Risk of Coronary Heart Disease in Different Criterion of Impaired Fasting Glucose

A Meta-Analysis

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INTRODUCTION

The term prediabetes is used to define individuals with intermediate states of abnormal dysglycemia between normoglycemia and overt type 2 diabetes mellitus (T2DM), including those with impaired fasting glucose (IFG) and those with impaired glucose tolerance (IGT). Subjects with IFG or IGT are at high risk for developing T2DM. It has also been reported that IGT is associated with increased risk of cardiovascular disease (CVD). However, the association of IFG and risk of CVD is far more unclear. Furthermore, the 2003 American Diabetes Association (ADA) guideline lowered the fasting plasma glucose (FPG) cut-point for diagnosing IFG from 110–125 to 100–125 mg/dL, in order to better identify subjects with future T2DM risk. Although more than a decade has passed, this change is still contentious and not adopted by the World Health Organization (WHO) Expert Group or other international guidelines. One of the main arguments against the cut-point of IFG proposed by 2003 ADA is that it greatly increases the number of subjects labeled with IFG, while without clear evidence of association with clinical complications. A recently published meta-analysis reported that the risk of stroke was increased in people with IFG defined as FPG 110 to 125 mg/dL (IFG 110) but not in those with IFG defined as FPG 100 to 125 mg/dL (IFG 100). However, another meta-analysis showed that the risks for CVD are similar in subjects with IFG 110 and IFG 100. These inconsistencies may be caused by the differences in inclusion criteria and endpoint assessment.

Considering these inconsistent results, we aimed to evaluate the association between different definitions of IFG and risk of coronary heart disease (CHD).

METHODS

Ethics Statement

This study does not involve patients, so ethical approval was not required.

Search Strategy and Selection Criteria

The search strategy was performed in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group. Electronic databases (PubMed and EMBASE) were searched for prospective cohort studies to May 31, 2015, using a combined text and MeSH heading search strategy with the terms “blood glucose,” “impaired fasting glucose,” “hyperglycaemia,” or “borderline diabetes” and “cardiovascular events,” “cardiovascular disease,” “ischemic heart disease,” “coronary heart disease,” “coronary artery disease,” “myocardial ischemia,” “myocardial...
Data Synthesis and Analysis

We analyzed the RR of CHD in individuals with different definition of IFG. Subgroup analyses were conducted according to sex (women vs men), ethnicity (Asian vs non-Asian), specific end points (fatal vs fatal plus nonfatal CHD), participant’s age (average <50 vs ≥50 years), follow-up duration (<10 vs ≥10 years), possibility of enrolling patients with diabetes (yes vs no), and adjustment of risk factors (adequate vs un-adequate).

We extracted the most adjusted RRs and 95% CIs from each included studies and logarithmically transformed these values, calculated the corresponding standard errors (SEs) to stabilize the variance and normalize the distribution.15,16 The inverse variance method was used to combine the log RRs and SEs using random effects models. The I^2 statistic was used to estimate between-study heterogeneity. Values of I^2 > 50% were considered to indicate significant heterogeneity. The estimated RRs were calculated using random-effects models. The test for subgroup differences was calculated by calculated by Chi-square statistics. Publication bias was assessed by inspecting funnel plots for each outcome in which the natural log of RR was plotted against its SE. Sensitivity analyses were conducted by omitting one study at a time and recalculating the estimated RRs and CIs. P values were 2-tailed, and the statistical significance was set at 0.05. All analyses were performed with RevMan software (version 5.3 for Windows; The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Studies Retrieved and Characteristics

A total of 26,853 manuscripts were retrieved in the initial search. After screening of the titles and abstracts, 42 reports qualified for full review. Finally, 17 prospective cohort studies, comprising 527,021 individuals, were included in our analysis17–33 (Fig. 1).

All of the included studies were derived from the general population. The characteristics of the 17 studies are presented in Table 1. Nine of the studies were from the US and Europe17,19–21,24–26,30,31 and 8 were from Asia.18,22,23,27–29,32,33 One study only enrolled men26 while all of the others included both men and women for analysis. The follow-up duration ranged from 4 to 20 years.

Oral glucose tolerance tests (OGTTs) were only performed in 6 studies and patients with increased 2 hours plasma glucose (2-h PG) were excluded for the analysis of risk in IFG.17,18,23,24,27,31 However, 11 studies only measured FPG at baseline without OGTT; therefore, these studies may enrolled patients with increased 2-h PG (IGT or T2DM defined by 2-h PG).19–22,25,26,28–30,32,33

All studies were graded as good quality accessed by the NOS. The details of the quality assessment are presented in Supplemental Table 2, http://links.lww.com/MD/A453.

FIGURE 1. Flow of papers through review. CHD = coronary heart disease, CIs = confidence intervals, IFG = impaired fasting glucose, RR = relative risk.
| Study       | Country      | IFG Definition and Prevalence, % | Sample Size (% Women | Age, year, Average (Range or SD) | Follow-Up, year | Baseline CVD Excluded | Events for Analysis | Confounder Adjusted | Possibility of Enrolling Patients With Increased 2-h PG |
|------------|-------------|---------------------------------|---------------------|---------------------------------|-----------------|------------------------|---------------------|---------------------|----------------------|
| DECODE 2001 | European    | IFG 110 (10.1%)                 | 22514 (31.7%)       | 53 (30–89)                      | 8.8             | No                     | Fatal CHD          | Sex, age, center, TC, BMI, SBP, smoking | No                   |
| Tai 2004    | Singapore   | IFG 100 (18.3%)                 | 5091 (NA)           | 37.2 (12)                       | 9.1             | Yes                    | Fatal and nonfatal CHD | Age, sex, ethnicity | No                   |
| McNeill 2005 | United States | IFG 110 (12.3%)              | 12089 (56.9%)       | 54 (45–64)                      | 11              | Yes                    | Fatal and nonfatal CHD | Age, sex, race/ARIC center, LDL-C, and smoking | Yes                  |
| Palmieri 2006 | Italy       | IFG 110 (7.7%)                  | 20447 (63.6%)       | 50.4 (35–69)                    | 10.4            | No                     | Fatal and nonfatal CHD | Age, sex, center | Yes                  |
| McNeill 2006 | United States | IFG 100 (45.5%)              | 3585 (62%)          | 72 (65–92)                      | 11              | Yes                    | Fatal and nonfatal CHD | Age, sex, smoking, family history of CVD, TC | Yes                  |
| Liu 2007    | China       | IFG 100 (21.1%)                 | 30378 (46.5%)       | 46.9 (35–64)                    | 10              | Yes                    | Fatal and nonfatal CHD | Age, sex, education, occupation, smoking, diabetic family history, and TC | No                   |
| Wang 2007   | China       | IFG 100 (56.5%)                 | 541 (43.4%)         | 47.8 (25–)                      | 5               | Yes                    | Nonfatal CHD        | Age, sex, race, center, smoking, hypertension, LDL-C, HDL-C, TG, use of lipid-lowering medications, BMI, and waist circumference | No                   |
| Pankow 2007 | United States | IFG 100 (42%)                 | 6888 (47%)          | 62.3 (52–75)                    | 6.3             | Yes                    | Fatal and nonfatal CHD | Age, sex, race, center, smoking, hypertension, LDL-C, HDL-C, TG, use of lipid-lowering medications, BMI, and waist circumference | No                   |
| Levitzky 2008 | United States | IFG 100 (NA) IFG 110 (NA)    | 4058 (53.3%)        | 48.5 (10)                       | 4               | Yes                    | Fatal and nonfatal CHD | Age, sex, SBP, hypertension treatment, TC/HDL ratio, smoking, and BMI | Yes                  |
| Wannamethee 2008 | UK         | IFG 110 (NA)                  | 5128 (0%)           | NA (40–59)                      | 20              | Yes                    | Nonfatal CHD        | Age, smoking, social class, physical activity and alcohol intake | Yes                  |
| Doi 2010    | Japan       | IFG 100 (NA) IFG 110 (NA)     | 2421 (57%)          | 57.6 (40–79)                    | 14              | Yes                    | Fatal and nonfatal CHD | Age, sex, SBP, ECG abnormalities, BMI, TC, HDL-C, smoking, alcohol intake, and regular exercise | No                   |
| Kokubo 2010 | Japan       | IFG 100 (28%)                 | 5321 (53%)          | 55 (30–79)                      | 11.7            | Yes                    | Fatal and nonfatal CHD | Age, sex, BMI, hypertension, hyperlipidemia, smoking, drinking | Yes                  |
| Khang 2010  | Korea       | IFG 100 (32%)                 | 9791 (55.2%)        | 43.2 (15)                       | 5.8             | Yes                    | Fatal and nonfatal CHD | Survey year, age, sex, central obesity, hypertriglyceridemia, low HDL-C, high blood pressure | Yes                  |
| Study       | Country  | IFG Definition and Prevalence, % | Sample Size (% Women) | Age, year, Average (Range or SD) | Follow-Up, year | Baseline CVD Excluded | Events for Analysis | Confounder Adjusted | Possibility of Enrolling Patients With Increased 2-h PG |
|------------|----------|---------------------------------|-----------------------|---------------------------------|----------------|-----------------------|---------------------|---------------------|---------------------------------------------|
| Yeboah 2011<sup>30</sup> | United States | IFG 100 (13.9%) | 6753 (52.9%) | 62.2 (45–84) | 7.5 | Yes | Fatal and nonfatal CHD | Age, sex, race/ethnicity, BMI, SBP, TC, HDL-C, TG, smoking, BP medications and statin use. | Yes |
| Deedwania 2013<sup>31</sup> | United States | IFG 100 (47%) | 4602 (57%) | 73 (65–) | 13 | No | Nonfatal CHD | Age, sex, race/ethnicity, married, education, income, BMI, activities of daily living, smoking, alcohol use, ankle am index ratio, hemoglobin, TC, albumin, uric acid, C-reactive protein, serum insulin, LV hypertrophy, atrial fibrillation, bundle branch block, LV systolic dysfunction, chronic disease and medicine | No |
| Onat 2013<sup>32</sup> | Turkey | IFG 110 (5.9%) | 2619 (51.3%) | 47.8 (11.8) | 7.2 | Yes | Nonfatal CHD | Age, sex, SBP, non-HDL-C, waist circumference, smoking, and C-reactive protein | Yes |
| Kim 2013<sup>33</sup> | Korea | IFG 100 (17.7%) | 384,795 (39.3%) | 45.5 (20–) | 9.4 | Yes | Nonfatal CHD | Age, sex, SBP, antihypertensive medication, LDL-C, HDL-C, smoking, BMI, family history of CVD | Yes |

**ARIC** = Atherosclerosis Risk in Communities Study cohort, **BMI** = body mass index, **CHD** = coronary heart disease, **CVD** = cardiovascular disease, **DECODE** = Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe, **HDL-C** = high-density lipoprotein cholesterol, **LDL-C** = low-density lipoprotein cholesterol, **NA** = not available, **SBP** = systolic blood pressure, **TC** = total cholesterol, **TG** = triglyceride.
Furthermore, according to the confounders adjusted, 7 studies did not meet our criteria for adequate adjustment\(^{18–23,26}\) and 10 studies were adequate adjusted for other potential confounders.\(^{17,24,25,27–33}\)

### Association Between IFG and Risk of CHD

Twelve studies comprising 475,347 participants reported data for risk of CHD associated with IFG 100 compared with NFG, defined as FPG \(< 100 \text{ mg/dL}\).\(^{18,19,22–25,27–31,33}\) There was moderate between-study heterogeneity in these studies (\(I^2 = 33\%)\). Meta-analysis using random-effects models showed that the risk of CHD was significantly increased in individuals with IFG 100 (RR 1.11, 95% CI 1.02–1.21, Fig. 2).

Nine studies comprising 73,402 participants were included for the analysis of risk of CHD in IFG 110 compared with FPG \(< 110 \text{ mg/dL}\).\(^{17,19–21,23,25–27,32}\) There was no between-study heterogeneity detected in these studies (\(I^2 = 0\%)\), and the risk of CHD was significantly increased in individuals with IFG 110 (RR 1.18, 95% CI 1.10–1.28, Fig. 3).

Visual inspection of funnel plots suggested that there was no evidence of publication bias for either IFG 100 (supplementary Figure S1, http://links.lww.com/MD/A453) or IFG 110 group (supplementary Figure S2, http://links.lww.com/MD/A453).

Sensitivity analyses confirmed that the risk of CHD in people with IFG 100 or IFG 110 were not influenced by the use of random-effects models compared with fixed-effects models, or recalculating the RRs by omitting one study at a time.

### Subgroup Analyses

The results of subgroup analyses are presented in Table 2.

| Subgroups | No of Studies | RR (95% CI) | \(P^2 \) Value* | No of Studies | RR (95% CI) | \(P^2 \) Value* |
|-----------|--------------|-------------|----------------|--------------|-------------|----------------|
| Ethnicity |              |             |                |              |             |                |
| Asians    | 7            | 1.16 (1.02, 1.31) | 0.41/0% | 3            | 1.09 [0.79, 1.49] | 0.60/0% |
| Non-Asians| 5            | 1.07 (0.93, 1.23) | 0.95/0% | 6            | 1.19 [1.09, 1.30] | 0.53/0% |
| Sex       |              |             |                |              |             |                |
| Male      | 6            | 1.11 (1.01, 1.23) | 0.67/0% | 7            | 1.17 [1.07, 1.29] | 0.60/0% |
| Female    | 6            | 1.11 (1.0, 1.23)  | 0.67/0% | 6            | 1.27 [1.01, 1.60] | 0.60/0% |
| Participant’s average age | | | | | | |
| <50 years | 6            | 1.10 (1.03, 1.18) | 0.31/2.9% | 3            | 1.24 [0.98, 1.56] | 0.88/0% |
| ≥50 years | 6            | 1.06 (0.90, 1.25) | 0.31/2.9% | 5            | 1.15 [0.99, 1.33] | 0.88/0% |
| Follow-up duration | | | | | | |
| <10 years | 7            | 1.07 (1.02, 1.22) | 0.24/26.6% | 4            | 1.16 [0.97, 1.38] | 0.91/0% |
| ≥10 years | 5            | 1.18 (0.98, 1.42) | 0.24/26.6% | 5            | 1.18 [1.05, 1.32] | 0.91/0% |
| CHD endpoint | | | | | | |
| Nonfatal  | 3            | 1.07 (1.02, 1.11) | 0.02/80.8% | 3            | 1.18 [1.04, 1.33] | 0.41/0% |
| Nonfatal and fatal | 9  | 1.16 (1.02, 1.32) | 0.02/80.8% | 5            | 1.19 [1.03, 1.38] | 0.41/0% |
| Possibility of enrolling patients with increased 2-h PG | | | | | | |
| None      | 7            | 0.98 (0.86, 1.11) | 0.02/80.8% | 3            | 1.09 [0.88, 1.35] | 0.53/0% |
| Might enrolled | 5  | 1.19 (1.06, 1.33) | 0.02/80.8% | 6            | 1.20 [1.10, 1.31] | 0.53/0% |
| Adjustment of confounders | | | | | | |
| Adequate | 7            | 1.05 [0.96, 1.15] | 0.02/81.9 | 4            | 1.12 [0.93, 1.35] | 0.53/0% |
| Not adequate | 5  | 1.27 [1.12, 1.45] | 0.02/81.9 | 5            | 1.20 [1.08, 1.32] | 0.53/0% |

CHD = coronary heart disease, 2-h PG = 2 hours plasma glucose level of during an oral glucose tolerance test, IFG 100 = impaired fasting glucose defined as fasting glucose 100 to 125 mg/dL, IFG 110 = impaired fasting glucose defined as fasting glucose 110 to 125 mg/dL, IFG = impaired fasting glucose.

* For heterogeneity among subgroups.

† Adequate adjustment denoted adjustment of at least 6 of 8 factors: age, sex, blood pressure or antihypertensive treatment, body mass index or other measure of overweight/obesity, physical activity, cholesterol concentration or lipid-lowering medication use, history of CVD or exclusion of CVD at baseline, and smoking.
In this meta-analysis, we found that in the general population, IFG was significantly associated with future risk of CHD. The risk of CHD was increased when FPG was as low as 100 mg/dL according to the lower cut-point of IFG by the ADA.

The 2003 ADA criterion of IFG had been criticized as it significantly increased the prevalence of IFG while without improvement of prediction for risk of CVD.34 In this study, there was sufficient power to show that the presence of IFG, defined by the WHO or ADA criterion, was associated with increased risk of CHD. These findings support the lower IFG cut-point proposed by the ADA and highlight the importance of early management of mild hyperglycemia for the prevention of CHD. Our results were different with a prior meta-analysis, which showed that the risk of stroke was increased in people with IFG defined by the WHO but not in those defined by the ADA.10 These inconsistent findings may be caused by differences in the events assessed. Furthermore, in the prior meta-analysis, they combined studies from general population, as well as studies from patients with coronary artery disease for analysis.10 However, we only used studies from general population for analysis. Our more stringent inclusion criteria are important for avoiding between-study heterogeneity and reaching more reliable conclusion. In our study, the risk of CHD associated with IFG was significantly increased in studies with possibility of enrolling patients with increased 2-h PG, but not in studies excluded participants with increased 2-h PG. These results showed that the risk of CHD in people with FPG maybe confounded by the undetected increased 2-h PG (IGT or T2DM defined by 2-h PG). Many studies have shown that IGT was a stronger predictor of cardiovascular events than IFG.17,35 However, routine detection of IGT had been questioned due to the inconvenient use of OGTT and the results are not highly reproducible. Our results highlight the notion that OGTT could be required for further diagnosing individuals with IFG.36

It has been estimated that, by the year of 2025, the number of people with prediabetes will be 472 millions.37 Successful interventions in this large population could have a major public health impact. It had been proved that lifestyle is a fundamental management approach that can effectively prevent the progression from prediabetes to diabetes.38 Furthermore, recently data showed that lifestyle intervention in IGT can reduce incidence of cardiovascular and all-cause mortality.39 However, the evidence regarding CVD prevention in people with IFG is still absent.

The main strengths of our study are the very large sample size with general population included from prospective cohort...
studies. Detailed subgroup analyses also found interesting results that the risk of CHD associated with FPG may be confounded by the undetected increased 2-h PG and other cardiovascular risk factors. However, our study also has some limitations. First, individuals with IFG are more likely to progress to DM than those with normoglycemia, but most of the included studies did not adjust for subsequent blood glucose levels. So, the long-term risk of CHD in people with IFG was caused by the mild elevation of blood glucose or the future progression of DM remains unknown. However, it had been indicated that coronary atherosclerosis detected by intravascular imaging modalities is already ongoing in prediabetic status. Second, the adjusted confounders in the included studies were inconsistent and may be a potential source of bias in our study. However, it is interesting that, in both IFG 100 and IFG 110 subgroup analysis, the risk of CHD was increased in studies with inadequate adjustment, but not in those with adequate adjustment of other cardiovascular risk factors. These results reinforce the importance of detection of other cardiovascular risk factors in risk stratification of people with IFG.

In conclusion, this meta-analysis showed that IFG was associated with an increased risk of CHD. The risk increased in people with FPG as low as 100 mg/dL. These results reaffirm the importance of screening for prediabetes using the ADA criteria. Furthermore, detection of 2-h PG and other cardiovascular risk factors are important for risk stratification in people with IFG. These informations are important for the prevention of DM and CVD.

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