjusted for age, smoking status, blood pressure, and lipids (fixed-effects summary estimate of RR: 1.20, 95% CI: 1.06 to 1.35). For 7 of the 8 studies that also included estimates for IFG 110, the fixed-effects summary estimate of RR for IGT was 1.25 (95% CI: 1.11 to 1.41), and the fixed-effects summary estimate of RR for IFG 110 was 1.17 (95% CI: 1.02 to 1.34). Four of the 8 studies defined IGT on the basis of fasting and 2-h glucose criteria (21,30,39,44), and the

fixed-effects summary estimate of RR was 0.97 (95% CI: 0.79 to 1.21). For the other 4 studies that defined IGT only on the basis of 2-h glucose criteria, the fixed-effects summary estimate of RR was 1.30 (95% CI: 1.13 to 1.48) (19,25,38,42).

Five studies created categories of dysglycemia that combined IFG and IGT (20,24,25,31,38). The studies included 29,893 participants. All publications included men and women. Follow-up times ranged from 5 to 21.5 years. Two publications included participants of Asian heritage or from Asia, 2 studies were conducted in Europe, and 1 study was conducted in the U.S. There was no statistical evidence for heterogeneity ( $p = 0.731$ ,  $I^2 = 0\%$ ), and the fixed-effects summary estimate of RR was 1.10 (95% CI: 0.99 to 1.23) (Fig. 4).

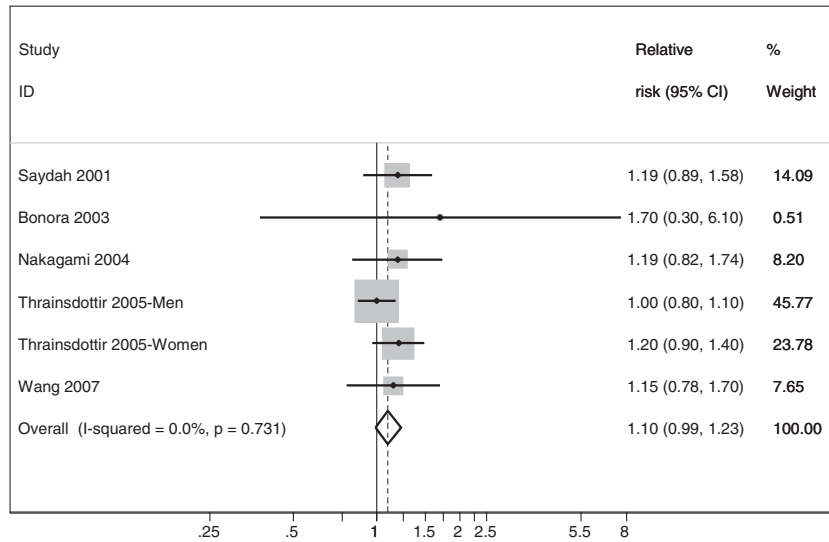
We also examined the summary estimates of RR for a set of studies that provided estimated RRs for both IFG 100 and IFG 110 (Fig. 5) (33,34,37,38,40). The fixed-effects summary estimates of RR were 1.37 (95% CI: 1.21 to 1.55) for IFG 110 and 1.19 (95% CI: 1.08 to 1.32) for IFG 100. **Sex differences.** Five publications with information about IFG 110 provided separate estimates of RR for men and women (Fig. 6A) (19,29,33,37,40). The fixed-effects summary estimate of RR was 1.17 (95% CI: 1.05 to 1.31) for men and 1.30 (95% CI: 1.10 to 1.54) for women. However, the 2 estimates did not differ significantly ( $p = 0.251$ ).

Three publications with information about IFG 100 provided separate estimates of RR for men and women (Fig. 6B) (33,37,40). The fixed-effects summary estimate of RR was 1.23 (95% CI: 1.06 to 1.42) for men and 1.16 (95% CI:



**Figure 3** Measures of Association Between Impaired Glucose Tolerance and Cardiovascular Outcomes

Moving from left to right, each row of information shows the first author and year of publication, a graphical portrayal of the estimate of relative risk (RR) (represented by the diamond) and confidence interval (CI) (the square box portrays graphically the weight each estimate contributed to the analysis), the estimate of RR and CI, and the weight that each data point contributed to the analysis. The overall summary estimate of RR is shown on the last row of the graph. Impaired glucose tolerance is associated with a small increase in risk for cardiovascular disease. \*Studies that used only the 2-h glucose measurement to define impaired glucose tolerance; other studies used 2-h and fasting concentrations of glucose to define impaired glucose tolerance.



**Figure 4** Measures of Association Between Combined Impaired Fasting Glucose and Impaired Glucose Tolerance and Cardiovascular Outcomes

Moving from left to right, each row of information shows the first author and year of publication, a graphical portrayal of the estimate of relative risk (RR) (represented by the diamond) and confidence interval (CI) (the square box portrays graphically the weight each estimate contributed to the analysis), the estimate of RR and CI, and the weight that each data point contributed to the analysis. The overall summary estimate of RR is shown on the last row of the graph. The category of combined impaired fasting glucose and impaired glucose tolerance is associated with a small nonsignificant increase in risk for cardiovascular disease.

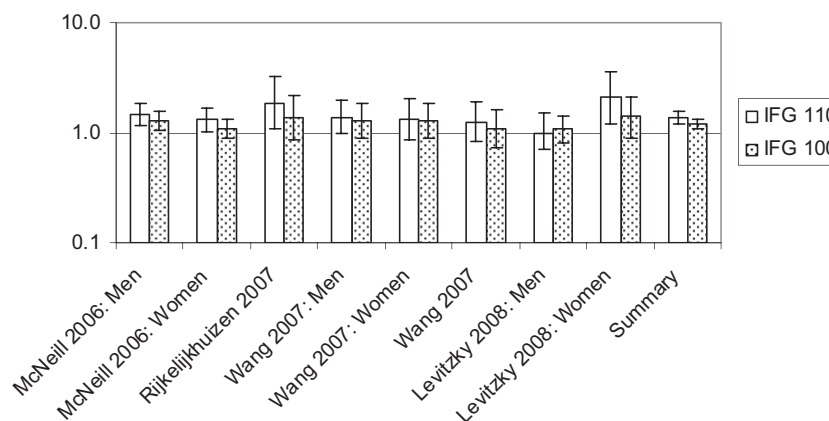
0.99 to 1.36) for women. However, the 2 estimates did not differ significantly ( $p = 0.614$ ).

### Discussion

Our review indicates that the estimated RR for cardiovascular disease associated with IGT might range from 0.97 to 1.30 and that associated with IFG ranges from approximately 1.12 to 1.37, depending on the set of studies included in a particular analysis. Furthermore, the risk

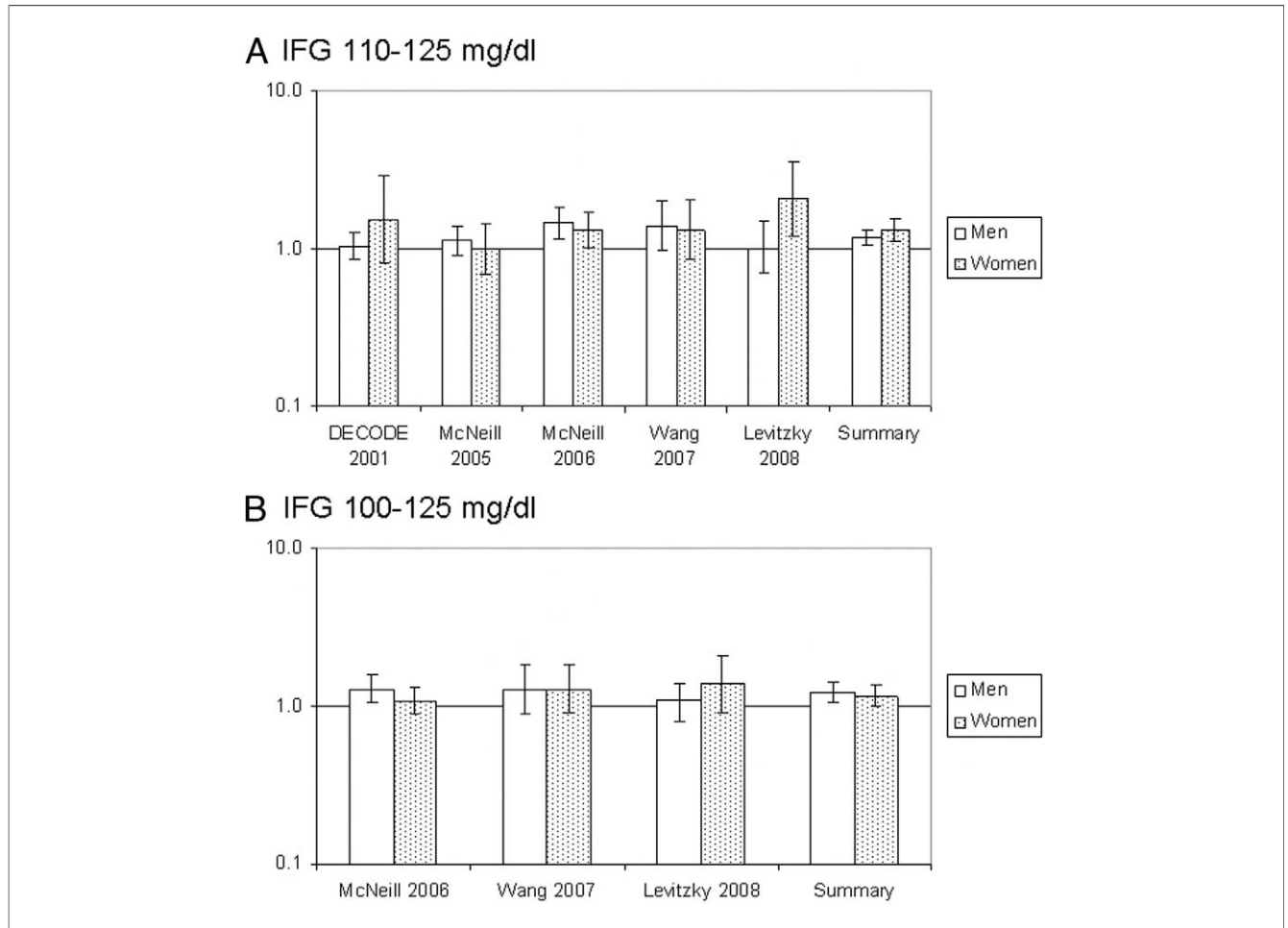
associated with IFG 110 was larger than that for IFG 100. At present, the available data are insufficient to confirm the presence of a sex difference in the risk between pre-diabetes and cardiovascular disease.

Some reviews have suggested that IGT increased the risk for macrovascular disease by approximately 2-fold (45). Such conclusions reflected the results of some studies that did find that IGT approximately doubled the risk for cardiovascular disease (46–50). Subsequent studies that



**Figure 5** Estimated RRs for Cardiovascular Outcomes for Studies that Examined Impaired Fasting Glucose Defined as 110 to 125 mg/dl (IFG 110) and as 100 to 125 mg/dl (IFG 100)

The results show that the magnitude of the estimated relative risk (RR) associated with IFG 110 (RR: 1.37, 95% confidence interval [CI]: 1.21 to 1.55) is larger than that associated with IFG 100 (RR: 1.19, 95% CI: 1.08 to 1.32). However, the CIs overlap considerably.



**Figure 6 Sex-Specific Estimates of RR Between IFG 110 and IFG 100 and Cardiovascular Outcomes**

(A) Impaired fasting glucose (IFG) 110 defined as IFG 110 to 125 mg/dl. (B) IFG 100 defined as IFG 100 to 125 mg/dl. The summary estimates of relative risk (RR) do not differ significantly between men and women for either IFG 110 or IFG 100. DECODE = Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe.

were based on the 1980 or 1985 WHO criteria in which IGT was defined as a fasting plasma concentration of glucose of <140 mg/dl and a 2-h concentration of glucose of 140 to <200 mg/dl also reported an approximate doubling of risk for cardiovascular disease among participants with IGT (51,52). However, other studies using the 1980 or 1985 WHO classification found estimates of RR of approximately 1.15 to 1.22 (18,21,53). By reclassifying normal glucose tolerance and IGT, it is likely that the absolute risk for developing cardiovascular disease was lowered for people meeting the WHO 1999 criteria for normal glucose tolerance and IGT. However, the net effect of this reclassification on the RR associated with IGT remained unclear.

Our analysis of studies examining the impact of IGT on cardiovascular disease included several studies that only used the 2-h glucose criteria of  $\geq 140$  to <200 mg/dl. Thus, these studies also included participants with diabetes defined on the basis of fasting glucose criteria. The risk for developing cardiovascular disease among these participants

was likely higher than that for participants whose fasting glucose concentration was <126 mg/dl. In fact, the estimated summary RR was 1.30 for the 3 publications examining the 2-h glucose abnormality compared with 0.97 for the 4 studies using WHO criteria for IGT, although the 2 estimates were not significantly different.

Some early studies suggested that the estimated RR of mortality from coronary heart disease was greater among women with borderline diabetes than men (48). The limited sex-specific data concerning the risks for cardiovascular disease associated with pre-diabetes included in the present study did not support a significant sex difference in the estimates of RR. Although more data were available for IFG 110 than for IFG 100, the number of such studies was still limited. Regarding IGT, there are currently insufficient data to arrive at a conclusion concerning potential sex differences. Of note is the finding from the DECODE study in 2001 that the RRs for cardiovascular disease among participants with 2-h glucose abnormalities corresponding to IGT were very similar for men and women (19). More

studies are needed to better delineate the sex-specific risks attributable to IFG and IGT.

Because most prospective studies employ a single determination of glycemic status at baseline, the question arises as to whether the risk for developing cardiovascular disease is confined to people with pre-diabetes who develop diabetes or whether the risk is still increased among people with pre-diabetes even if they never develop diabetes. At least 2 attempts have been made to address this issue and have failed to produce definitive insights into this issue (34,54).

Current recommendations to screen for pre-diabetes are inconsistent. The U.S. Preventive Services Task Force does not support screening for pre-diabetes, whereas the ADA supports screening among people at increased risk on the basis of age and body mass index. One of the key issues to be addressed when recommendations concerning screening are being debated is the seriousness of potential consequences in terms of morbidity and mortality if a condition is not detected. The rather modest summary estimates of RR for cardiovascular disease that we calculated suggest that any future consideration concerning screening for pre-diabetes is likely to be governed principally by the risk of developing diabetes rather than cardiovascular disease. Nevertheless, an economic analysis that incorporates the prevention of cardiovascular disease might provide additional useful information to steer future discussions concerning the need to screen for pre-diabetes in the general population or in specific population groups at high risk. Furthermore, our results, which show rather similar estimates of RR for cardiovascular disease for IFG and IGT, might also contribute to the debate as to whether an OGTT is really needed to identify people at increased risk for cardiovascular disease or whether a fasting glucose measurement suffices. If the RRs for cardiovascular disease for the 2 forms of hyperglycemia are similar, then the chief advantage of conducting an OGTT is reduced to identifying greater numbers of people with pre-diabetes. Of course, this comes at the expense of greater cost and patient inconvenience.

The degree of adjustment for potential confounders was limited in many studies, especially in studies that provided risk estimates for the individual components of the metabolic syndrome. Furthermore, some potential confounders such as physical activity were rarely incorporated into the analyses. Thus, it is possible that the true RR for cardiovascular disease attributable to pre-diabetes might be even less than that estimated in this study. Another point worth considering is that the number of events among participants with pre-diabetes was rather small in a number of studies, leading to considerable uncertainty about the magnitude of the RR as reflected by the wide CIs. Although we did not detect publication bias, our ability to do so was limited because of the small number of data points in most analyses.

## Conclusions

The exact magnitude of the risk for cardiovascular disease associated with IFG or IGT remains opaque at present. Depending on the set of studies examined, our analyses could be interpreted as implying no increase in risk for cardiovascular disease or at most a very modest increase in risk. Furthermore, there is no compelling evidence to suggest that the estimated RR for IGT is greater than that for IFG. Given the sizeable and growing percentage of adults who have pre-diabetes in some countries like the U.S. (13), a small increase in risk, assuming a causal relationship between pre-diabetes and cardiovascular disease, might still translate into substantial numbers of adults developing or dying from cardiovascular disease. The limited number of studies examining the risk for cardiovascular disease associated with IFG 100 and IGT according to WHO criteria should spur sustained efforts to clarify the relationship between pre-diabetes and cardiovascular disease.

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**Key Words:** cardiovascular diseases ■ coronary heart disease ■ hyperglycemia ■ meta-analysis ■ prediabetic state ■ review.

#### ▶ APPENDIX

For the selected characteristics of studies that were included in our analyses, please see the online version of this article.