Diagnosis, Prognosis, and Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose

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The information in this report is intended to help health care decisionmakers, patients and clinicians, health system leaders, and policymakers make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report as they would any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.

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Structured Abstract

Research questions. This systematic review evaluated the evidence to address the following research questions:

1) What is the test reproducibility of the diagnosis of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)?
2) What is the relationship between IFG and IGT? For those individuals identified with IFG or IGT, what are the short- and long-term risks for developing negative health outcomes? Does this risk vary by subpopulation, such as sex, race, obesity, age, or other such risk factors as blood pressure or elevated lipid levels?
3) What is the effectiveness of pharmaceutical and behavioral interventions for reducing the risks associated with IFG/IGT? Are some treatments more effective than others, and does the effectiveness of interventions vary by subpopulation (e.g., age, sex, and obesity)?
4) What is known about the development of IFG/IGT in the pediatric population?

Data sources. Studies were identified by searching the following databases: MEDLINE, Cochrane Central Register of Controlled Trials, HealthSTAR, CINAHL, AMED (alternative medicines), PsycINFO, and EMBASE as well as the personal files of the advisory team and the reference lists of included articles.

Eligibility criteria. Primary studies were eligible for further evaluation if they assessed subjects with IFG or IGT, were published after 1978, and were written in English. Study design eligibility varied with the research question. For the diagnosis of IFG or IGT research questions (with a maximum of eight-week re-test for reproducibility), all study designs were eligible. Similarly, for the children’s (age 0 to 18 years) research questions, all designs were considered. For prognosis, prospective cohort studies, randomized controlled trials (RCTs) or controlled clinical trial (CCTs) with a minimum of one-year follow-up were eligible. Any RCT that analyzed the effects of lifestyle or behavioral or pharmaceutical treatment (with a minimum of six months’ follow-up) was evaluated for the research question on treatment.

Data collection and analysis. Data were extracted for all studies and included the sample size, age of subjects, population characteristics, criteria used for diagnosis, and the study duration. For the prognosis questions, proportions were extracted to estimate risk for disease progression (annualized risk, unadjusted relative risk, and attributable risk). Adjusted estimates of risk reported in studies were also extracted. Similarly, estimates of risk were extracted for studies related to the treatment of IFG or IGT. The methodological quality of studies was assessed.

Main results. Diagnosis: Although, the number of evaluated studies was small, the reproducibility for both IFG and IGT categorization was shown to be poor. Comparison of IFG and IGT categories shows a wide degree of variation among populations. The prevalence of IGT is greater than IFG in almost all studies. High-risk populations have an equal or greater proportion of IFG compared to IGT diagnoses. The kappa coefficients varied from 0.04 to 0.56 for IGT and from 0.22 to 0.44 for IFG.
Statistically, the proportion of study participants classified as IGT by the 2-hour plasma glucose (2-hr PG) alone, is greater than the proportion classified by the diagnostic criteria, combined 2-hr PG/fasting plasma glucose (FPG). This will affect the conclusions of prognosis and possibly treatment data in population studies using only 2-hr PG criteria.

Prognosis: There is consistent evidence that IFG and IGT are both risk factors for the development of diabetes mellitus (DM). The pooled relative risk for new DM is 6.02 (95% CI 4.66 to 7.38) in people with IGT, 4.70 (95% CI 2.71 to 6.70) in people with IFG, and 12.21 (95% CI 4.32 to 20.10) in people with both disorders. They are also both risk factors for fatal and nonfatal cardiovascular outcomes; however, the evidence is less consistent for these outcomes. The pooled relative risk ranged from 1.48 to 1.66 for cardiovascular disease (CVD) mortality and all-cause mortality in people with IGT, and from 1.19 to 1.28 for nonfatal myocardial infarction (MI), nonfatal CVD, CVD mortality, and all-cause mortality in people with IFG.

Treatment: Fourteen RCTs evaluated the effect of lifestyle or pharmacotherapeutic interventions on individuals with IFG or IGT. Trials that evaluated the effect of a combined diet and exercise program on the risk for developing DM found a significant risk reduction (46%). Dietary advice alone significantly reduced the risk for progressing to DM in one of two trials. Exercise alone significantly reduced progression to DM in one trial. Two of four studies that evaluated the effect of pharmacotherapeutic interventions (acarbose, metformin) on the risk for progressing to DM in IGT subjects showed evidence of reduced risk (25%). Two retrospective subgroup analyses evaluating the effect of statin therapy (pravastatin) on individuals with IFG with a previous MI found CVD benefits.

Pediatric populations: Only 2 out of 36 articles provided data specific to the pediatric population. However, neither of these studies provided substantive information. A gap in the literature has been identified.

Conclusions. Diagnosis: The reproducibility for both IGT and IFG categorization is poor. Therefore, an absolute FPG and 2-hr PG measurement may be more informative than categorization into IFG and IGT, respectively. The distribution of study participants in the IGT category varies significantly with the diagnostic criteria used. This will affect findings in epidemiological studies evaluating prognosis and treatment.

Prognosis: Many studies consistently show that both IFG and IGT are strong risk factors for the development of DM. Fewer studies show that they are also risk factors for future CVD, all-cause mortality, and lipid disturbances.

Treatment: There is evidence that combined diet and exercise, and drug therapy (metformin, acarbose), are effective at preventing progression to DM in IGT subjects.

Pediatric populations: The literature on pediatric subjects with IFG or IGT is limited and future research is warranted.
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Note: Appendixes are provided electronically at: www.ahrq.gov/clinic/epcindex.htm
Diabetes mellitus (DM) and its associated disease outcomes are a growing concern worldwide. The current global prevalence of DM for all ages has been estimated at 2.8 percent and is predicted to reach 4.4 percent by 2030.1 There is intense interest in identifying and treating risk factors that may prevent the onset of this disease and minimize morbidity.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are the intermediate metabolic states between normal and diabetic glucose homeostasis. These conditions are thought to be the precursors of DM, but the progression to overt disease is not straightforward. The risk for both macrovascular and microvascular complications increases across the distribution of blood glucose concentrations well below the overt DM, and the risk is more strongly associated with post-challenge hyperglycemia than fasting glucose levels. However, it is unclear whether this “glucose effect” is independent of classical risk factors, such as blood pressure and lipids, or occurs due to abnormalities of other metabolites, such as free fatty acids.

Objective of This Systematic Review

The goal of this systematic review is to evaluate the state of the evidence in the areas of the diagnosis, prognosis, and treatment of IFG or IGT. This evidence report was requested by the American College of Physicians-American Society of Internal Medicine; other partners were the American Academy of Pediatrics and the American Academy of Family Physicians.

Key Questions

Preliminary questions were subsequently modified and refined in consultation with the partner medical agencies, the Agency for Healthcare Research and Quality, and McMaster University Evidence-based Practice Center. The revised key questions are as follows:

1. **Diagnosis**—What is the reliability of the diagnosis of IFG or IGT (e.g., does individual variability or measurement error require multiple measurements to ensure reliability of diagnosis)? What is the relationship between IFG and IGT?

2. **Prognosis**—For those identified with IFG or IGT, what are the short- and long-term risks for developing the following outcomes:
   a) Progression to DM or reversion towards normal glucose tolerance or fasting glucose level.
   b) Cardiovascular events and stroke (fatal and nonfatal).
   c) Microvascular disease, specifically retinopathy and nephropathy as measured by proteinuria, microalbuminuria, elevated creatinine, albumin-to-creatinine ratio in the urine, dialysis, or renal transplant.
   Does this risk vary by subpopulation, such as sex, race, obesity, age or other risk factors (e.g., blood pressure, elevated lipid levels)?

3. **Treatment**—What is the effectiveness of pharmaceutical and behavioral interventions for reducing the risks associated with IFG or IGT on the following outcomes:
a) Delay in onset of DM or reversion towards normal glucose tolerance or fasting glucose level.
b) Reducing risk for cardiovascular events and stroke (fatal and nonfatal).
c) Reducing risk for microvascular disease, including early markers such as retinopathy/proteinuria.
d) Improving other metabolic parameters, independently associated with increased risk, such as blood pressure and lipid levels.

Are some treatments more effective than others for any of the above outcomes, and does the effectiveness of interventions vary by subpopulation (e.g., age, sex, and obesity)?

4. Pediatric population—What is known of the development of IFG or IGT in the pediatric population?

Methods

Eligibility Criteria

Primary studies were eligible if they evaluated subjects with IGT or IFG, were published after 1978, and were written in the English language. Excluded publications included systematic reviews, narrative reviews, editorials, letters to the editor, unpublished position papers, consensus conference reports, and practice guidelines.

Study design eligibility varied with the research question:

- **Diagnosis**—All study designs with a maximum of 8-week retest for reproducibility were eligible.
- **Prognosis**—Any prospective cohorts, or randomized or controlled clinical trials (RCTs) were eligible for evaluation (with a minimum followup of 1 year).
- **Treatment**—Only RCTs that analyzed the effects of lifestyle, behavioral, or pharmaceutical treatment (with a minimum followup of 6 months) were eligible.
- **Pediatric population**—All study designs for children age 0 to 18 years were eligible.

The study had to include an IFG or IGT group as the study population or analyzed as a subgroup. The specific criteria reference (for example, WHO-85) used within a study was checked relative to the procedures described in the methods and results sections of each study. The following inclusion/exclusion criteria were used for the testing procedure for dysglycemia:

- All testing must have been done in a laboratory and not with a point-of-care device or not undertaken in an acute care setting, such as an emergency ward following a myocardial infarction (MI) or pneumonia.

Study outcomes included glycemic disturbances, nonfatal cardiac outcomes, fatal cardiac outcomes, mortality, lipid and blood pressure disorders, amputation, nephropathy, and ocular problems.

Literature Search Strategy

A comprehensive search was undertaken to capture all relevant studies. In addition to MEDLINE®, HealthSTAR, CINAHL®, AMED (alternative medicines), PsycINFO®, and EMBASE®, the personal files of the local research team and the reference lists of included articles were searched from 1979 onward.

Study Selection and Extraction

The title and abstract lists and the full-text papers were screened using the eligibility criteria, standardized forms, and a guide manual. Data from the Access database were summarized into summary tables, which included data about the general study characteristics (study design, location, source of funding, population, mean age, and diagnosis criteria), interventions, and outcomes assessed.

Studies were grouped according to classification of the IFG and IGT status. Five categories were considered, including: 1) isolated IGT (I-IGT), 2) isolated IFG (I-IFG), 3) non-isolated IGT, 4) non-isolated IFG, and 5) combined IGT/IFG.

A classification of I-IGT indicates that 2-h OGTT level was between 7.8 and 11.0 mmol/L and the fasting plasma glucose (FPG) level was less than 6.1 mmol/L. Similarly, the I-IFG classification indicates that the 2-h OGTT level was less than 7.8 mmol/L and the FPG level was between 6.1 and 7.0 mmol/L.

The isolated classifications indicate that both forms of glucose testing were undertaken and only one of the two tests was abnormal. Each eligible study was rated for quality using standardized instruments.

Results

The original search yielded 25,521 citations for all four questions combined. From these, 1,243 proceeded to full-text screening. After the final eligibility screening, data were extracted from a total of 156 studies.

Key Question 1: Diagnosis

Fifty-three studies provided data on the reproducibility of repeat testing of fasting glucose or OGTTs, comparison of IGT diagnosis by different criteria, and the relationship between IGT and IFG diagnosis in the same population.
Reproducibility of IGT and IFG Tests. Five reports of four studies\(^6^9\) assessed the reproducibility of the OGTT for diagnosis of IGT and three reports of two studies\(^5^7^9\) assessed the reproducibility of FPG for the diagnosis of IFG in publications after 1978. All repeat tests were done within 6 weeks of the first test. The populations studied were mostly Caucasians,\(^5^7\) except for two reports of one study on Hong Kong Chinese.\(^8^9\)

The study populations were subgroups of larger studies and did not provide detailed characterization for the subgroup. All studies used the same classification criteria. IGT was FPG < 7.8 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L and IFG was FPG 6.1 to 6.9 mmol/L.

The kappa coefficients for IGT ranged from 0.04 to 0.56, indicating poor to moderate agreement. The proportion of participants classified as IGT by the first OGTT and upon repeat testing ranged from 33 percent to 48 percent. A similar proportion (range 39.3 percent to 46.2 percent) of participants was reclassified as normal glucose tolerance, with the remainder reclassified as DM (range 6 percent to 12.6 percent).

Two studies retested participants based on FPG for IFG.\(^6^9\) The kappa coefficients for these studies were 0.22 and 0.44, indicating fair to moderate reproducibility. The proportions of participants classified as IFG by the first FPG and upon repeat testing were 63.7 percent and 51.4 percent, respectively. The reclassified subjects had mostly normal fasting glucose with some newly diagnosed DM. Two studies that evaluated coefficient of variation for biological variation (CV\(_I\)) for repeat testing gave similar CV\(_I\) for FPG (6 percent and 6.3 percent) and 2-hr PG (18 percent and 16.6 percent) concentrations, indicating consistency in variation between the different populations studied.\(^5^7\)

Comparison of IGT diagnosis using different criteria. Only four studies\(^10^11\) provided data for a comparison between diagnosis using different IGT criteria (i.e., using both IFG and 2-hr PG concentrations for classification). Studies that assessed IGT based on the 2-hr PG concentration only (WHO epidemiological criteria) were excluded.\(^14\)

The characteristics of the study populations represent a broad spectrum of populations (Asian, Dutch, Pima Indians, and women with previous gestational DM). The IGT criteria included were WHO-85, WHO-98, and WHO-99. All of these criteria use a 2-hr PG range of 7.8 to 11.0 mmol/L, but the WHO-85 criteria use an FPG cutpoint of < 7.8 mmol/L whereas both the WHO-98 and WHO-99 criteria use a cutpoint of < 7.0 mmol/L. More IGT diagnoses were made using a FPG cutpoint of < 7.8 mmol/L (13.6 percent to 31.5 percent) than 7.0 mmol/L (8.3 percent to 29.7 percent). There were fewer cases of I-IGT (6.0 percent to 11.9 percent) compared to IGT regardless of the FPG cutpoint.

Relationship between IGT and IFG. Forty-nine studies provided data on the relationship between diagnostic criteria for IGT and IFG. Most studies were prospective cohort studies (n = 14) and cross-sectional studies (n = 31). Data were extracted to give seven classifications:

1) IGT—2-hr PG 7.8 to 11.0 mmol/L.
2) IGT—FPG < 7.8 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L.
3) IGT—FPG < 7.0 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L.
4) IFG—FPG 6.1 to 6.9 mmol/L.
5) I-IGT—FPG < 6.1 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L.
6) I-IFG—FPG 6.1 to 6.9 mmol/L and 2-hr PG < 7.8 mmol/L.
7) Combined IFG/IGT—FPG 6.1 to 6.9 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L.

Comparison of studies that present both IGT and I-IGT data show that the number of participants in the IGT classification is approximately 40 percent greater than in the I-IGT group (p < 0.0001). Also, IGT classification using the limited criteria, which omits the fasting plasma glucose value, classified 10 percent more participants as IGT (p = 0.0033). Evaluation of studies containing data for all classification categories (n = 16) show a change in proportion between each classification group and between studies. In general, the proportion of participants decreased with increased stringency of the diagnostic criteria—that is, IGT as 2-hr PG > IGT as FPG and 2-hr PG > I-IGT > IFG > I-IFG > IFG/IGT.

The prevalence of IGT and IFG varied greatly among studies ranging from a few percent to over 30 percent. Comparisons between categories of IGT and IFG were significant (p < 0.01) for all combinations except for I-IGT versus IFG and I-IFG versus IGT/IFG. Correlations were much higher for IGT and I-IGT than for IFG and I-IFG.

Key Question 2: Prognosis

A total of 104 studies met the initial eligibility criteria. From these, only some provided sufficient data (frequency counts) versus a reference group of subjects with normal glucose to estimate the following:

- Annualized risk per 100 persons in the exposed group.
- Unadjusted annualized relative risk (RR), with the confidence interval (CI).
- Risk difference\(^1\)
- Attributable risk (AR), expressed as a percentage for the observed study duration.

All included studies prospectively followed cohorts; 90 were observational studies and 14 were RCTs (placebo arm only). The duration of followup varied from 1 year to 18 years. Five

\(^1\) Risk differences are discussed in the full evidence report.
The number of studies that estimated risk for diabetes mellitus (DM) and cardiovascular disease (CVD) outcomes (fatal and nonfatal), and mortality. Most of these studies had small sample sizes. In the remaining five diagnostic groups: (a) IGT, (b) I-IGT, (c) IFG, (d) I-IFG, and (e) combined IFG/IGT. Findings are summarized for three main outcomes: progression to DM, cardiovascular disease (CVD) outcomes (fatal and nonfatal), and mortality.

Risk for progression to DM. The number of studies that provided data for the five classification groups varied. Studies with IGT subjects (n = 36) were the most numerous, whereas five studies included people with IFG and three studies included people with I-IGT, I-IFG, and both IGT/IFG.

Annualized risk per 100 persons in the exposed groups. The minimum and maximum annualized risk estimates for each of the five dysglycemic classification groups are as follows:

- IGT group—1.83 (minimum) to 34.12 (maximum)
- I-IGT group—4.35 to 6.35
- IFG group—1.60 to 23.44
- I-IFG group—6.07 to 9.15
- IGT/IFG group—9.96 to 14.95

Two studies and four RCTs had high annualized risk estimates, and these included populations with many risk factors for DM. The variation in the annualized risk per 100 persons observed are likely related to the different populations, mean age, and the sample sizes evaluated within these studies.

Unadjusted annualized relative risk. Three of the 28 studies evaluating women only, and nine studies evaluating men only. The mean age and the ranges varied significantly among studies, but most included middle-aged and older subjects. There was a broad representation of populations.

The measures of risk were calculated from data provided in prospective studies that included both normal and dysglycemic people in either observational studies or the placebo arm of RCTs. The risk estimates for all outcomes were classified into five diagnostic groups: (a) IGT, (b) I-IGT, (c) IFG, (d) I-IFG, and (e) combined IFG/IGT. Findings are summarized for three main outcomes: progression to DM, cardiovascular disease (CVD) outcomes (fatal and nonfatal), and mortality.

Risk for nonfatal CVD outcomes. Estimates of risk for any nonfatal CVD outcomes were based on six studies. The outcomes characterizing CVD included atherothrombosis, nonstenotic atherosclerosis, clinical MI, percutaneous transluminal coronary angioplasty (PTCA), stroke, unstable angina, heart failure, and combinations of these (major event or any event). Study durations varied from 5 to 9 years and studies were published from 1998 forward. Three of the five studies evaluating IFG as the risk factor are RCTs.

Annualized risk per 100 persons in the exposed groups. Estimates of annualized risk per 100 persons varied between the types of CVD events. The highest observed annualized risk was within the only IGT study for the outcome of nonstenotic atherosclerosis. The lowest observed annualized risk was for stroke in people with IFG. The annualized risk estimates for any nonfatal CVD event are as follows: IGT group—range 52.8 percent to 97.0 percent; I-IGT group—68.8 percent to 86.6 percent; IFG group—57.3 percent to 86.9 percent; I-IFG group—77.1 percent to 88.5 percent; IGT/IFG group—78.6 percent to 93.3 percent.

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**Attributable risk in the exposed group.** The AR for CVD outcomes was higher in the IGT group (range 52.8 percent to 52.9 percent) than in the IFG group (0 percent to 32.9 percent).

**Risk for fatal CVD outcomes.** Eight studies reported fatal CVD outcomes. Some studies subdivided the outcomes into ischemic heart disease, cardiocerebrovascular disease, and coronary heart disease (CHD). There were no eligible studies to evaluate the I-IFG and IFG/IGT combined classifications. The duration of the studies varied from 7 to 18 years. Three of the studies, were based on a male-only cohort (Paris Police study) for the IGT, I-IGT, and IFG groups. Similarly, one study within the IFG group included only postmenopausal women with a history of MI. Two other studies in the IFG group recruited subjects with a history of either MI or CHD.

**Annualized risk per 100 persons in the exposed groups.** The annualized risks in the exposed group per 100 persons are as follows: IGT group—0.06 to 0.76; I-IGT group—0.23 to 0.34; IFG group—0.10 to 1.54. The differences in annualized risk are likely a function of the different study populations and categorizations of the CVD mortality subgroup classification.

**Unadjusted annualized relative risk.** Only four studies, had unadjusted annualized RRs that were significant. The calculated estimates are as follows:

- IGT group—range 1.67 (95 percent CI 1.23 to 2.26) to 3.08 (1.47 to 6.47)
- I-IGT group—1.59 (1.07 to 2.28) to 1.72 (1.23 to 2.41)
- IFG group—1.32 (1.04 to 1.67)³

In a meta-analysis, within the IGT group, CVD and ischemic heart disease were grouped and the pooled overall estimate of relative risk was 1.66 (95 percent CI 1.21 to 2.11). Within the IFG group, estimates for the CHD/CVD subgroup (1.25 [0.99 to 1.51] and ischemic-related disease subgroup (1.27 [1.06 to 1.54]) were pooled; these estimates did not differ substantively. Overall, the pooled estimates do not provide evidence of a significant association with IFG or IGT and fatal CVD outcomes.

**Attributable risk in the exposed group.** The AR for fatal CVD outcomes varied as follows: IGT group—range 24.8 percent to 67.3 percent; I-IGT group—36.8 percent to 41.2 percent; IFG group—11.8 percent to 39.5 percent. With the exception of one study, the AR did not exceed 41 percent. Tominaga et al.³⁸ evaluated CVD outcome in both the IGT and IFG groups concurrently, and the AR was 67.3 percent and 39.5 percent, respectively.

**Risk for mortality.** In general, most studies reporting mortality outcomes had the largest sample sizes and the longest followup duration (up to 18 years). Eligible studies included the IGT, I-IGT and IFG classifications; the I-IGT group was based on two studies on the same cohort.

**Annualized risk per 100 persons in the exposed group.** The annualized risks per 100 persons for mortality (all-cause, cancer, and cirrhosis categories) are as follows: IGT group—0.09 to 2.44; I-IGT group—0.10 to 1.34; and IFG group—0.56 to 1.39.

**Unadjusted annualized relative risk.** The all-cause mortality estimates along with 95 percent CI are as follows:

- IGT group—range 1.36 (95 percent CI 1.12 to 1.66) to 3.18 (1.79 to 5.63)
- I-IGT group—1.60 (1.33 to 1.92) to 7.19 (3.37 to 15.37)
- IFG group—1.18 (1.03 to 1.35) to 1.45 (1.27 to 1.66).

One study showed a strong association between I-IGT and the outcome of death due to cirrhosis (RR 7.19)³⁵ for male police officers and also showed the highest AR (86 percent) for mortality outcomes. Three studies, evaluated both all-cause mortality and CVD mortality; both the RR and the AR estimates were approximately double in magnitude for the CVD-related mortality relative to all causes with the exception of one study. Two studies, compared all-cause mortality to cancer-related deaths, and the RR and AR did not differ substantively for these two mortality outcomes.

Meta-analysis for all-cause mortality in the IGT and IFG groups was undertaken. The overall pooled estimates were 1.48 (95 percent CI 1.09 to 1.86) for the IGT group and 1.21 (95 percent CI 1.05 to 1.36) for the IFG group.

**Attributable risk in the exposed group.** The ARs for all-cause mortality are as follows: IGT group—range 0 percent to 67.2 percent; I-IGT group—35.1 percent to 86.0 percent; IFG group—13.9 percent to 61.2 percent. The single study with an AR equal to 0 percent has been previously noted for its sample size issues. As with the other risk metrics for mortality, the AR was highest (86 percent) for cirrhosis-related mortality.

**Key Question 3: Treatment**

Twenty-three reports of 14 RCTs published between 1992 and 2003 evaluated lifestyle or pharmacotherapeutic interventions in adults with IFG or IGT. Duration of followup ranged from 6 months to 6 years. Studies involved 14 to 3,234 participants from Europe, North America, Australia, and Asia with their mean ages ranging from 37.5 to 70 years. Interventions included diet and exercise, oral hypoglycemic agents (metformin, acarbose, and chromium), a statin (pravastatin), and an ACE inhibitor (enalapril). Outcomes included progression to DM or reversion to normal glucose tolerance, cardiovascular events, mortality, and effects on blood pressure and lipid levels.
Progression to DM or reversion to normal. Most studies of the effects of lifestyle or pharmacotherapeutic interventions involved people with IGT.

Lifestyle interventions. Six RCTs evaluated the effect of lifestyle interventions on the risk for developing DM or reverting to normal glucose tolerance in adults with IGT. Intensive combined diet and exercise programs that involved frequent study visits were compared with lifestyle advice alone in five studies.\textsuperscript{40-44} One study\textsuperscript{41} compared an exercise program with advice alone, and two studies\textsuperscript{40,44} evaluated the effect of dietary intervention alone. One trial, the Diabetes Prevention Program, also included a metformin arm.\textsuperscript{40}

All but one of the trials that evaluated a combined diet and exercise program found a significant reduction in the risk for developing DM, or a higher rate of reversion to normal glucose tolerance, with aggressive lifestyle modification. The absolute risk reduction of progressing to DM per year in the studies was between 1.6 percent and 7.1 percent, corresponding to a number needed to treat for 1 year to prevent a case of DM between 14 and 62. Dietary intervention alone significantly reduced the risk for progressing to DM in one trial\textsuperscript{40} but had no effect in a second study.\textsuperscript{43} The trial\textsuperscript{41} that evaluated an exercise intervention alone showed a significantly reduced rate of progression to DM (absolute risk reduction 3.9 percent, number needed to treat 25.5, relative risk reduction 37 percent).

Pharmacotherapeutic interventions. Four RCTs evaluated the effects of pharmacotherapeutic interventions on the risk for developing DM in people with IGT.\textsuperscript{40,46-48} These studies assessed the effect of acarbose and metformin.

The study\textsuperscript{40} with acarbose demonstrated a reduced risk of progressing to DM (32 percent versus 42 percent; relative risk reduction 0.25, 95 percent CI 0.10 to 0.37). This effect did not vary by age, sex, or body mass index (BMI). The study also demonstrated an increased rate of reversion to normal glucose tolerance with acarbose relative to placebo (35 percent versus 31 percent, \(p < 0.0001\)).

A large study\textsuperscript{40} found a significantly reduced risk for progressing to DM when taking metformin relative to placebo (7.8 percent versus 11.0 percent per year; relative risk reduction 0.31, 95 percent CI 0.17 to 0.43). Two smaller studies\textsuperscript{47,48} in people with IGT found no difference in those treated with metformin.

The effect of enalapril in people with IFG and left ventricular dysfunction was assessed in a retrospective post-hoc subgroup analysis. This study\textsuperscript{40} found a decreased risk for progression to DM in the enalapril arm relative to the placebo arm (3.3 percent versus 48 percent, \(p = 0.0001\)). The effect of pravastatin on the development of DM in people with IFG and a previous MI was assessed in a retrospective post-hoc subgroup analysis. This study found no effect on the rate of development of DM, based on a fasting blood glucose level of \(\geq 7\) mmol/L, or reported use of oral hypoglycemic medication or insulin.

Lifestyle versus pharmacotherapeutic interventions in people with IGT. Only one trial to date, the Diabetes Prevention Program,\textsuperscript{40} has directly compared lifestyle intervention with pharmacotherapeutic intervention for the prevention of diabetes in people with IGT. It found a significantly lower risk for progressing to DM with aggressive lifestyle intervention compared with taking metformin (4.8 percent versus 7.8 percent per year; relative risk reduction 0.39, 95 percent CI 0.24 to 0.51), especially in individuals 60 years of age or older.

Cardiovascular event outcomes. No RCTs of lifestyle interventions evaluated cardiovascular outcomes.

Pharmacotherapeutic interventions in people with IGT. A single trial\textsuperscript{10} evaluated the effect of acarbose on cardiovascular event rates in people with IGT.

The primary outcome found a significant reduction in the risk for developing a major cardiovascular event in the acarbose arm compared with the placebo arm of the study (relative risk reduction 0.49, 95 percent CI 0.05 to 0.72, absolute risk reduction 2.5 percent).

Pharmacotherapeutic interventions in people with a previous MI and IFG. Two post-hoc retrospective subgroup analyses evaluated the effect of pravastatin therapy on cardiovascular event rates in people with a previous MI and IFG. In one trial,\textsuperscript{40} the rate of cardiovascular death or nonfatal MI was significantly lower in the pravastatin group; the relative risk was not significantly different from the values for the post MI patients. In a second trial\textsuperscript{41} the relative risk for the outcome of cardiovascular death or a nonfatal MI in individuals with IFG was also not significantly different from those within individuals with normal fasting glucose levels at baseline.

Mortality outcomes. One trial\textsuperscript{10} reported the effect of lifestyle intervention on total mortality rates in individuals with IGT. One trial\textsuperscript{10} reported the effect of statin therapy on mortality rates in individuals with a previous MI and IFG. In both trials, mortality rates did not differ significantly between groups.

Effects on blood pressure and lipid levels. All studies involved people with IGT.

Lifestyle interventions. Three RCTs\textsuperscript{43,44,51} evaluated the effect of lifestyle interventions on blood pressure and lipid levels. Significant differences (decline) in blood pressure (systolic and diastolic) were found in two studies and in lipid levels (ratio of total to HDL cholesterol and serum triglycerides only) in one study.

Pharmacotherapeutic interventions. Four RCTs reported the effects of oral hypoglycemic agents on blood pressure and lipid levels. Two trials\textsuperscript{47,48} reported the effects of metformin on blood pressure levels in people with IGT and demonstrated no significant effect of metformin on blood pressure or lipid levels.
One study reported the effects of acarbose therapy on blood pressure and lipid levels in people with IGT and found significant differences in blood pressure (systolic and diastolic) and hypertension (defined as a blood pressure of at least 140/90 on two consecutive visits or the addition of antihypertensive medications between visits). The trial noted a significant reduction in triglyceride levels. A trial of chromium found no significant effects on lipid levels.

**Key Question 4: Pediatric Population**

All articles that met the general criteria (English language, full-text publication, published since 1979, and results for IFG or IGT analyzed separately from other study populations) and included children with IFG or IGT were collected (36 articles). Of these, a subset of five articles met the criteria for diagnosis, prognosis, or treatment according to the criteria outlined in the methodology. These articles are included in the analysis of their respective sections above.

Four articles included within the analysis (one diagnosis, three prognosis) included participants 15 to 18 years of age, but the pediatric data were not presented separately. These studies were therefore excluded from the pediatric analysis. Nineteen studies were excluded for the following reasons: nine discussed cystic fibrosis, one discussed endemic fluorosis, one dealt with Turner's syndrome, six related to type 1 DM risks, and no specific pediatric data could be extracted in two articles.

Thus, 13 of 36 articles had extractable pediatric data in articles relevant to either the prevalence, diagnosis, prognosis, or treatment of IFG and/or IGT. The information from these articles forms the basis of the analysis that follows.

Most studies (12 out of 13) addressed the prevalence of IFG or IGT in various at-risk populations and in the population at large. Two studies compared IFG and IGT diagnosis in children. Four studies examined longitudinal followup of a cohort of children and addressed the prognosis of IFG or IGT. One study examined treatment in an open-label trial with metformin.

**Prevalence.** As DM in childhood was initially recognized in Aboriginal populations, most prevalence studies examine these groups. Population-based prevalence of IGT in childhood Aboriginal populations varies from 3.5 percent in Tuvalu to 6.25 percent of Australian Aboriginals aged 7 to 18 years.

The prevalence of IFG has been studied in one population-based study. The Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994, measured fasting glucose in 1,083 adolescents age 12 to 19. IFG (glucose 6.1 – 6.9 mmol/L) was present in 1.8 percent (n = 20/1,083). Of these 20 children, 4 were non-Hispanic white, 9 were non-Hispanic black, and 7 were Mexican American. The majority of the children were overweight (mean BMI at 86th percentile), but the range extended from the 10th to 99th percentile. Prevalence of IGT in children not “at-risk” is available from the control group of a single study in which 2.5 percent of 80 children age 10 to 16 had IGT.

The prevalence of IGT in obese children has been examined in two studies of children referred to a tertiary care center for obesity management; IGT was found in 25 percent of children (age 4 to 10 years) and 21 percent of adolescents (age 11 to 18 years) in a U.S. study and in 4.2 percent of 6- to 18-year-olds using the same diagnostic criteria in an Italian population. In the U.S. study, 51 percent of those with IGT were non-Hispanic white, 30 percent were non-Hispanic black, and 19 percent were Hispanic (compared to 58 percent, 23 percent, and 19 percent, respectively, in the population studied). “Silent” DM was diagnosed in four participants (two non-Hispanic black and two Hispanic).

Other “at-risk” populations have been identified. These include children with a history of DM in first degree relatives. In a study of 150 Latino children with a family history of DM, 28 percent were noted to have IGT. Furthermore, 25 percent of Hispanic children whose sibling had type 2 DM had IGT.

Offspring of mothers with pregestational or gestational DM (ODM) also have a higher prevalence of IGT. In a longitudinal study, the prevalence of IGT in ODM was 1.2 percent in children < 5 years (n = 168), 5.4 percent in 5- to 9-year-olds (n = 111), and 19.3 percent (95 percent CI 12.1 to 28.6) in 10- to 16-year-olds (compared to 2.5 percent [95 percent CI 0.4 to 8.1] in controls). Although the control group was somewhat lighter (BMI 20.3 ± 4.0 versus 22.8 ± 5.4 kg/m²) and had 37 percent of participants other than Caucasian compared to 51 percent in the ODM group, it is unlikely that these differences would account for the difference in IGT prevalence. Within this same cohort, 36 percent of those in the ODM group have had at least one abnormal OGTT result by 14 to 17 years of age.

Finally, 11 of 21 adolescents with polycystic ovary syndrome had abnormal OGTT results (9 IGT, 2 DM).

The prevalence of IGT is related to increasing age in several studies, but few studies have examined children less than 10 years of age. Children under 10 with obesity have IGT rates comparable to adolescents, although type 2 DM is reported with much less frequency in this young group. Two longitudinal studies with repeated OGTT in Aboriginal and ODM children suggest that rates of IGT increase with increasing age, particularly during the peripubertal period.

**Diagnosis.** A comparison of IGT with IFG is presented in two articles and IFG and hemoglobin A1c are compared in the NHANES III study. In obese children, 6.6 percent of children and adolescents with IGT had IFG, indicating that this method of screening for IGT is very insensitive.
Similarly, hemoglobin A1c is a poor screen for IFG in children. The reproducibility of OGTT testing has not been well studied. Sinha et al. showed that, upon retesting, 10 of 10 children (4 with normal glucose tolerance and 6 with IGT) had the same categorization 3 months later. One article included in the full review for reproducibility of diagnosis that included adolescents concluded that the reliability of test results was likely lower in younger populations.

Prognosis. The prognosis of IGT in childhood and adolescence has not been well studied. Three studies had longitudinal data in IGT, but the numbers were very small and did not allow a prediction or rate of conversion from IGT to DM. All of these longitudinal studies were in high-risk populations (two in Aboriginal populations in the United States and the South Pacific) and one in ODM.

Treatment. Treatment of IGT in childhood has been examined in a single small open-label trial of metformin for 3 months in 15 adolescents with polycystic ovary syndrome and IGT. Eight of 15 children had normal glucose tolerance when re-evaluated after 3 months of metformin therapy. This was associated with a significant decline in BMI, although there was no significant change in fat mass.

Discussion

Diagnosis

An accurate diagnosis of DM is required because the consequences for the individual are considerable and lifelong. The diagnosis of IFG or IGT is used as a risk indicator for future DM and/or CVD. The problem with these arbitrary classifications is that test reproducibility is poor, and this encourages repeat testing that adds to the uncertainty and confusion of the diagnosis when results are different.

Reproducibility of IGT and IFG. The observed reproducibility for both IGT and IFG classification in these studies was roughly 50 percent. The kappa coefficients for the IGT category were quite low and indicate overall fair agreement. The potential factors contributing to the variation and poor reproducibility were not assessed for this review.

The probability that a significant change has occurred in serial measurements can be estimated by calculating the reference change value (RCV). For FPG, the RCV = 2^{1/2} * 1.96 * (1.42 + 6.32)\(^{1/2}\) or 17.9 percent. For 2-hr PG, the RCV = 2^{1/2} * 1.96 * (1.42 + 16.62)\(^{1/2}\) or 46.4 percent. The difference between two fasting glucose values would therefore need to be greater than 17.9 percent to be significantly different. A lower RCV would increase the sensitivity to change, or reduce the variation noise, and could be achieved if the analytical and/or the biological variation are lowered. In the best case scenario, the lowest biological variability reported for fasting glucose was an FPG CVI of 4.8 percent. If this value is used along with an intra-laboratory imprecision of 1 percent and no bias, the RCV can be reduced to 13.6 percent. This is the very best or lowest amount of variation possible for a fasting plasma glucose measurement.

Comparison of IFG and IGT diagnosis. This review also compared among studies the proportion of participants classified as IGT (2-hr PG), IFG (FPG and 2-hr PG), I-IGT, IFG, I-IFG, and IGT/IFG. Comparisons among these categories were statistically significant except for I-IGT versus IFG and I-IFG versus IGT/IFG. This exemplifies the importance of clearly distinguishing categories as this can affect the proportion of study subjects and the conclusions from prognosis and treatment data.

The reproducibility for both IGT and IFG categorization is poor by both observed and kappa analysis. Because of the large variability in glucose measurement, the absolute FPG and 2-hr PG measurements may be more informative than categorization into IFG and IGT, respectively. Comparison of IGT and IFG categories shows a wide degree of variation among populations. The prevalence of IGT is greater than for IFG in almost all studies. High-risk populations have an equal or greater proportion of IFG compared to IGT diagnoses. Statistically, the proportion of study participants classified as IGT by 2-hr PG alone is greater than if the diagnostic criteria of both 2-hr PG and FPG are used. This will affect the conclusions of prognosis and possibly treatment data in population studies using only the 2-hr PG concentration (WHO epidemiological criteria).

Prognosis

This review provides further evidence of the relevance of the OGTT as a diagnostic test. Despite the many shortcomings of the OGTT reviewed here, it detects a very high-risk group for future DM and may either need to be more accessible to clinicians or replaced by a simpler test that provides comparable predictive information. The OGTT also detects a group at risk for CVD; and if IGT is causally related to CVD, the AR estimates suggest that its treatment may reduce CVD risk by as much as 20 percent to 40 percent.

These studies highlight the relevance of fasting and post-challenge glucometabolic abnormalities to clinically relevant outcomes. Intervention studies have already shown that DM can be prevented in these individuals with some interventions.

Risk for progression to DM. The results of this systematic review clearly show that IGT, IFG, I-IGT, I-IFG, and combined IGT/IFG are strong risk factors for future DM. The combined group has the strongest risk factor, and this observation is not surprising given the fact that the diagnostic threshold for DM is just a farther point along the dysglycemic spectrum than the threshold for either IFG or IGT. Nevertheless, these large risk estimates clearly do suggest that any clinical approach directed at preventing DM should include a policy of detecting IFG or IGT. They do not support
suggestions that measures of glucose are not necessary to detect individuals at risk for future DM. However, such a policy may be useful to reduce the number of individuals who require a glucose test.

**Risk for CVD outcomes.** The reviewed studies provide confirmation that IFG or IGT are risk factors for fatal and nonfatal CVD and are consistent with other studies that were excluded because whole blood or capillary samples were used to assay glucose levels. Moreover, the suggestion that IGT is a greater risk factor for CVD than IFG is supported by this systematic review but is based on the findings of a single study.85 This is not surprising given the fact that IGT is detected in response to stressing the physiology with a nonphysiological glucose load, thus exposing a degree of metabolic dysregulation that would not be apparent on the basis of fasting glucose levels alone.

**Treatment**

**Prevention of DM: lifestyle interventions.** This systematic review clearly demonstrates that DM can be prevented or delayed with lifestyle modification. All but one of the five studies that evaluated a combined diet and exercise program found significant benefits, with a pooled relative risk of 54 percent for progression to diabetes. The only trial to show no effect of a combined diet and exercise intervention was of short duration (6-month followup). Interventions with diet or exercise alone showed mixed results between studies. Efforts to modify dietary intake and activity levels in individuals at increased risk for developing DM are clearly warranted.

**Prevention of DM: pharmacotherapeutic interventions.** Only four trials to date have evaluated the effect of pharmacotherapeutic interventions on the risk for developing DM in individuals with IGT. Two of these studies, one involving acarbose and one involving metformin, demonstrated reduced rates of progression to DM with a relative risk reduction of about 25 percent. Given this relative paucity of information, recommendation of pharmacological intervention for the prevention of DM would seem premature at this time.

**Pediatric Population**

Despite the paucity of population-based studies, several cohort studies in high-risk groups suggest that IGT is a significant and potentially growing problem in the pediatric population. Indeed, larger proportions of children may have IGT than is currently recognized. It is critical to acquire an understanding of the precursors of type 2 DM development in children and youth. However, few conclusions can be made based on the current pediatric literature. Further investigation of prevalence in children and adolescents is necessary to clarify the magnitude of the problem.

**Diagnosis.** The reproducibility of the diagnosis of IGT with OGTT testing and the clinical significance of IFG versus IGT have not been widely examined in the pediatric literature. Although young age has been implicated as a predictor of poor reproducibility of OGTT results in adults, suggesting that reproducibility may be worse in adolescents and children, this was not the experience in one small pediatric study (n = 10).77

Clearly, further investigation of the reliability of diagnostic criteria for IFG and IGT is warranted. Furthermore, given the importance of the prevention of type 2 DM, it may be advantageous to identify children who have disturbed glucose metabolism (insulin resistance and/or beta cell dysfunction) before they develop IFG or IGT.

**Prognosis.** An understanding of how disturbed glucose metabolism progresses to IGT and to type 2 DM is key to the primary prevention of DM. Currently, details of this progression are completely lacking in the pediatric population. Prevalence data for type 2 DM suggest prognosis may vary with age, pubertal status, and ethnicity. Family history of DM, exposure to a diabetic environment in utero, fitness and physical activity, fat distribution, and characteristics of nutritional intake may also influence the prognosis of IFG and IGT. Longitudinal studies are required to examine mid- and long-term outcomes of IGT and the determinants of outcome in multiple ethnic groups and across a broad age range. Investigation of other metabolic outcomes in children and adolescents with IFG and IGT would further improve our understanding of disturbance in health in this population. Better understanding of the prognosis of IGT in children and adolescents will clarify the need for intervention and contribute to optimal intervention study design.

**Treatment.** A single study has described the pharmacological treatment of IGT, and no randomly controlled lifestyle intervention has been reported in the pediatric age group. Given the increasing rates of IFG/IGT, research on the optimal approach to the management of these children should be a research priority. This research should compare lifestyle intervention and pharmacotherapy and identify optimal methodologies for young populations and their families. Although glycemic status is a key outcome variable, other metabolic and psychosocial outcomes should also be examined.

**Conclusions**

Analysis from this systematic evidence review suggests the following:

- **Diagnosis**—The reproducibility for both IGT and IFG categorization is poor. Therefore the absolute FPG and 2-hr PG measurement may be more informative than categorization into IFG and IGT respectively. The distribution of study participants in the IGT category varies significantly with the diagnostic criteria used. This will affect findings in epidemiological studies evaluating prognosis and treatment.

- **Prognosis**—Many studies consistently show that both IFG and IGT are strong risk factors for the development
of DM. Fewer studies also show that they are risk factors for future CVD and all-cause mortality.

• **Treatment**—There is evidence that combined diet and exercise, as well as drug therapy (metformin, acarbose), may be effective at preventing progression to DM in IGT subjects.

• **Pediatric population**—IGT is relatively common in childhood, particularly in children who are overweight. Further clarification of population-based prevalence and investigation to improve understanding of the diagnosis, clinical significance, and optimal management of IFG and IGT in childhood is required.

## Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the McMaster Evidence-based Practice Center under Contract No. 290-02-0020. It is expected to be available in September 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 128, *Diagnosis, Prognosis, and Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose*. In addition, Internet users will be able to access the report and this summary online through AHRQ’s Web site at www.ahrq.gov.

## Suggested Citation


## References


11
Evidence Report
Chapter 1. Introduction

Background

Magnitude and Importance of the Problem of IFG/IGT

Diabetes mellitus (DM) and its associated disease outcomes are a growing concern worldwide. The current global prevalence of DM for all ages has been estimated at 2.8% and is predicted to reach 4.4% by 2030. In the United States (U.S.), the prevalence of diagnosed DM was estimated at 5.1% in 1997 for adults between the ages of 40 and 74 years. In 2002, costs for treating DM and the resulting complications were high, with expenditures and lost productivity estimated at $132 billion in the U.S. Due to the high prevalence of DM and the economic and health outcome burdens associated with this disease, there is intense interest in identifying and reducing the impact of risk factors in order to prevent the onset of DM and minimize morbidity.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) refer to the intermediate metabolic states between normal and diabetic glucose homeostasis. One or both of these conditions are thought to be the precursors of DM, but how they progress to overt disease is not well understood. The risk for both macrovascular and microvascular complications increases across the distribution of blood glucose concentrations well below the level for overt DM, and is more strongly associated with post-challenge hyperglycemia than fasting glucose levels. However, it is still unclear from the literature whether this ‘glucose effect’ is independent of other classical risk factors such as blood pressure (BP) and lipids. It is also unclear whether this pathology is related to only blood glucose levels or also involves abnormalities of other metabolites such as free fatty acids. There is accumulating evidence that some microvascular complications emerge in these glucose ‘intolerant’ individuals.

The term IFG was introduced in 1997 to define those individuals with fasting plasma glucose (FPG) between the upper limit of normal FPG and the lower limit of diabetic FPG. IGT refers to those individuals with a 2-hour post-load plasma glucose (2-hr PG) between the upper limit of normal and the lower limit of diabetic. The International Diabetes Federation IFG/IGT Consensus Workshop concluded, based on these criteria, that IGT and IFG differ in their prevalence, population distribution, phenotype, sex distribution, and risk for total mortality and cardiovascular disease (CVD). Similarly, the Third National Health and Nutrition Examination Survey found differences in the percentage of the U.S. population with IFG for men (8.8%) versus women (5.0%) and for non-Hispanic white (6.8%), non-Hispanic black (7.0%), and Mexican-American (8.9%) people. Thus, there is also interest in identifying those subgroups with IFG/IGT who are at greater risk for progression to DM and other health outcomes.

Historical Development of IGT and IFG Classifications

Both IFG and IGT are associated with glycemic disturbances that represent different metabolic processes with different prognostic consequences. Some evidence suggests that IGT is primarily associated with insulin resistance and IFG is associated with impaired insulin
secretion and suppression of hepatic glucose output. Also, IGT is more consistently associated with increased risk for CVD, but IFG is not. Similarly, the magnitude of the risk for developing DM differs for these two metabolic states.

The historical development of IGT and IFG also has relevance to this systematic review. The diagnostic group of IGT was first defined in 1980 by the World Health Organization (WHO) expert committee on DM. IGT was not defined as a disease in itself but rather as a metabolic state (or disease process) associated with increased risk for adverse health outcomes. IGT was defined as dysglycemia between normal and DM. Moreover, it was used to identify individuals at high risk for DM and possibly CVD.

The relationship between IFG and IGT has generated controversy about how best to evaluate dysglycemia using either the oral glucose tolerance test (OGTT) or the FPG test. There is particular interest in which of these glycemic disturbance states is a better predictor of progression to DM or CVD. There are also questions regarding the reliability of FPG and OGTT due to the biological variability and the clinical implications for confirming glycemic disturbance and the increased risk for progression to DM and other health outcomes. Moreover, there is a need to evaluate which interventions (pharmacological or lifestyle) are effective in modifying glycemic disturbance in IFG or IGT populations and identify the gaps in the literature to provide direction for future research.

The prevalence of type 2 DM continues to be higher amongst aboriginal peoples of North America (1% of children six to 17 years of age and 4% of adolescent girls in a Pima population). Previously undiagnosed DM was also noted in four out of 112 obese adolescents (11 to 18 years) referred to a tertiary-care obesity clinic. Given the increasing trends in childhood obesity, it is imperative that our understanding of the precursors to type 2 DM in children is advanced. Furthermore, as the prevalence of obesity in children and adolescents has increased in North America, so too has obesity-related co-morbidities, previously thought only to occur in adulthood. Type 2 DM in childhood and adolescence, first recognized in aboriginal populations, is now also recognized in many other minorities (Black, Hispanic) and in those of European descent.

**Analytic Framework**

The analytic framework of the variables influencing the health of individuals with glycemic disturbance states is shown in Figure 1. For example, a direct relationship may exist between the general population and CVD. Alternatively, the health of individuals may be influenced indirectly by several risk factors that culminate in CVD. The distinction between the direct and indirect pathways was not always possible for some of the cohort studies eligible for this review.

**Objectives and Scope of This Systematic Review**

The goal of this systematic review is to evaluate the state of the evidence in the areas of the diagnosis, prognosis, and treatment of IFG or IGT. This topic was nominated by the American College of Physicians (ACP). The American Academy of Family Physicians (AAFP) and the American Academy of Pediatrics (AAP) joined the project as partners, and the McMaster University Evidence-based Practice Center (EPC) was contracted through the Agency for
Healthcare Research and Quality (AHRQ) to develop the report. The ACP, AAFP, and AAP will use these findings to inform clinical decision-making, develop clinical practice guidelines, and make recommendations. Additionally, research gaps will be identified and recommendations for future research directions will be discussed.

Preliminary questions posed by the AHRQ were subsequently modified and refined in consultation with the partner medical agencies, the AHRQ, and McMaster University EPC. The revised key questions to be addressed in this systematic review are as follows:

**Diagnosis Question**

What is the reliability of the diagnosis of IFG or IGT (e.g., does individual variability or measurement error require multiple measurements to ensure reliability of diagnosis)? What is the relationship between IFG and IGT?

**Prognosis Question**

For those identified with IFG or IGT, what are the short and long-term risks for developing the following endpoints:

a) Progression to DM or reversion towards normal glucose tolerance (NGT) or fasting glucose level,

b) Cardiovascular events and stroke,

c) Microvascular disease, specifically retinopathy and nephropathy as measured by proteinuria, microalbuminuria, elevated creatinine, albumin to creatinine ratio in the urine, dialysis, and/or renal transplant.

Does this risk vary by subpopulation, such as sex, race, obesity, age, or other risk factors (e.g., BP, elevated lipid levels)?

**Treatment Question**

What is the effectiveness of pharmaceutical and behavioral interventions for reducing the risks associated with IFG or IGT on the following endpoints:

a) Delay in onset of DM or reversion towards NGT or fasting glucose level,

b) Reducing risk of cardiovascular events and stroke,

c) Reducing risk of microvascular disease, including early markers such as retinopathy/proteinuria,

d) Improving other metabolic parameters associated with increased risk, such as BP and lipid levels.

Are some treatments more effective than others for any of the above endpoints, and does the effectiveness of interventions vary by subpopulation (e.g., age, sex, obesity)?
Pediatric Question

What is known about the development of IFG or IGT in the pediatric population?
Chapter 2. Methods

Topic Assessment and Refinement

The Research Team

A multidisciplinary research team representing epidemiology and systematic review methods (P. Raina, PhD; P.L. Santaguida, PhD), internal medicine and endocrinology (H. Gerstein, MD; D. Hunt, MD), clinical chemistry (C. Balion, PhD), and pediatric endocrinology (K. Morrison, MD) was assembled. The core research team, including experienced staff at the McMaster EPC (L. Booker, BA; M. Gauld, BA; L. Cocking; E. Estrabillo, B.Sc.) and a statistician (H. Yazdi, PhD), participated in regular meetings and reached consensus on key methodological issues. An international Technical Expert Panel (TEP; see Appendix D*) was assembled to provide high-level content expertise and participate in conference calls as needed. Participants in this panel include: Vincenza Snow (ACP), Amir Qaseem MD, PhD, MHS (ACP), Rodney Hornbake MD (ACP representative), Tommy Cross MD (ACP representative), Belinda Ireland MD, MS (AAFP), Kevin Patterson MD, MPH (AAFP representative), Francine Ratner Kaufman MD (AAP representative).

A teleconference with the partner organizations, the Task Order Officer (TOO) from AHRQ, the invited technical experts, and the McMaster team was held early during protocol development. The meeting’s purpose was to define the scope of the systematic review and to achieve consensus about the preliminary research questions. As a result of these discussions, some modifications were made to the original questions to address, in particular, important gaps in the knowledge needed by family physicians to diagnose patients for IFG or IGT.

Eligibility Criteria

Publication types, year, and language.
These criteria were applicable to all research questions:
1) Publication year: 1979 forward,
2) Publication language: English, and
3) Publication types: primary studies
Excluded: Systematic reviews, narrative reviews, editorials, letters to the editor, theses, unpublished position papers, consensus conference reports, and practice guidelines.

Study design.
Diagnosis question. No study design exclusions for primary studies.

Prognosis question. Primary studies with prospective cohort and randomized control trials (RCT) study designs with at least one year of follow-up.
Excluded: Case-control studies.

Treatment question. Only RCT designs were eligible. However, studies evaluating non-pharmacological interventions (lifestyle, behavioral, or surgical treatment) using non-RCT

* Appendixes are available electronically; see http://www.ahrq.gov/clinic/epcindex.htm for Appendixes A-G.
designs (controlled clinical trials and concurrent cohort trials) were captured in an annotated bibliography and no other data were extracted. (Appendix C)

*Pediatric question.* All study designs were eligible.

**Study population.**

*General criteria for IFG and IGT classification.* Eligible citations had to include IFG or IGT groups as the study population or analyzable subgroup. The criteria for classifying dysglycemia were key to identifying this specific population. The glucose threshold values used to define DM, IFG, and IGT have varied over the past 25 years (see Table 1). The specific criteria reference (e.g., WHO 85) used within a study was noted. For the diagnosis question, additional checks were undertaken to compare the testing procedures described in the methods and results sections of each eligible study.

**Laboratory testing procedures.**

Laboratory test inclusion:

1. All laboratory testing for glucose had to be undertaken on venous blood plasma or venous blood serum.
2. OGTT must have used the following parameters: subject was given 75 g of oral glucose (1.75 g per kg to maximum of 75 g for children) and measurement was taken at two hours post-glucose ingestion.
3. All measurements must have been done in a laboratory and not with a point-of-care device.

Laboratory test exclusion:

1. The testing was done on whole blood or on capillary samples.
2. The laboratory testing was undertaken in an acute care setting (e.g. emergency ward, intensive care ward following, for example, a myocardial infarction or pneumonia).

These general criteria for the classification of IFG or IGT were applied to all four questions with the exception of the pediatric question.

*Pediatric question.* Increased recognition of type 2 DM in children has only occurred within the last two decades. Thus, we anticipated a limited number of articles addressing IFG or IGT in this population. Children were defined as 18 years of age or under. Any study that evaluated children, even if it did not meet all of our eligibility criteria for diagnosis, prognosis, or treatment, was included. We indicated “Include for Children” in the screening form (see Appendix B) if the study met the publication type, language criteria, and testing criteria for IFG and IGT.

**Study interventions.**

*Diagnosis question.* The research questions on the diagnosis of IFG or IGT were formulated using two distinct characteristics:

1. Test-retest reliability, and
2. The relationship between IFG and IGT.

The reliability of the IFG and IGT diagnostic criteria was assessed using a maximum boundary of eight weeks between the first test and repeated testing. There was consensus among
the TEP that true change in the disease status would not likely occur during this time interval, and it represented a typical interval for repeat tests in clinical practice.

For the relationship between the 2-hour OGTT and the FPG and the subsequent diagnosis of IGT and IFG, there was a general consensus that the two tests did not necessarily measure the same population. It was recognized that the literature does not agree as to which test is best or should be used to diagnose glycemic disturbance (IFG versus IGT); thus the degree of association between these two diagnostic tests was of interest.

It was also of interest to evaluate the variation between repeated laboratory measures in subjects. This question was not intended to examine the biochemical basis of the test. Instead, the intention was to describe the change in diagnostic category between having IFG, IGT, normal glycemic levels or DM on repeat testing. It was also of interest to describe any related factors that could contribute to the observed variance.

For the relationship between IFG and IGT, studies were included if they used both the FPG and the OGTT to evaluate subjects for dysglycemia.

_Treatment question._ There was no restriction on the types of interventions used on an IFG or IGT population. It was expected that these interventions would be categorized into four groups: pharmacological, behavioral, lifestyle, or surgical. Moreover, a minimum follow-up of six months was required.

The specification of interventions was not applicable for the prognosis and pediatric questions.

_Study outcomes._

The outcomes selected for this study applied to both the prognosis question and the treatment question. Nine disease categories were selected, and then possible medical or procedural outcomes were further specified within each of these categories (see list below). For example, within the cardiovascular disease category, 11 different cardiac-related outcomes were itemized. Studies were considered eligible if they evaluated at least one of the disease categories or one of the disease outcomes within the category.

_Glycemic:_
- Progression to DM (if measured with eligible testing criteria).
- Reversion towards NGT (if measured by eligible testing criteria).

_Cardiovascular disease:_
- Angina requiring a minimum 24-hour hospitalization.
- Myocardial infarction (MI).
- Acute coronary syndrome.
- Cardiac revascularization.
- Peripheral revascularization.
- Cardiac mortality.
- Angiographic percutaneous coronary interventions (PCI).
- Coronary artery bypass grafting (CABG).
- Stent insertion.
- Angioplasty.
• Stroke events.

**Mortality:**
• All cause.
• Disease specific (cardiac mortality was included in fatal CVD outcomes).

**Nephropathy:**
• Proteinuria.
• Microalbuminuria.
• Dialysis.
• Renal transplant.
• Elevated creatinine.
• Elevated albumin-to-creatinine ratio in the urine.

**Ocular:**
• Cataracts.
• Blindness.
• Retinopathy requiring laser photocoagulation.
• Vitrectomy.
• A retinal photograph assessed by standard criteria showing at least a two-step change in retinal images.

**Hypertension/blood pressure:**
• Concurrent therapy for hypertension or measured BP values. It was noted that studies may give baseline values of numbers of subjects on BP medications, and the number of subjects ending with BP medications. This was an acceptable outcome measure.

**Lipid level disturbance:**
• If subjects reported baseline and endpoint mean lipid levels for at least one of the following: low density lipids (LDL), total cholesterol levels, high density lipids (HDL), or triglycerides.

**Other:**
• Amputation (foot, lower limb, or foot digits).

---

**Literature Search Strategy**

A comprehensive approach to searching the literature was undertaken in order to capture all relevant reports. We performed a search for all studies involving IFG or IGT without limiting the search to diagnosis, prognosis, or treatment. In this way, we were less likely to miss any studies. After capturing all of the citations, we screened them for inclusion or exclusion pertaining to diagnosis, prognosis, or treatment. Our search for relevant articles included MEDLINE®, Cochrane Central Register of Controlled Trials, HealthSTAR, CINAHL®, AMED, PsycINFO®, and EMBASE® along with the personal files of the research team and the reference
lists\(^{16}\) of included articles (Table 2). Appendix A outlines the search strategy used for each database.\(^{16}\)

**Study Selection**

A team of study assistants was trained to apply the eligibility criteria in preparation for screening the title and abstract lists and the full-text papers. Standardized forms and a training manual explaining the criteria were developed and reviewed with the screeners (Appendix B).

For the title and abstract phase, two reviewers evaluated the citations for eligibility. Those articles that met the criteria were retrieved as well as those where there was insufficient information to determine eligibility. The article was retrieved if either one of the two screeners identified it for retrieval. For screening of full-text articles, two screeners came to consensus on the identification, selection, and abstraction of information. Disagreements that could not be resolved by consensus were resolved by one of our McMaster research team members. The level of agreement for inclusion of studies was measured using kappa statistics.

**Data Extraction**

All eligible studies from the selection phase (full-text screening) were abstracted onto a data form according to predetermined criteria. Appropriate data collection forms were developed for use in the systematic review (Appendix B). The articles were grouped according to the questions they addressed: diagnosis, prognosis, and treatment. One data extractor transferred the data onto data forms, and another data extractor checked the answers for accuracy before they were entered into a Microsoft Access database.\(^{17}\)

**Quality Assessment**

One member of the research team rated each eligible study within the prognosis and treatment categories for methodological quality (see Appendix B). RCTs were evaluated using the modified Jadad scale.\(^{18}\) A scale developed by MacKay et al.\(^{19}\) for non-RCT studies was used to rate the prospective cohort studies. The MacKay checklist had three subscales that could yield a score out of 5 possible points for reporting, 12 possible points for internal validity, and 1 possible point for external validity. The summary scores for methodological quality (Tables 8 and 21) were used to determine the strength of the evidence and to select those studies with the best methodological scores for subsequent meta-analysis.

**Summarizing Results: Descriptive and Analytic Approaches**

Data from the Access database were summarized in evidence tables, which included data about the general study characteristics (study design, location of study, population characteristics, mean age, and diagnosis criteria for dysglycemia), interventions, and outcomes assessed.

**Five classifications of dysglycemia.** Studies were grouped according to classification of the IFG/IGT status. Five dysglycemia classifications were considered as risk factors and these included:
1) isolated IGT (I-IGT),
2) isolated IFG (I-IFG),
3) non-isolated IGT,
4) non-isolated IFG, and
5) combined IGT and IFG (IGT/IFG).

The threshold values for these five diagnostic groups are detailed in Table 1 as a function of the changing criteria for classification over time. A diagnosis of isolated IGT excludes those diagnosed with IGT who have a FPG between 6.1 and 7.0 mmol/L (110 and 126 mg/dL). A diagnosis of isolated IFG excludes those without a 2-hour OGTT result and those with an OGTT level greater than 7.8 mmol/L (140 mg/dL). For example, a classification of I-IGT using the WHO 98 criteria implies that the FPG was not within the specified range of 6.1 to 6.9 mmol/L, which is indicative of IFG. Thus, this implies that a FPG test was undertaken and deemed negative. However, the OGTT was within the specified range of 7.8 to 11.0 mmol/L and considered positive. A negative FPG and a positive OGTT are required for the classification of I-IGT. Table 1 shows that the classifications of IFG, I-IFG, I-IGT, and combined IFG/IGT are more recent classifications of dysglycemia, commencing with the WHO 1998/99 criteria. Some preliminary evidence suggests that these dysglycemic classifications may represent different subgroups with potentially different mechanisms leading to glucose disturbance.

It should be noted that the criteria for diagnosis of dysglycemia in observational studies have been defined by the WHO — specifically, as the epidemiological criteria which enable researchers to classify subjects using just their blood glucose concentration, measured after an overnight fast or 2 hours after a 75 g oral glucose load, without any confirmatory symptoms or blood/plasma determinations. Thus, the recommendation for such large population studies was a single glucose test at the start of the study.

**Analysis**

**Diagnosis question.** Kappa estimations for the degree of concordance between IFG and IGT.

**Prognosis question.**

Measures of association between IFG or IGT and outcomes of interest. To evaluate the strength of the association between the exposure of IFG or IGT and the outcomes of interest (DM, CVD, mortality, lipid disturbances, etc), several metrics of risk were selected to evaluate both the risk in prognosis studies and the placebo arms of clinical trials testing interventions.

1) Annualized risk of progressing to the outcome of interest within the exposed group (i.e., diagnosed with IFG or IGT).
2) Unadjusted annualized relative risk (RR) with the confidence interval (CI).
3) Risk difference between the exposed group (IFG or IGT) and the normal group (NGT) or normal fasting glucose (NFG)). This difference was based on the annualized rates.
4) Attributable risk (due to the IFG or IGT exposure alone) expressed as a percent of the total risk for the duration of the study.

**Treatment question.**

1) Absolute risk difference (ARD).
2) Number needed to treat (NNT).
3) Relative risk reduction (RRR).

Equations Used To Calculate Measures of Association

**Diagnosis question.** Kappa coefficients are used to estimate the average rate of concordance between two repeated tests (categorical data) and also take into account chance occurrence.\(^{21,22}\) The equation and methods for calculating variance and 95% CI are shown in Appendix G, Section A.

**Prognosis question.** The equations for these measures of association for the prognosis question can be derived from a basic 2x2 table. Table 3 shows an example of a 2x2 table with the dichotomous classification (yes or no) for the outcome of interest, in this example DM, for those with the exposure (IFG or IGT) and those without the exposure status (NGT or NFG). From this table, the incidence for the duration of the study is derived. Eligible studies varied in duration from one to 18 years, thus it was difficult to compare measures of association between studies. For this reason, we converted estimates of risk, RR, and risk difference to annualized values.

*Annualized risk for those with IFG or IGT and in normal subjects.* The incidence was calculated as the rate of those individuals who developed the outcome of interest relative to those at risk, expressed as \(\frac{a}{n} \) in Table 3. Incidence rate is conceptually related to the risk (or probability) for developing an outcome over a specified time period.\(^{23}\) The method used to convert an incidence rate to the risk for those patients with IFG or IGT developing the outcome of interest for a specified period of time can be seen in Appendix G, Section B. The advantage of these equations is that it does not assume that the rate of change is linear, as would be the case of simple division of the estimated rate by the number of years.\(^{23}\)

The studies evaluated in this systematic review varied in duration from six months to 18 years. In order to allow comparison across studies, the time period was standardized to a one-year period when reporting risk of the exposed for the outcome of interest. Appendix G, Section B allows for conversion of the varied time periods across studies to a common time period of one year. To facilitate presentation of the annualized risk, values are shown as per 100 persons.

The annualized risk for those with IFG or IGT who then progressed to the endpoint of interest, which, in the example of DM, was calculated as follows: \(^{23}\)

\[
\hat{R}_{E_t} = \text{Annualized risk in the exposed group (IFG or IGT) at time } t \text{ and calculated as:}
\]

\[
\hat{R}_{E_t} = 1 - e^{-\lambda E_t}
\]

*Relative risk for those with IFG or IGT relative to NFG or NGT.* The RR is the ratio of the incidence in the exposed group (IFG or IGT) over the incidence of the unexposed group (NFG or NGT). Details of the derivation of RR are presented in Appendix G, Section B.

\[
\hat{RR} = \frac{\hat{R}_{E_t}}{\hat{R}_{C_t}}
\]

Calculation of the CI is presented in Appendix G, Section C.
Risk difference. The risk difference estimates the difference in risk that is attributable solely to the exposure of having IFG or IGT. This estimate is based on the annualized risk estimates and expressed per 100 persons.

Risk difference ($RD_i$) is calculated as:

$$RD_i = \hat{R}_{E_i} - \hat{R}_{C_i}$$

Attributable risk for those with IFG or IGT relative to NFG or NGT for the study duration. The attributable risk (AR) represents the proportion of excess risk of the disease outcome (above the background risk) in the exposed group. It is calculated using the incidence in the exposed group (IFG or IGT) and then subtracting the incidence in the non-exposed group (NFG or NGT). This numerator is then divided by the incidence in the exposed group (IFG or IGT) and multiplied by 100 in order to be expressed as a percent. Note that this estimate of the AR was not based on annualized estimates and was therefore not converted to an annualized proportion. The percent AR was expressed for the duration of the study. The AR was estimated using the following equation:

$$AR = \left(\frac{a}{n} - \frac{c}{n} \right) / \left(\frac{a}{n}\right)$$

Treatment question. The metrics of association (AR, RR, and AR) presented for studies evaluated in the treatment question are based on annualized risk estimates (from extracted data where permitted). However, many of the studies also presented these same estimates for the study duration but may not have reported sufficient data to permit annualized estimates. Thus, where possible both annualized and study duration estimates were presented.

ARD, NNT, and RRR. The ARD is a metric frequently used in clinical epidemiology that expresses the absolute risk difference between the event rate in the treatment group and that of the control/placebo group. The ARD compares the outcome rates on an arithmetic scale and is expressed in absolute terms.

$$ARD = \text{absolute value}[(R_{Ei} - R_{Ci})]$$

An alternative way of expressing the difference between groups is with the number of patients needed to treat (NNT). The NNT expresses the number of patients that a clinician must treat (with the intervention used in the study in question) in order to prevent one patient from having a target outcome. Clinicians may find this estimate of the risk difference to be a useful expression of the magnitude of the treatment effect. The NNT is calculated as the inverse of the ARD caused by treatment and is detailed, as follows:

$$NNT = 1 / ARD$$
Lastly, the RRR is an additional metric used in clinical epidemiology to express the risk that is taken away by the intervention used in the study. It assists in comparing studies with different baseline risks as it considers the ARD and then divides this by the risk for the placebo/control group. The equation used to estimate the RRR is as follows:

\[
RRR = \frac{ARD}{R_c} 
\]

**Meta-Analysis**

Quantitative meta-analyses were undertaken within each of the dysglycemia classification groups with a minimum of two studies for the unadjusted annualized RR. Some of the prospective cohort studies were related and not independent. One cohort could have multiple publications that reflected analyses done at different time intervals or on different groups within the same population cohort. Therefore, one representative publication was selected from the series of related studies to be included within the meta-analysis. The representative study was selected by consideration of the methodological quality score, the larger sample size, and the year of publication.

An overall pooled estimate was calculated across all study populations. Tests for heterogeneity were undertaken and, when statistically significant, only the results from the random-effects model (REM) were used to calculate the pooled estimate. Statistical software (SAS, version 8.2) was used to calculate the test for heterogeneity and the pooled estimates. Studies were weighted according to the inverse of their variances. Individual study effect sizes were calculated and plotted by year of publication.

**Tests of heterogeneity.** Tests of heterogeneity are statistical analyses for examining whether the observed variation in study results is compatible with the variation expected by chance alone. The test for heterogeneity selected for this review (Q) is detailed in Appendix G, Section D. The smaller the p value of the Q test (that is the more significant the test), the greater the likelihood that the observed differences between the studies was not due to chance alone. If the value of the Q test is relatively low (for example, one in 10 or one in 20) then the observed differences in the results between studies is likely related to factors other than chance. The potential factors that account for these differences can be numerous, and caution should be used when attempting to explore the nature of these differences. A single factor may not be the only important source of heterogeneity.

Tests of heterogeneity have some limitations that can make interpretation difficult. It has been suggested that the statistical power of the Q test in most cases is low (due to a small number of combined studies). As such, the test may indicate that it is not statistically significant at conventional levels, but, in reality, heterogeneity is present. Similarly, if the sample sizes of the studies are very large, the Q test may be significant even when individual effect sizes do not really differ. Furthermore, design flaws and publication biases can also make the interpretation of heterogeneity tests difficult. For example, if all the studies meta-analyzed have the same design flaw, a consistent bias is present that could make the effect sizes appear more reliable than they really are. Conversely, if the studies have different design flaws, the meta-analysis could show a positive test for heterogeneity, but, in reality, reflect the same underlying population.
In summary, caution must be used when interpreting the Q statistic. Some have argued that this test should be omitted while others have suggested that it should only be used as a diagnostic tool until further research accounts for variation between studies. One method recommended for dealing with sources of heterogeneity is the REM for meta-analysis.27 Rather than attempting to explain or adjust for the variability between studies, the REM takes into account the variation in the underlying effect sizes. The use of the REM is often used when the source of the variance cannot be identified.27 As such, the REM cannot investigate the causes of the heterogeneity.

When meta-analyses in this systematic review revealed a significant test for heterogeneity (Q), the REM was used to calculate the overall pooled estimate. Exploratory sensitivity analyses were undertaken for those meta-analyses that had five or more studies. In these analyses, each study was removed from the pooled estimate, and the Q test and the overall pooled estimate were reviewed. These data were used to judge whether any individual studies should be removed from the combined estimate.

**Peer Review Process**

A list of potential peer reviewers was assembled from a number of sources including our TEP, our partners, the McMaster research team, and the AHRQ (see Appendix D.)
Chapter 3. Results

The original search yielded 25,521 citations for all three questions combined. From the title and abstract screening, 1,243 articles proceeded to full-text screening. After the final eligibility screening, a total of 156 studies were abstracted for data for the diagnosis, prognosis and treatment questions and an additional 12 articles (which did not meet the criteria for the previous sections) were analyzed for the pediatric population alone. Figure 2 details the number of eligible studies for each research question. The results of the review are presented in this chapter according to the four main areas of investigation: diagnosis, prognosis, treatment, and pediatrics.

Diagnosis

General Characteristics of the Diagnosis Studies

Fifty-six reports describing 53 unique studies provided data on the reproducibility of repeat testing of FPG or OGTT, comparison of IGT diagnosis by different criteria, and the relationship between IGT and IFG diagnosis in the same population. General characteristics of these studies can be found in Table 4.

Reproducibility of IGT and IFG Tests

Four studies in five reports\textsuperscript{29-33} assessed the reproducibility of the OGTT for diagnosis of IGT, and two studies\textsuperscript{30,31,33} assessed the reproducibility of FPG for the diagnosis of IFG in publications after 1978 (Table 5). All repeat tests were done within six weeks of the first test. No triplicate testing was done. The populations studied were mostly Caucasians,\textsuperscript{29-31} except for one study on Hong Kong Chinese in two reports.\textsuperscript{32,33} The study populations were subgroups of larger studies and as such did not provide detailed characterization for the subgroup. The selection of the subgroups was essentially random, but not in all cases. Mooy and de Vegt used different subgroups of individuals from the Hoorn study. Mooy’s group\textsuperscript{29} included participants randomly selected from those individuals with a 2 hour post glucose challenge plasma glucose level (2-hr PG) of < 7.5 mmol/L, stratified by age and sex, plus all participants with a 2-hr PG ≤ 7.5 mmol/L (22% IGT by the first OGTT). de Vegt,\textsuperscript{30} however, used a reconstructed sample that represented participants without known DM (10.5% IGT by the first OGTT). Ko\textsuperscript{32,33} reported reproducibility for IGT and IFG from the same random sample of the working Hong Kong Chinese study in two separate publications. Farrer\textsuperscript{31} reported reproducibility of IGT in a high-risk group of mostly male post-CABG surgery patients. No details were given as to how the subgroup sample was selected. All studies used the same classification criteria: FPG ≥ 7.8 mmol/L and 2-hr PG 7.8 to 11.1 mmol/L for IGT, and FPG 6.1 to 6.9 mmol/L for IFG.

The reproducibility of the IGT and IFG tests was assessed by calculating the kappa coefficient, and the percent positive agreement between participants categorized as IFG or IGT on both tests. The kappa coefficients for IGT ranged from 0.04 to 0.56, indicating poor to moderate agreement.\textsuperscript{24} The proportion of participants classified as IGT by the first OGTT who remained classified as IGT upon repeat testing ranged from 33% to 48%. Most participants were reclassified as NGT (39.3% to 46.2%) with the remainder reclassified as DM (6% to 12.6%). The two Hoorn substudies gave essentially the same reproducibility, even though Mooy used a higher risk group to examine the reproducibility.\textsuperscript{29} The study that gave the lowest reproducibility (kappa = 0.04) involved mostly men who had undergone CABG and were
considered at high risk for IGT and DM. This study population had a significantly higher prevalence of abnormal glucose tolerance compared to the expected proportion of a population with the same 2-hr PG mean and SD.

Two studies retested participants based on FPG for IFG. The kappa coefficients for these studies were 0.22 and 0.44, indicating fair to moderate reproducibility. The proportion of participants classified as IFG by the first FPG, who were classified as IFG again upon repeat testing, was 63.7% and 51.4% for the Ko and de Vegt studies, respectively. The reclassified subjects had mostly NFG with some newly diagnosed DM. The low IFG prevalence in the Ko study population of 2.5% compared to 16.5% in the de Vegt study population may have accounted for the difference in reproducibility.

Another measure of reproducibility reported in two studies was within individual coefficient of variation (CV\textsubscript{I}) for IFP and 2-hr PG\textsuperscript{29,31}. The coefficient of variation is the ratio of the standard deviation to the mean and is used as a measure of the relative spread or precision. The CV\textsubscript{I} is a measure of random variation around a homeostatic set point for each individual. This variation is distinct from analytical variation (CV\textsubscript{A}) of a test method. Both studies gave similar CV\textsubscript{I} for FPG (6% and 6.3%) and the 2-hr PG (18% and 16.6%) concentrations,\textsuperscript{29,31} indicating consistency in variation between the different populations studied. Mooy’s study also reported no association between test-retest differences with age, sex, obesity (body mass index [BMI] or waist-hip ratio [WHR]), or BP. However, there was a positive association with heart rate on the difference between the 2-hr PG tests (mean difference 2, 95% CI 1.1 to 2.9 beats/min, p = 0.01).\textsuperscript{29} Furthermore, when the FPG and the 2-hr PG tests were categorized into NGT, IGT, and DM, the FPG CV\textsubscript{I} was greater for participants classified as DM (7.0%) compared to IGT (5.9%) or NGT (4.6%). The 2-hr PG CV\textsubscript{I} gave opposite results with a slightly better CV\textsubscript{I} for participants classified as DM (12.6%) compared to IGT (14.9%) or NGT (16.3%). No p values were provided, so it is not known if these differences were statistically significant.

**Comparison of IGT Diagnosis Using Different Criteria**

Four studies\textsuperscript{35-38} compared diagnoses using different IGT criteria (i.e., both IFG and the 2-hr PG concentrations).\textsuperscript{35-38} Studies that assessed IGT based on the epidemiological criteria (i.e., the 2-hr PG glucose concentration only) were excluded.\textsuperscript{20} Study population characteristics varied and thus represent a broad spectrum of populations (Asian, Dutch, Pima Indians, and women with previous gestational DM). The IGT criteria included were WHO 85, WHO 98, and WHO 99. All of these criteria use a 2-hr PG range of 7.8 to 11.0 mmol/L, but the WHO 85 uses an FPG cut point of < 7.8 mmol/L whereas both the WHO 98 and WHO 99 criteria use a cut point of < 7.0 mmol/L.

Table 6 summarizes the data from the four studies. More IGT diagnoses were made using an FPG cut point of < 7.8 mmol/L (13.6% to 31.5%) than of 7.0 mmol/L (8.3% to 29.7%). There were fewer cases of I-IGT (6.0% to 11.9%) compared to IGT by either FPG cut point.

Of the three studies using FPGs of < 7.8 mmol/L and < 7.0 mmol/L to classify IGT, two large population-based studies showed a similar negative change of 3.1% and 3.4%. One study showed a negative change of 5.8%. The latter study had fewer participants than the other two studies and consisted of a cohort of women with a history of gestational DM. The Pima Indian study group provided cumulative data from 1965 to 1999 for individuals aged ≥15 years. The DECODA study included Asian participants from five Asian countries (India, China, Indonesia, Japan, and Singapore) and the U.S. (Los Angeles and Hawaii).
The reduction in IGT classification using an FPG of < 6.1 mmol/L compared to < 7.0 mmol/L was greater in the Hoorn follow-up study (27.9%) compared to the Pima Indian study (19.0 %) and the DECODA study (19.3%). The Hoorn follow-up study excluded participants from the prospective-cohort baseline group who had died, moved away, had missing glucose values, or had DM (1142 of 2484 participants). In contrast, the Pima Indian and the DECODA groups were population-based and included all individuals.

**Relationship Between IGT and IFG**

Forty-nine studies provided data on the relationship between the diagnostic criteria for IGT and IFG. Most studies were prospective cohort studies (n = 14) and cross-sectional studies (n = 31). The majority of the studies used the WHO 98, WHO 99, ADA 97, or ADA 98 criteria for IGT. These diagnostic criteria are identical to each other (Table 1). The other major set of criteria used for IGT was the WHO 85 criteria that differed only in the FPG value (< 7.8 mmol/L compared to < 7.0 mmol/L). Many of the studies that reported IGT results with the WHO 85 criteria also reported results with the later criteria (WHO 98, WHO 99). One study used the WHO 80 criteria for IGT diagnosis. The diagnostic criteria for IFG are the same for the ADA and WHO in any year. However, the data were reported differently across studies. For example, studies may have used the term IFG or IGT but actually reported data for the I-IFG or the I-IGT, respectively. Also, studies reporting IGT classifications may have used only the 2-hr PG value rather than FPG and 2-hr PG values. Therefore, to relate studies according to the diagnostic criteria in Table 1, additional calculations were needed in some studies.

The data were extracted to give seven classifications, regardless of which criteria were described in each article. If the data were available to fit into these classifications, they were extracted to provide maximal information for comparison among studies. The seven classifications include IGT (2-hr PG 7.8 to 11.0 mmol/L), IGT (FPG < 7.8 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L), IGT (FPG < 7.0 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L), IGT (FPG 6.1 to 6.9 mmol/L), I-IGT (FPG < 6.1 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L), I-IFG (FPG 6.1 to 6.9 mmol/L, 2-hr PG < 7.8 mmol/L), and the combined group of IFG and IGT (FPG 6.1 to 6.9 mmol/L and 2-hr PG 7.8 to 11.0).

The difference between IFG and I-IFG classifications among the studies shown in Figure 3 is approximately 2.8 fold (p < 0.0001). Comparison of studies that have both IGT and I-IGT data show that classification is approximately 40% greater for IGT compared to I-IGT (p < 0.0001). Also, an IGT classification using the WHO epidemiological criteria, which omits the FPG value, classified 10% more participants as IGT (p = 0.0033).

Table 7 shows a summary of the percent of study subjects with the diagnoses of IGT, I-IGT, IFG, I-IFG, both IGT/IFG, and ratios of IGT to IFG and I-IGT to I-IFG. Studies containing data for all classification categories (n = 16) are expressed graphically in Figure 3. A line connects each classification group within each to show the change in proportion between each classification group and between studies. In general, the proportion of participants decreased with increased stringency of the diagnostic criteria—that is, IGT (2-hr PG) > IGT (FPG and 2-hr PG) > I-IGT > IFG > I-IFG > IFG and IGT. Four studies had a higher proportion of IFG compared to I-IGT, and three studies had a similar proportion of IFG and I-IGT. The three studies that had a higher proportion of IFG were hospital-based and selected patients who were at higher risk for DM. The other study was conducted on a distinct population of 7018 male police officers in Paris. Only one other study illustrated in Figure 3 was hospital-based,
but this study excluded all patients with disorders that would likely affect glucose metabolism.\textsuperscript{47} Other studies described high-risk populations but from non-hospital settings. The three studies with a similar proportion of IFG and I-IGT were from populations in Taiwan,\textsuperscript{44} Ghana,\textsuperscript{45} and Australia.\textsuperscript{46} None of the other 16 studies included participants from these countries.

The prevalence of IGT and IFG varied greatly among the studies, ranging from a few percent to over 30\% (Table 7). Comparisons between categories of IGT and IFG among the studies in Figure 3 were significant (paired t-test, \(p < 0.01\)) for all combinations except for I-IGT versus IFG and I-IFG versus IGT and IFG. Correlations between IGT and I-IGT and IFG and I-IFG classifications are expected to be high because of the similarity in test criteria. The correlation was much higher in these 16 studies for IGT versus I-IGT than for IFG versus I-IFG. The Passing-Bablok regression equations were IGT versus I-IGT, \(y = 0.879x – 1.29, r = 0.95, p = 0.0084\); IFG versus I-IFG, \(y = 0.521x – 0.78, r = 0.63, p \leq 0.0001\) (see Figures 4 and 5). Two studies were identified as outliers in the comparison of IFG versus I-IFG: the Paris police study\textsuperscript{43} and the Bangkok study.\textsuperscript{40} These studies were unique because the policemen study included men only and the Bangkok study included patients who had a history of borderline fasting glucose values.

### Prognosis

This systematic review addressed the question of whether being classified as IFG or IGT affected the future risk for adverse health outcomes such as DM, CVD (fatal and nonfatal), mortality, and microvascular diseases. This section summarizes studies that address these prognostic questions. As noted in Chapter 2, the eligibility criteria for this entire systematic review excluded studies in which participants were classified on the basis of whole or capillary blood testing. Thus, the well-known DECODE series of studies\textsuperscript{48} was excluded as the testing protocols for glycemic status included whole blood assays. Similarly, studies (or data within eligible studies) that evaluated predictors for developing IFG or IGT in people without IFG or IGT were excluded because the focus of this report was on the prognosis of those already classified with IFG or IGT.

### General Characteristics of the Prognosis Studies

A total of 104 studies met the initial eligibility criteria; a subset of these provided sufficient data (frequency counts) to estimate the annualized risk, the unadjusted annualized RR (with the CI), the risk difference, and the AR (expressed as a percentage for the observed study duration). Table 8 details the study characteristics for the eligible studies for the prognosis question. All studies prospectively followed cohorts; 90 were epidemiological studies and 14 were RCTs from which data were extracted from the placebo arm only.

The duration of follow-up varied from one year to 18 years. Five studies\textsuperscript{49-53} evaluated women only, and nine studies evaluated men only.\textsuperscript{43,54-61} The mean age and the ranges varied significantly among studies, but most included middle-aged and older subjects (Table 8). There was a broad representation of populations, including Pima Indians; Canadian First Nations people; Oriental populations from China, Taiwan, and Japan; Nauruans; Black Americans; Hispanic Americans; Caucasian Europeans (Finland, France, Netherlands, Malta, Europe); and South African Indians.
Evaluation of Short- and Long-term Risk and Progression to Endpoints of Interest

The estimates of short and long-term risk from eligible prospective cohort studies (Tables 9 to 15) and RCTs (placebo arm only) (Tables 16 to 19) presented sufficient data to compute the four selected measures of risk for different outcomes. The following four metrics of risk were selected to evaluate the short- and long-term risk of subjects with IFG or IGT and the progression to the outcomes of interest:

1) The annualized risk for those with the exposure (IFG or IGT) for developing the outcome per 100 persons by one year. This annualized risk represents the incidence of the outcome for those with the exposure. Because the studies evaluated had different durations (1 to 18 years), risk estimates were standardized for one-year periods across all studies.

2) The annualized RR compares the risk in the exposure group (IFG or IGT) relative to the non-exposed group (NFG or NGT). The annualized RRs are based on the annualized risk calculations and are therefore unadjusted estimates. The 95% CI is also presented.

3) The risk difference estimates the difference in risk that is attributable solely to the exposure, in this case having IFG or IGT. This estimate is based on the annualized risk estimates.

4) The AR estimates the risk beyond the background risk for which the exposed and non-exposed groups are subject to. All persons irrespective of their exposure status are subject to progressing to DM. This risk is also termed the background risk due to factors other than their impaired glycemic status. AR, in part, assumes the potential for a causal relationship between the exposure (IFG or IGT) and the outcome of interest. The AR was expressed as a percent and computed for the duration of the study. The study duration varies, which means that the AR estimates cannot be directly compared across studies.

Each table lists the duration of each study, the raw numbers of the subjects with and without the outcome in each of the exposed (IFG or IGT) and unexposed (NFG or NGT) groups, and the estimates of risk. For example, the study by Charles et al. in Table 9 lists four measures of the risk for developing DM in an individual with IGT. First, it shows that the annual risk of progressing to DM is 3.90 per 100 persons. Second, the table lists the unadjusted annualized RR, which is a measure of the strength of association between the exposure (IGT) and the outcome of interest (DM). In this example, an individual with IGT is 10.60 times more likely to develop DM within one year than an individual without IGT (95% CI 6.38 to 17.60). The fact that the CI excludes one, shows that this estimate is significant. Third, Table 9 lists the risk difference, which is the difference in annual risk between individuals with IGT and those without IGT (i.e., 3.54 per 100 persons in one year). Fourth, it lists the AR, which expresses the most that the risk could be reduced if the exposure (IGT) was both causally related to DM and completely eliminated. The estimate of 90.4% for the two-year duration of the study suggests that 9.6% of the risk for developing DM is due to other factors (background risk) and that 90.4% of DM cases could potentially be prevented if the IGT were successfully treated or eliminated. The AR may be used to inform decisions for prioritizing future population-based and clinical preventive interventions.
The annualized risk estimates for the outcome of reversion to NFG or NGT may present some challenge to the traditional clinical interpretation of risk. The typical understanding of risk is one associated with a negative consequence. Most therapeutic interventions are directed towards a change to normal glycemic status, and as such do not view reversion to normal levels as a pejorative outcome. For this reason, Table 10 presents only the annualized risk and risk difference (i.e., difference in risk for being normoglycemic at follow-up in dysglycemic versus normoglycemic people). Finally, several studies reported adjusted estimates of risk. These estimates were evaluated by various statistical models, including logistic regression, multivariate analyses, or proportional hazards modeling, and several covariates were evaluated. Some studies evaluated IFG or IGT populations only in their adjusted analyses. Others included the whole population of subjects (NFG or NGT or DM). As the analyses from these latter studies included an IFG or IGT variable, the “adjusted” estimate of risk for the outcome could be compared with the unadjusted estimate calculated in this report. This report describes some of these results.

Risk for Progression to DM

Tables 9 and 16 detail the studies that evaluated progression to DM. The number of studies that provided data for the five classification groups varied. Studies of people with IGT (n = 36) were the most numerous, whereas five studies included people with IFG and three studies included people with I-IGT, I-IFG, and both IGT and IFG. In general the methodological quality of the epidemiologic studies varied from 9 to 17.35 For RCTs, the Jadad scores varied from 3 to 8 (Table 8).

**Estimates of annualized risk per 100 persons in the exposed groups for progression to DM.** The minimum and maximum annualized risk estimates for each of the five dysglycemic classification groups are as follows (Tables 9 and 16):

- IGT group: 1.83 to 34.12
- I-IGT group: 4.35 to 6.35
- IFG group: 1.60 to 23.44
- I-IFG group: 6.07 to 9.15
- IGT and IFG group: 9.96 to 14.95

Two epidemiological studies and four RCTs had particularly high annualized risk estimates. The epidemiological studies included populations with many risk factors for DM. The IGT study with an estimate of 34.12 per 100 persons included subjects with a family history of DM, history of gestational DM, history of IGT, or obesity (with BMI > 27 kg/m2). The IFG study with an estimate 23.44 per 100 persons came from the same centre as the above IGT study and included subjects with a family history of DM, history of gestational DM, obesity (with BMI > 25kg/m2), or hypertension (systolic BP > 140 mm Hg or diastolic BP > 90 mmHg). An RCT of people with IFG included people with unstable angina or an MI in the previous month; three other RCTs selected for people at high risk for conversion to DM as they were testing strategies to prevent DM.

The variation in the annualized risk per 100 persons observed in Tables 9 and 16 are likely related to the different populations, mean ages, and sample sizes in these studies. For example, in a series of studies evaluating Pima indigenous populations for the IGT classification group, the annualized risk varied from 6.39 to 10.53 per 100 persons. In part, this could be due to subgroup analyses of the larger cohort, use of different criteria for determining IGT and DM.
(WHO 85 versus ADA 97), and varying follow-up lengths. The differences in methodological quality may also have contributed to the variation.

**Estimates of unadjusted annualized RR for progression to DM.** Table 9 also shows the unadjusted annualized RR and CI for 28 studies. Three of the studies within the IGT classification group were non-significant (i.e., contained one in the CI), indicating no association between IGT and progression to DM. Most of these studies had relatively small sample sizes. Three related studies all evaluating the same cohort of South African Indians had very high unadjusted annualized RRs (39.44 to 31.71). These high estimates are most likely artifacts reflecting both the small sample sizes and the fact that no NGT subjects developed DM. For the remaining studies, the unadjusted annualized RR with 95% CI varied as a function of the diagnostic groups in the following manner (Tables 9 and 16):

- **IGT group:** 3.58 (2.12 to 6.06) to 10.60 (6.38 to 17.60)
- **I-IGT group:** 3.51 (2.22 to 5.54) to 8.63 (5.46 to 13.64)
- **IFG group:** 2.40 (1.71 to 3.37) to 9.04 (6.28 to 13.03)
- **I-IFG group:** 5.05 (2.86 to 8.90) to 9.85 (6.65 to 14.60)
- **IGT and IFG group:** 5.50 (3.25 to 9.30) to 20.69 (12.51 to 34.22)

As with the annualized risk per 100 persons, fewer studies were found in diagnostic categories other than IGT, and, as such, interpretation across classification groups may be limited.

**Meta-analysis of the unadjusted annualized RR for progression to DM.** Meta-analysis of unadjusted annualized RRs of DM were undertaken for each dysglycemic group. A series of studies had no NGT subjects progress to the outcome of interest. To compute estimates of risk, a factor of 0.5 was added to all frequency counts in these studies (Table 9). The unadjusted RR estimates varied widely and we judged these to be inappropriate to include in the meta-analysis. It is likely that these estimates reflected the small sample size, and thus these studies were not included in the meta-analyses. As noted in Chapter 2, the pooled estimates were calculated using fixed-effects models unless there was evidence of statistical heterogeneity, in which case a random effects model was used. Evidence of heterogeneity was present for all of the dysglycemic groups except the I-IFG group.

Seventeen of 28 studies of people with IGT were included in the meta-analysis (Figure 6), and between three and five studies of people with the other glycemic classifications were included (Figure 7 to 10). The I-IGT, I-IFG, and IFG and IGT combined groups had approximately half the sample size of the remaining two dysglycemic groups and were based on estimates from the same three studies. The pooled estimates with the 95% CI are as follows (Tables 9 and 16):

- **IGT group:** 6.02 (4.66 to 7.38) (p < 0.0001)
- **I-IGT group:** 5.55 (3.15 to 7.95) (p = 0.002)
- **IFG group:** 4.70 (2.71 to 6.70) (p = 0.0003)
- **I-IFG group:** 7.24 (5.30 to 9.17) (p = 0.0001)
- **IFG and I IGT group:** 12.21 (4.32 to 20.10) (p = 0.0054)

To determine if statistical heterogeneity in the IGT group was due to one particular study, the analysis was repeated by removing one study at a time. This did not eliminate the heterogeneity. To determine if it was due to methodological weaknesses, the analysis was repeated after
removing the three studies with the lowest methodological scores. This approach similarly did not reduce heterogeneity.

**Estimates of annualized risk difference per 100 persons/year for progression to DM.**
The range of estimate of annualized risk differences are as follows (Table 9):

- IGT group: 1.64 to 24.60
- I-IGT group: 3.62 to 5.51
- IFG group: 0.93 to 18.95
- I-IFG group: 5.35 to 7.33
- IFG and IGT group: 8.15 to 14.22

Two studies recruited high-risk subjects, which could account for the higher risk differences (18.95 and 24.60). Similarly, the Vermes et al. study recruited subjects with previous MIs, which may be a factor in the higher risk difference of 13.86 in the IFG group (Table 9).

**Estimates of the AR (%) in the exposed group for the entire study duration for progression to DM.**

High estimates of AR were calculated for the outcome of DM in dysglycemic individuals. Estimates for each dysglycemic group are as follows (Table 9):

- IGT group: 52.8% to 97.0%
- I-IGT group: 68.8% to 86.6%
- IFG group: 57.3% to 86.9%
- I-IFG group: 77.1% to 88.5%
- IGT and IFG group: 78.6% to 93.0%

Thus, if there is a causal relationship between IFG or IGT and progression to DM, as many as 97% of cases of DM within the IGT group could be prevented by treating or eliminating dysglycemia.

**Comparison of studies with different diagnostic groups for progression to DM.**

Table 20 lists estimates of risk for the three studies that evaluated more than two dysglycemic diagnostic groups. These studies represent very different populations, including Pima Indians, Asians, and Scandinavian subjects, which could account for the differences in risk magnitude.

Although comparison across the dysglycemic classification groups is limited to these few studies, it suggests a gradient of increasing DM risk (as assessed by any metric) from IGT to IFG, and from IFG to both IFG and IGT. Two of these studies reported adjusted analyses that also showed evidence of the gradient observed in the unadjusted estimates.

**Evaluation of adjusted estimates of risk in studies evaluating progression to DM.**

Only 32 of the 104 studies reported multivariate regression analyses and estimates of risk associated with other risk factors. The types of statistical approaches, the population used in the statistical modeling (which often was a subgroup of the study population), and the covariates that were evaluated or significant in the model were abstracted. The factors evaluated in models included age, sex, BMI, WHR, family history of DM, smoking, hypertension, FPG, 2-hr PFG, (2-hour) fasting C-peptide, 2-hr fasting plasma insulin, 2-hr fasting plasma proinsulin, 2h-non-esterified fatty, fasting plasma triglyceride, genotype, hemoglobin-alpha, HDL, ratio of fasting insulin to glucose, iliac-to-thigh ratio, and photoparoxysmal response.
Proportion of Individuals Reverting to NGT/NFG

Tables 10 and 17 list the annualized risk of reversion from IFG or IGT to normoglycemia (i.e., neither IFG nor IGT) and the absolute difference in this risk between these individuals and individuals who were normoglycemic at baseline.

Estimates of annualized risk per 100 persons in the exposed groups for reversion to normal glycemic status. Only two of the five dysglycemic groups (IGT and IFG) had eligible studies. The ranges of annualized risk of reverting to normal within the exposed group (per 100 persons) are as follows (Tables 10 and 17):

- IGT group: 2.66 to 51.35
- IFG group: 28.55

Five studies had relatively high annualized risk of reversion (15.77 to 51.35 per 100 persons) and three of these studies evaluated subjects of Asian descent\(^{63,64,81,82}\) (Tables 10 and 17); one study evaluated male Paris police officers only\(^5\) (risk 41.10 per 100 persons). The only study of women with polycystic ovary syndrome (PCOS)\(^49\) had the lowest rate of reversion (risk 2.66 per 100 persons).

The absolute value of the annualized risk differences ranged from 12.53 to 53.06 per 100 persons. Thus up to 53% fewer people with IFG or IGT than normoglycemic people were normoglycemic after one year of follow-up.

Meta-analysis of unadjusted RR. Ten studies that reported reversion rates were pooled (Figure 11). The overall pooled estimate was 0.33 (0.23 to 0.43). The overall estimate would suggest that approximately one third of those with IGT will revert to normoglycemic status at follow-up. Test for heterogeneity was significant (p < 0.0001), suggesting the variability was not due to chance, and further exploration of the causes would be required. Most studies evaluated changes in dysglycemic status using a single test and likely this high rate of reversion is related to misclassification.

Risk for Nonfatal CVD Outcomes

Table 11 details the estimates of risk for nonfatal CVD outcomes for IGT (n = 1) and IFG (n = 5). The outcomes characterizing CVD included atherothrombosis, non-stenotic atherosclerosis, clinical MI, PTCA, stroke, unstable angina, heart failure, and combinations of these (major event, any event). Study durations varied from five to nine years. All of the studies were published from 1998 forward. Three\(^52,83,84\) of the five studies evaluating IFG as the risk factor are RCTs. One of these studies evaluated post-menopausal women with a history of MI from three to 20 months before recruitment.\(^52\)

Estimates of annualized risk per 100 persons in the exposed groups for nonfatal CVD outcomes. Estimates of annualized risk per 100 persons varied between the types of CVD events. The highest observed annualized risk was for the outcome of non-stenotic atherosclerosis in the IGT study\(^85\); the lowest observed annualized risk was for stroke in people with IFG.\(^52\) The range of annualized risk estimates are listed below (Table 11):

- IGT group: 11.58 to 12.39
- IFG group: 0.63 to 9.68
Estimates of unadjusted annualized RR for nonfatal CVD outcomes. Only two studies had significant unadjusted annualized RR (Table 11). The IGT study\textsuperscript{85} had similar (2.43 and 2.46) estimates and CIs for both atherosclerosis groups. The risk estimate was 1.41 for the outcome of any CVD event within the IFG group for one study.\textsuperscript{86} A second study\textsuperscript{83} had a RR equal to 1.24 for the outcome of any CVD event. All of these studies had a lower boundary CI near one, suggesting near non-significance. The results (95% CI) for studies with significant unadjusted RRs were as follows (Table 11):

<table>
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<tr>
<th></th>
<th>IGT group: 2.43 (1.44 to 4.10) to 2.46 (1.46 to 4.12)</th>
<th>IFG group: 1.24 (1.08 to 1.43) to 1.41 (1.17 to 1.69)</th>
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</thead>
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Meta-analysis of unadjusted annualized RR estimates for nonfatal CVD outcomes

Figures 12 to 14 depict the meta-analyzed results for nonfatal outcomes. Nonfatal CVD outcomes were combined for the three subgroupings of 1) PTCA (and CABG), 2) stroke, and 3) any or major cardiovascular event.

Tests for heterogeneity were not significant so a fixed-effects model was used. For the pooled estimates, two of the meta-analyses were not significant for the subgroups of PTCA and stroke (Figures 12 and 13). The pooled estimate for the outcome of any major cardiovascular event (Figure 14,) was significant (1.28 (1.15 to 1.41, p = 0.0001).

Estimates of annualized risk difference per 100 persons/year for nonfatal CVD outcomes. The highest risk differences were observed in the sole IGT study; note that these values encompass different nonfatal CVD endpoints and they are as follows (Table 11):

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<th>IGT group: 6.81 to 7.35</th>
<th>IFG group: 0.01 to 1.90</th>
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</table>

Estimates of the AR (%) in the exposed group for the entire study duration for nonfatal CVD outcomes. The ARs for CVD outcomes were higher in the IGT group than in the IFG group. The estimates are as follows (Table 11):

<table>
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<tr>
<th></th>
<th>IGT group: 52.8% to 52.9%</th>
<th>IFG group: 0% to 32.9%</th>
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</table>

Evaluation of adjusted estimates of risk in studies evaluating nonfatal CVD outcomes.

Nine studies undertook statistical analyses to evaluate the independent contribution of the various risk factors. Five of these studies\textsuperscript{52,83,84,86,87} employed proportional hazard modeling. Of the two studies\textsuperscript{85,88} that evaluated IGT, one study\textsuperscript{88} found IGT to be statistically significant for the outcome of carotid atherosclerosis, but the magnitude was not reported. The other study\textsuperscript{85} found IGT to be non-significant and was based solely on the IGT population. A single study\textsuperscript{89} evaluated IFG as an independent risk factor and was also not significant. One study\textsuperscript{86} evaluated FPG and the 2-hr PG concurrently; however, only the FPG was significant (RR 1.66, 95% CI 1.39 to 1.98) for the outcome of any CVD event.

The multivariable analysis in these nine studies also evaluated age, smoking, cholesterol (HDL, LDL, and triglyceride), fibrinogen, sex, BMI, race, hypertension, prevastatin treatment group, FPG, 2hFG, FPI, gemfibrozil, creatinine, ferritin, apolipoprotein B, and alcohol consumption. Models that did not pre-adjust for age showed that it was marginally significant in two studies.\textsuperscript{85,90} Most models pre-adjusted for age, sex, and ethnicity; sex or ethnicity were not shown to be significant risk factors, whereas three studies\textsuperscript{85,87,88} showed age to be significant.
Risk for Fatal CVD Outcomes

Eight studies reported fatal CVD outcomes, which were subdivided into ischemic heart disease, cardiocerebrovascular, and coronary in some studies (Table 12). Although the classification of subgroups varied somewhat among studies, most used the International Classification of Diseases (ICD) coding system. The I-IFG and IFG and IGT combined classifications could not be evaluated as there were no eligible studies. Study duration varied from five to 18 years. Three of the studies were based on a male cohort (Paris Police study) for the IGT, I-IGT, and IFG groups. Similarly, one study within the IFG group included only post-menopausal women with a history of MI. Two other studies in the IFG group recruited subjects with a history of either MI or coronary heart disease.

Estimates of annualized risk per 100 persons in the exposed groups for fatal CVD outcomes. The annualized risks per 100 persons in the exposed group are listed in Table 12 and 18. The ranges for the annualized estimates are as follows (Table 12):

- IGT group: 0.06 to 0.76
- I-IGT group: 0.23 to 0.34
- IFG group: 0.10 to 1.54

The differences in annualized risk are likely a function of the different study populations described previously above and the categorization of the CVD mortality subgroup classification.

Estimates of unadjusted annualized RR for fatal CVD outcomes. Four of eight studies listed in Table 12 had unadjusted annualized RRs that were significant. The calculated estimates (95% CI) are as follows (Table 12):

- IGT group: 1.67 (1.23 to 2.26) to 3.08 (1.47 to 6.47)
- I-IGT group: 1.59 (1.07 to 2.28) to 1.72 (1.23 to 2.41)
- IFG group: 1.32 (1.04 to 1.67)

A single study within the IFG group had a marginally significant unadjusted RR. Tominaga et al. evaluated CVD outcomes in both the IGT and IFG groups concurrently, and the annualized risks were 0.42 and 0.28 respectively per 100 persons.

Meta-analysis of the unadjusted annualized RR for fatal CVD outcomes. Figures 15 to 17 show the meta-analyses for the IFG and IGT groups. Within the IGT group CVD and ischemic heart disease were combined (Figure15). The pooled overall estimate was 1.66 (95% CI 1.21 to 2.11). Within the IFG group, two studies were based on the same cohort from the Bezafibrate Infarction Prevention trial, and one of these was selected for meta-analysis. Two subgroups of fatal cardiovascular outcomes were selected for pooled estimates. Figure 16 shows the coronary heart disease (CHD)/CVD subgroup, and Figure 17 shows the pooled estimate for the subgroup of ischemic-related CVD mortality. The pooled estimates between the IGT and IFG groups do not differ substantively in magnitude; however only the IGT analysis was significant (with ischemic outcomes marginally so). Overall, the pooled estimates do not provide evidence of a significant association with IFG or IGT and fatal CVD outcomes.

Estimates of risk difference per 100 persons/year for fatal CVD outcomes. The risk differences vary within each dysglycemic classification as follows (Table 12):

- IGT group: 0.01 to 0.30
I-IGT group:   0.09 to 0.14  
IFG group:   0.01 to 0.60

Tominaga et al.\textsuperscript{93} evaluated CVD outcomes in both the IGT and IFG groups concurrently and the risk differences were 0.28 to 0.11, respectively.

**Estimates of the AR (%) in the exposed group for fatal CVD outcomes.** The AR for fatal CVD outcomes varied as follows (Table 12):

IGT group: 24.8% to 67.3%  
I-IGT group: 36.8% to 41.2%  
IFG group: 11.8% to 39.5%

With the exception of one study,\textsuperscript{93} the AR did not exceed 41%. Tominaga et al.\textsuperscript{93} evaluated CVD outcomes in both the IGT and IFG groups concurrently, and the ARs were 67.3% and 39.5%, respectively.

**Risk for Mortality**

In general, most studies that reported mortality outcomes had the largest sample sizes and some had the longest follow-up duration (up to 18 years) (Table 13 and 18). There were eligible studies within the IGT, I-IGT, and IFG classifications only; the I-IGT group was based on two studies on the same cohort.

**Estimates of annualized risk per 100 persons for mortality in the exposed groups.** Table 13 shows the annualized risk per 100 persons for mortality (all-cause, cancer, and cirrhosis categories). The ranges of the annualized risk are as follows (Tables 13 and 18):

IGT group: 0.09 to 2.44  
I-IGT group: 0.10 to 1.34  
IFG group: 0.56 to 1.39

The annualized risks for mortality from cancer-related and cerebrovascular disease in the IGT group were the lowest values. In contrast, cirrhosis-related mortality was the highest for the I-IGT group.

**Estimates of unadjusted annualized RR for mortality.** Two studies in the IGT group\textsuperscript{88,94} had non-significant results. The RR for all-cause mortality varied from 1.36 to 3.18 for the IGT group, and from 1.60 to 7.19 for the I-IGT group. One study showed a strong association between I-IGT and the outcome of death due to cirrhosis (RR 7.19)\textsuperscript{59} for male police officers and also showed the highest AR (0.86) for mortality outcomes. Three studies\textsuperscript{43,89,93} within the IFG group had non-significant results for all cause mortality.

Three studies\textsuperscript{55,91,93} evaluated both all-cause mortality and CVD mortality; both the RR and the AR estimates were approximately double in magnitude for the CVD-related mortality relative to all causes with the exception of one study.\textsuperscript{93} Two studies\textsuperscript{43,95} compared all-cause mortality outcomes to cancer-related deaths, and the RR and AR did not differ substantively for these outcomes.

The all-cause mortality estimates (95% CI) are as follows (Table 13):

IGT group: 1.36 (1.12 to 1.66) to 3.18 (1.79 to 5.63)  
I-IGT group: 1.60 (1.33 to 1.92) to 7.19 (3.37 to 15.37)  
IFG group: 1.18 (1.03 to 1.35) to 1.45 (1.27 to 1.66)
Meta-analysis of the unadjusted annualized RR for mortality. Figures 18 and 19 depict the meta-analysis for all-cause mortality in the IGT and IFG groups, respectively. Both these outcomes are marginally significant. As the Q test for heterogeneity was significant for the IGT group, a random effects model was used. The overall pooled estimates were 1.48 (1.09 to 1.86) for the IGT group and 1.21 (1.05 to 1.36) for the IFG group. To determine if statistical heterogeneity in the IGT group was due to one particular study, the analysis was repeated by removing one study at a time. In this analysis, the exclusion of one study\(^{64}\) changed the significance of the test for heterogeneity (Q test 5.78, p = 0.216); the overall pooled estimate increased from 1.48 (95% CI 1.09 to 1.86) to 1.58 (1.29 to 1.86).

Estimates of risk difference per 100 persons/year for mortality. The ranges for the risk difference are as follows for all-cause mortality (Table 13):

<table>
<thead>
<tr>
<th>Group</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>0.05 to 1.67</td>
</tr>
<tr>
<td>I-IGT</td>
<td>0.06 to 0.50</td>
</tr>
<tr>
<td>IFG</td>
<td>0.08 to 0.42</td>
</tr>
</tbody>
</table>

The difference for one study\(^{64}\) may be related to the small sample size (fewer normal subjects than IGT subjects). This study also contributed significantly to the heterogeneity in the meta-analysis.

Estimates of the AR (%) in the exposed group for the study duration for mortality. The ARs for all-cause mortality are summarized below (Table 13):

<table>
<thead>
<tr>
<th>Group</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>0.00% to 67.2%</td>
</tr>
<tr>
<td>I-IGT</td>
<td>35.1% to 86.0%</td>
</tr>
<tr>
<td>IFG</td>
<td>13.9% to 38.9%</td>
</tr>
</tbody>
</table>

The single study\(^{64}\) with an AR equal to 0% has been previously noted for its sample size issues. As with the other risk metrics for mortality, the AR was highest (86%) for cirrhosis-related mortality.\(^{59}\)

Risk for Lipid Disturbances, Hypertension, and Other Outcomes

Tables 14, 15, and 19 detail risk estimates for the studies that evaluated metabolic and other outcomes. The three studies that reported sufficient details regarding lipid type disturbances (Table 19) only reported mean change scores and therefore unable to estimate risk for these outcomes. In Table 14 one study\(^{96}\) was specific to pancreas-kidney transplant patients and had limited generalizability to other populations. Another study\(^{98}\) in Table 14 showed that the RR and AR for the outcome of hypertension was not significant for men but was for women. One study\(^{97}\) evaluated the outcome of retinopathy and showed no significant relationship with IFG (Table 15).

Treatment

General Characteristics of the Treatment Studies

Twenty-three reports of 14 RCTs published between 1992 and 2003 evaluated lifestyle or pharmacotherapeutic interventions in adults with IFG or IGT. Table 21 shows the general characteristics of all studies. Duration of follow-up ranged from six months to six years. Studies
involved 14 to 3234 participants with their mean ages ranging from 37.5 to 70 years. The studies included subjects from Europe, North America, Australia, and Asia. The trials evaluated a range of interventions, including diet and exercise, oral hypoglycemic agents (metformin, acarbose, and chromium), a statin (pravastatin), and an ACE inhibitor (enalapril). Outcomes included progression to DM or regression to NGT, cardiovascular complications, and the effects on BP and lipid levels (Tables 22 to 26). A meta-analysis was performed for the outcome of progression to DM by combining the four studies that used the intervention of diet and exercise (Figure 20).

Progression to DM: Lifestyle Interventions

Six RCTs evaluated the effect of lifestyle interventions on the risk for developing DM or reverting to NGT. The studies all involved adults with IGT. To be eligible, participants were required to have evidence of IGT on two separate OGTTs, or to have an IFG level along with evidence of IGT on a single OGTT. Two trials enrolled individuals on the basis of a single OGTT. Table 22 details these studies.

Five studies compared intensive combined diet and exercise programs that involved frequent study visits with lifestyle advice alone. One study compared an exercise program with advice alone, and two studies evaluated the effect of dietary intervention alone. One trial, the Diabetes Prevention Program (DPP), also included a metformin arm. The studies involved 64 to 3234 participants and the duration of follow-up ranged from six months to six years. Methodological quality scores ranged from 3 to 5 out of 8 for the modified Jadad scale, with a maximum possible score of 6 out of 8, given the fact that these trials were not blinded.

All but one of the trials that evaluated a combined diet and exercise program found a significant reduction in the risk for developing DM, or a higher rate of regression to NGT, with aggressive lifestyle modification. The absolute risk reduction for progressing to DM per year in the studies varied between 1.6% and 7.1%. The relative risk reduction (RRR) for progressing to DM in the intervention arms of the trials compared with the control arms was between 31% and 55%. The NNT for one year to prevent a case of DM was between 14.2 and 62.5.

Dietary intervention alone significantly reduced the risk for progressing to DM in one trial, but had no effect in a second study. The trial that evaluated an exercise intervention alone showed a significantly reduced rate of progression to DM (ARD 8.4%, NNT 11.9, RRR 49.8%).

The meta-analysis of the 4 studies that evaluated a combined diet and exercise intervention on progression to DM yielded a RR of 0.54 (95% CI 0.42 –0.70).

Progression to DM: Pharmacotherapeutic Interventions

Four RCTs evaluated the effects of pharmacotherapeutic interventions on the risk for developing DM in people with IGT. These studies assessed the effect of acarbose and metformin. The effect of enalapril in people with IFG and left ventricular dysfunction was assessed in a retrospective post-hoc subgroup analysis. The effect of pravastatin on the development of DM in people with IFG and a previous MI was assessed in a retrospective post-hoc subgroup analysis.
Acarbose. The STOP-NIDDM trial\(^{68}\) involved 1429 people with IGT and a fasting blood glucose value of 5.6 to 7.7 mmol/L and randomized participants to placebo or acarbose at a dose of 100 mg three times daily. Follow-up was for a mean of 3.3 years. The methodological quality score was 8 out of 8 for the modified Jadad scale. The study demonstrated a reduced risk for progressing to DM (32% versus 42%; RRR 0.25, 95% CI 0.10 to 0.37). This effect did not vary by age, sex, or BMI. The study also demonstrated an increased rate of reversion to NGT with acarbose relative to placebo (35% versus 31%, p < 0.0001).

Metformin. Three RCTs evaluated the effect of metformin in people with IGT. The methodological quality scores for the studies ranged from 6 to 7 out of 8 for the modified Jadad scale.

The largest study was the Diabetes Prevention Program,\(^{102}\) which involved 3234 people with IGT and a fasting blood glucose value of 5.6 to 6.9 mmol/L and followed participants for a mean of 2.8 years. Metformin was taken at a dose of 850 mg twice daily. The study found a significantly reduced risk of progressing to DM when taking metformin relative to placebo (7.8% versus 11.0% per year; RRR 0.31, 95% CI 0.17 to 0.43).

An unplanned subgroup analysis found that metformin was significantly more effective in individuals with a markedly elevated BMI of > 35 kg/m\(^2\) than in individuals with lower BMI levels (RRR for individuals with BMI > 35 kg/m\(^2\) 53%, 95% CI 36% to 65%; RRR for individuals with BMI 30 to 35 kg/m\(^2\) 16%, 95% CI –19% to 41%; RRR for individuals with BMI 22 to 30 kg/m\(^2\) 3%, 95% CI –36% to 30%). Metformin was also significantly more effective in individuals with higher fasting glucose levels (RRR for individuals with fasting glucose 6.1 to 6.9 mmol/L, 48%, 95% CI 33% to 60%; RRR for individuals with fasting glucose 5.27 to 6.05 mmol/L 15%, 95% CI –12% to 36%).

A smaller study\(^{106}\) involving 40 people with IGT confirmed on two separate glucose tolerance tests followed participants for one year. Patients in the active arm were treated with metformin 500 mg twice daily. Progression to DM was identical in each arm of the study (5%). Regression to NGT was not significantly different between the arms (40% with metformin and 30% with control).

The third trial\(^{82}\) involved a total of 90 individuals with IGT confirmed on two separate glucose tolerance tests. Patients in the active arm of the study received metformin at a dose of 250 mg three times daily. Follow-up was for one year. The risk for progressing to DM was not significantly decreased when taking metformin (6.7% versus 13.3%; ARD 6.7%, 95% CI –6.9% to 20.2%). The study did note an increased rate of reversion to NGT with metformin (72.7% versus 51.1%; ARD 21.6%, 95% CI 0.6% to 42.6%).

Enalapril. A retrospective subgroup analysis of the SOLVD trial participants from a single site evaluated the effect of enalapril at a dose of five to 20 mg per day in people with IFG and left ventricular dysfunction.\(^{65}\) The subgroup included 55 individuals with IFG diagnosed on the basis of a baseline fasting glucose level of 6.1 to 6.9 mmol/L (110 to 125 mg/dL). The diagnosis of new onset DM during the trial was based on the finding of a fasting glucose level of 7.0 mmol/L or greater on two separate visits. Chart reviewers were blinded to treatment allocation. Duration of follow-up was 2.9 years. The study found a decreased risk for progression to DM in the enalapril arm relative to the placebo arm (3.3% versus 48%, p = 0.0001).
Pravastatin. In the LIPID trial, a subgroup of 940 individuals with IFG and a previous MI were randomly allocated to treatment with either pravastatin 40 mg daily or placebo and followed for six years. A retrospective analysis found no effect on the rate of development of DM (fasting blood glucose level of 7 mmol/L or greater) or reported use of oral hypoglycemic medication or insulin. DM developed in 9.7% of people with IFG in the pravastatin group and 9.2% of people with IFG in the placebo group (p > 0.05) as reported in the study.

Comparing Lifestyle with Pharmacotherapeutic Interventions for the Prevention of DM in Individuals with IGT

The Diabetes Prevention Program (DPP) has directly compared the effects of an aggressive lifestyle intervention that addressed both diet and exercise with a pharmacotherapeutic intervention (metformin) for the prevention of DM in individuals with IGT. The DPP followed 3234 people for a mean of 2.8 years. Metformin was taken at a dose of 850 mg twice daily. The methodological quality score for the study was 5 out of 8 for the modified Jadad scale. The study found a significantly lower risk for progressing to DM with aggressive lifestyle intervention compared with taking metformin (4.8% versus 7.8% per year; RRR 0.39, 95% CI 0.24 to 0.51).

The beneficial effects of lifestyle intervention, compared with metformin, were especially marked in individuals 60 years of age or older (age 60 years or older 3.1% versus 9.6% per year, RRR 0.69, 95% CI 0.47 to 0.82; age 45 to 59 years 4.7% versus 7.6% per year, RRR 0.41, 95% CI 0.18 to 0.57; age 25 to 44 years 6.2% versus 6.7% per year, RRR 0.08, 95% CI –0.36 to 0.37) and in people with a body mass index < 35 kg/m² (BMI 22 to 30 kg/m² 3.3% versus 8.8% per year; RRR 0.63, 95% CI 0.44 to 0.76; BMI 30 to 35 kg/m² 3.7% versus 7.6% per year; RRR 0.53, 95% CI 0.28 to 0.72; BMI 35 kg/m² or over 7.3% versus 7.0% per year, RRR 0.04, 95% CI 0.47 to 0.26).

Cardiovascular Outcomes: Lifestyle Interventions

No RCTs of lifestyle interventions evaluated cardiovascular outcomes.

Cardiovascular Outcomes: Pharmacotherapeutic Interventions in People with IGT

Acarbose. One RCT evaluated the effect of acarbose on cardiovascular event rates in people with IGT. The STOP-NIDDM trial involved 1429 people with IGT and a fasting blood glucose value of 5.6 to 7.7 mmol/L and randomized participants to placebo or acarbose at a dose of 100 mg three times daily. Follow-up was for a mean of 3.3 years. The methodological quality score was 8 out of 8 for the modified Jadad scale. The primary outcome was the development of a major cardiovascular event (MI, new angina, cardiac revascularization procedure, cardiovascular death, congestive heart failure, cerebrovascular event, and peripheral vascular disease). The trial found a significant reduction in the risk for developing a major cardiovascular event in the acarbose arm compared with the placebo arm of the study (RRR 0.49, 95% CI 0.05 to 0.72; ARD 2.5%). Participants’ mean age was 54.5 years.
Cardiovascular Outcomes: Pharmacotherapeutic Interventions in People with a Previous MI and IFG

Two post-hoc retrospective subgroup analyses evaluated the effect of pravastatin therapy on cardiovascular event rates in people with a previous MI and IFG. Both trials assessed IFG status using a single fasting glucose test at baseline (fasting glucose 6.1 to 6.9 mmol/L; 110 to 125 mg/dL). Table 24 details the annualized estimates from these trials.

In the LIPID trial, a subgroup of 940 individuals with IFG and a previous MI were randomly allocated to either pravastatin 40 mg daily or placebo and followed for six years. The rate of cardiovascular death or nonfatal MI was significantly lower in the pravastatin group. The RRR was 36% (absolute event rate 17.8% in the control arm versus 11.8% in the pravastatin arm, p = 0.009) as reported in the study. The RRR of 36% was not significantly different from the RRR of 23% found in individuals with NFG levels at baseline (absolute event rate 14.5% in the control arm versus 11.3% in the pravastatin arm, p < 0.001 as reported in the study).

In the CARE trial, a total of 342 individuals with IFG and a previous MI were randomly allocated to either pravastatin 40 mg daily or placebo and followed for an average of five years. The study found an RR for the outcome of cardiovascular death or a nonfatal MI of 0.77 (p > 0.05), a result that was not significantly different from the RR of 0.72 for individuals with NFG levels at baseline.

Mortality Outcomes: Lifestyle and Pharmacotherapeutic Interventions

One trial reported the effect of lifestyle intervention on total mortality rates in individuals with IGT. In the Da Qing trial, individuals with IGT were allocated to one of four groups (control, dietary intervention, exercise intervention, or combined dietary and exercise intervention) and followed for six years. The methodological quality score was 3 out of 8 for the modified Jadad scale. Mortality rates were not significantly different between the groups (2.3%, 2.3%, 0%, and 4.0%, respectively).

Microvascular Outcomes

No RCTs evaluated the effect of lifestyle interventions or pharmacotherapeutic interventions on microvascular outcomes in individuals with IFG or IGT.

Blood Pressure and Lipid Levels: Lifestyle Interventions

Three RCTs evaluated the effect of lifestyle interventions on BP and lipid levels in people with IGT. Table 26 details some of the findings for these studies. The Finnish Diabetes Prevention study randomized 522 individuals with IGT to an intensive lifestyle intervention program or a control group and followed them for a mean of 3.2 years. The methodological quality score was 6 out of 8 for the modified Jadad scale. BP levels improved significantly more in the intervention group relative to the control group. Systolic BP fell five mm Hg in the intervention arm and 0 mm Hg in the control group when measured after two years (p = 0.0005). Diastolic BP fell five mm Hg in the intervention group and 3 mm Hg in the control group (p = 0.0125). The total cholesterol-to-HDL cholesterol ratio declined significantly more in the intervention group (0.6) compared with the control group (0.3) after
three years (p = 0.0009). The total cholesterol and HDL cholesterol level changes did not differ in the trial. Serum triglyceride levels showed a greater decline in the active arm than in the control arm (0.1 mmol/L versus 0.0 mmol/L, p = 0.024).

In a smaller trial,104 67 people with IGT were randomly allocated to a diet and exercise program or control and followed for six months. A significant improvement in systolic BP was noted with the lifestyle intervention. Systolic BP fell 7.6 mm Hg more in the intervention arm than in the control arm (p = 0.05). In the same study, the reduction in the diastolic BP level was 4.9 mm Hg more in the intervention arm than in the control arm (p = 0.052). No significant changes were found in lipid levels. The methodological quality score was 5 out of 8 for the modified Jadad scale.

No significant differences in BP or lipid levels were noted between intervention and control arm patients involved in a small trial108 of exercise alone that involved a total of 14 participants followed for six months.

**Blood Pressure and Lipid Levels: Pharmacotherapeutic Interventions**

Four RCTs reported the effects of oral hypoglycemic agents on BP and lipid levels in people with IGT. Table 26 details the findings for these studies.

Two trials reported the effects of metformin on BP levels in people with IGT.82,106 The two trials involved 40 and 90 participants, respectively, and both had a follow-up duration of 12 months. Metformin was dosed at 500 mg twice daily in one trial and 250 mg three times daily in the second trial. The trials demonstrated no significant effect of metformin on BP or lipid levels.

The STOP-NIDDM trial reported the effects of acarbose therapy on BP and lipid levels in people with IGT.68,107 The study enrolled 1429 individuals and had a mean follow-up duration of three years. Systolic BP was reduced by 0.97 mm Hg in the treatment arm, compared with 0.05 mm Hg in the control arm, p < 0.001. Diastolic BP fell by 2.8 mm Hg in the treatment arm and 1.4 mm Hg in the control arm (p = 0.008). Hypertension was defined as a BP of at least 140/90 on two consecutive visits to the family physician or the addition of antihypertensive medications between visits. The risk for developing hypertension was significantly reduced with the use of acarbose. In the active arm, 11% of participants developed hypertension compared with 17% in the placebo group (RR 0.66, 95% CI 0.49 to 0.89, p = 0.006; ARD 5.3%). The trial noted a significant reduction in triglyceride levels. Triglyceride levels decreased by 0.18 mg/dL over three years in the active arm, compared with 0.04 mg/dL in the control arm.

A trial of chromium109 at a dose of 160 µg per day in 26 individuals with IGT found no significant effects on lipid levels at six months.

**Pediatric Population**

**General Characteristics of the Pediatric Studies**

It was expected that the number of pediatric studies would be limited. All articles that met the general criteria (English language, full-text publication, published since 1979, and results for IFG or IGT analyzed separately from other study populations) and included children with IFG or IGT were collected (36 articles). Of these, a subset of five articles met the criteria for diagnosis, prognosis, or treatment according to the criteria outlined in the Methodology (see Table 27). These articles are included in the analysis of their respective sections. Four articles (one
An additional 31 articles that met the general inclusion criteria, but not the criteria for inclusion in the diagnosis, prognosis, or treatment sections, included subjects < 18 years of age. In 12 of these studies, the pediatric information could be extracted separately and was relevant to IGT in individuals < 18 years of age. Most studies addressed the prevalence of IFG or IGT in various at-risk populations and in the population at large. Two studies compared IFG with IGT for diagnosis in children. Four studies examined longitudinal follow-up of a cohort of children and addressed the prognosis of IFG or IGT. One study examined treatment in an open-label trial with metformin (see Table 28).

The 19 studies not included in the further analysis below were excluded for the following reasons: 9 discussed cystic fibrosis, one endemic fluorosis, one Turner’s syndrome, six related to type 1 DM risks, and no specific pediatric data could be extracted in two articles.

**Prevalence**

DM in childhood was initially recognized in Aboriginal populations. Thus, most prevalence studies have been in Aboriginal populations. Population-based prevalence of IGT in childhood Aboriginal populations varies from 3.5% in Tuvalu to 6.25% of Australian Aboriginals aged seven to 18 years. In Nauru, the prevalence varied with gender as 2/28 males and 2/44 females < 19 years of age had IGT in a population-based study. The population was a subset of the larger follow-up study published in 1992 and was reviewed in the prognosis section.

One population-based study examining IFG has been published. In 1988 to 1994, the Third National Health and Nutrition Examination Survey (NHANES III) was conducted in the U.S., and 1083 12 to 19 year olds had a glucose level measured after a minimum eight-hour fast. Of these, 1.8% had a fasting glucose level between 6.1 and 7.0 mmol/L. Of these 20 children, four were non-Hispanic white, nine were non-Hispanic black, and seven were Mexican American. The mean BMI percentile for this group was 86th percentile, but the range extended from the 10th to 99th percentile.

Studies of IGT prevalence in children are largely restricted to specific “at-risk” populations. IGT estimates in non–at-risk children are limited to a single study. In a study examining IGT in ten-to-16-year-old offspring of diabetic mothers, 2.5% of the control group had IGT. A small study found that of eight siblings of Hispanic children diagnosed with type 2 DM, two had IGT.
Offspring of mothers with pre-gestational or gestational DM (ODM) also have a higher prevalence of IGT. In a longitudinal study, the prevalence of IGT in ODM is 1.2% in those < 5 years (n = 168), 5.4% in five-to-nine year olds (n = 111), and 19.3% (95% CI 12.1 to 28.6) in ten to 16 year olds (compared to 2.5% (95% CI 0.4 to 8.1) in controls).\(^{133}\) Although the control group was somewhat lighter (BMI 20.3 ± 4.0 versus 22.8 ± 5.4 kg/m\(^2\)) and had 37% non-Caucasian participants compared to 51% in the ODM group, it is unlikely that these differences would account for the difference in IGT prevalence. Within this same cohort, 36% of ODM have had at least one abnormal OGTT result by 14 to 17 years of age.\(^{136}\) Eleven of 21 adolescents with PCOS had abnormal OGTT results (9 IGT, two DM).

The prevalence of IGT is related to increasing age in several studies, although the articles in this review did not measure prevalence in children less than 10 years of age, except in well-defined populations of obese children referred for management of obesity. Two longitudinal studies with repeated OGTT in Aboriginal and ODM children suggest that rates of IGT increase with increasing age, particularly during the peri-pubertal period.

**Diagnosis**

A comparison of IGT with IFG is presented in two articles,\(^{12,134}\) and IFG and hemoglobin A1c (A1c) are compared in the NHANES III study.\(^{137}\) In obese children, 6.6% of children\(^{134}\) and less than 0.08% of children and adolescents\(^{12}\) with IGT had IFG, indicating that this method of screening for IGT is very insensitive. In the NHANES III study, only three of 20 adolescents with IFG had an A1c that exceeded 6%. Of those children with an A1c over 6% who had IFG measured, three of 10 had IFG, suggesting that A1c is not a good screen for IFG in children.

The reproducibility of OGTT testing was examined by Sinha et al.,\(^{12}\) albeit in a small study. Repeat OGTT in 10 of 10 children (four with NGT and six with IGT) had the same categorization three months later. One article included in the full review for reproducibility of diagnosis included adolescents.\(^{138}\) Although specific pediatric numbers were not presented, the reliability of test results was lower in younger populations.

**Prognosis**

The prognosis of IGT in childhood and adolescence has not been well studied. Three studies had longitudinal data in IGT, but the numbers were small and did not allow a prediction or rate of conversion from IGT to DM. All of these longitudinal studies were in high-risk populations (two in Aboriginal populations in the U.S. and the South Pacific and one in ODM). Further details on determinants of progression from IGT to DM are not presented.

**Treatment**

Only one study has examined treatment of IGT, and this was an open-label trial of metformin for three months in 15 adolescents with PCOS and IGT.\(^{139}\) Eight of 15 children had NGT when re-evaluated after three months of metformin therapy. This was an association with a significant decline in BMI, although there was no significant change in fat mass.
Chapter 4. Discussion

This systematic review evaluates the evidence for three major questions on the diagnosis, prognosis, and treatment of IFG and IGT.

Diagnosis

An accurate diagnosis of DM is required as the consequences for the individual are considerable and lifelong. The diagnosis of IFG or IGT does not carry with it the same implications as DM, but these categories are being used as risk indicators for future DM and/or CVD.

It is important to review briefly the origin and rationale of the diagnostic criteria used for the various categories of glycemia. Frequency distribution studies for glucose demonstrate skewed or bimodal distributions (Figure 21). The center point between the two subpopulations in the bimodal distribution is the cut point above which DM is defined (7.8 mmol/L and 11.0 mmol/L for FPG and 2-hr PG, respectively). However, the proportion of subjects classified as DM by the 2-hr PG exceeds that of the FPG cut-point. In order to make these proportions equal, an FPG cut point for DM of 7.0 mmol/L was chosen. The risk for retinopathy, the most specific complication of DM, shows a sharp inflection at this point. The upper cut point for normal glucose metabolism is arbitrarily defined as concentrations below which there does not appear to be a risk for microvascular complications (6.1 mmol/L). This leaves a zone between normal glucose metabolism and DM termed impaired glucose metabolism (IFG or IGT).

The problem with these arbitrary classifications is that test reproducibility is poor, particularly for IGT and IFG. Knowledge of the poor reproducibility for IGT and IFG encourages repeat testing and adds to the uncertainty and confusion of the diagnosis when results are different. Also, patients classified as IFG or IGT may revert to apparently normal glucose metabolism; and, in fact, a large proportion of patients do. This effect may in part be explained by variability in glucose measurement and the cut-offs chosen on the frequency distribution curve. Subjects classified as IFG or IGT may have values anywhere within the criteria used to define these categories. They may be at the low end or at the high end of the curve but are still grouped together. The frequency distribution of glucose values within this range is greater at the low end of the range and less at the high end of the range. Therefore, subjects with low glucose concentrations will have a higher probability of changing classification from IGT to NGT than subjects with higher glucose concentrations.

Reproducibility of IFG and IGT

This review examined the problem with reproducibility for IGT and IFG. Four studies published after 1979 fulfilled the inclusion criteria of repeat testing within eight weeks using a venous plasma sample. The rationale for using these inclusion criteria was to reduce the variability in diagnostic criteria among different sample types. Glucose measurement using capillary blood is not interchangeable with glucose measurement using plasma. There are variable and unpredictable differences that cannot be resolved by conventional formulas and are sufficiently large to lead to misclassifications of glucose status. The eight-week repeat time
interval was selected, based on expert opinion, to avoid any physiological changes that could affect glucose homeostasis over a longer period of time (e.g., diet and exercise). The observed reproducibility for both IGT and IFG classifications in these studies was roughly 50%. IFG reproducibility (51% and 64%) was only slightly better than IGT reproducibility (33%, 44%, 47%, and 48%), which was somewhat poorer than DM reproducibility (69% and 59% for FPG and 2-hr PG, respectively). Kappa coefficients were also calculated to express the agreement between IFG and IGT categorizations using the results of test one compared to the results of test two. The kappa coefficients were 0.04, 0.38, 0.42, and 0.56 for the IGT category and 0.22 and 0.44 for the IFG category. These kappa coefficients are quite low and overall indicate fair agreement. The variation in reproducibility among these studies may be a function of the population characteristics. For example, reproducibility of IFG compared to IGT in the Ko study, a random sample of healthy working Hong Kong Chinese participants, was higher (64% and 44%, respectively) than in de Vegt’s study, an older Caucasian Dutch population that excluded participants with known DM (47% and 51%, respectively).

Although population type may help explain the variation among studies, it does not explain the sources of variation within a study. The uncertainty in glucose measurement can be estimated by considering all possible variables. Three categories of variables characterize the uncertainty and are expressed as coefficients of variation (CV = mean/SD * 100%). They are pre-analytical variation, biological variation, and analytical variation (CV_A). Biological variation, also called physiological variation, can be further divided into the variation occurring within an individual (CV_I) and the variation occurring between individuals (CV_G). These concepts of variation have been thoroughly described in Fraser’s book Biological Variation: From Principles to Practice.

The potential factors contributing to the variation and poor reproducibility were not assessed for this review but are fundamental for explaining the results obtained from this review. As described above, the sources of variation include pre-analytical, biological, and analytical variation. Pre-analytical variation is often considered to be part of biological variation because it is difficult to quantify pre-analytical variation separately from biological variation. Furthermore, the pre-analytical component of variation is considered to be negligible under optimal conditions. The optimal conditions were recently investigated and the following recommendations made. Patients should be instructed to fast for a minimum of eight hours, refrain from smoking and heavy exercise within two hours of sample collection, and rest in a sitting position for a minimum of 15 minutes. The blood sample is best taken in a tube containing heparin as the anticoagulant and sodium fluoride as a glycolytic inhibitor between 6:30 am and 9:00 am and placed immediately on ice water for a maximum time of one hour. Plasma should be separated within one hour by centrifugation at a minimum of 1000xg for 10 minutes, after which the sample is stable for 48 hours at ambient temperature (22°C). The evidence for the recommendation of these sampling criteria comes from several supporting studies. One study demonstrated diurnal variation with a difference in glucose concentration by as much as 10% (highest in the morning). Increased FPG is also associated with increased BMI ≥ 27 kg/m², increasing age, and male sex.

Studies to determine biological variation are most often done in controlled settings on normal individuals, thereby minimizing pre-analytical variation. In large population-based studies, however, variation in how the pretest instructions were followed is largely unknown and difficult to ascertain. Did participants actually fast for as long as they said, refrain from anything but water, and refrain from any drugs that might alter glucose metabolism? Other variables, such as
time of day and stress, are not usually considered, but they have been shown to alter glucose concentration. Glucose concentration also increases with age, but the diagnostic criteria do not take this into consideration. The estimates of biological variation are limited to the studies in which they were obtained. These estimates may vary among different populations (e.g., age, sex, and ethnicity) as well as in the presence of disease. They are at best approximations and may not be appropriate for all situations or individuals. Due to these reasons, biological variation is often overlooked when assessing diagnostic tests.

The quantification of analytical imprecision and bias of the glucose test methods is, however, much easier to do and is a lot less variable. Data from laboratory proficiency surveys and peer-comparison programs show CVs of 3% to 5% for total-group method (similar analytical methodology) and 2%, typically, for individual methods. Excellent laboratories may achieve a CV$_A$ of 1%.$^{225}$ Analytical variation is a small component of the total variation of glucose measurements.

All three components of variation can be taken together to obtain an estimate of measurement uncertainty in an individual test result. The magnitude of the variation will determine the probability that an individual’s glycemic classification (normal, impaired, or diabetic) will be the same when measured again. The reference change value (RCV) estimates the probability that a significant change has occurred in serial measurements. The RCV calculation considers the total CV determined by calculating the sum of the squares of analytical variation (CV$_A$) and individual biological variation (CV$_I$) such that RCV = $2^{\frac{1}{2}} \times Z \times (CV_A^2 + CV_I^2)^{1/2}$. The number 2 accounts for both samples being compared, and Z is a multiplier or standard normal deviates and relates to the probability. Conventional Z-scores are 1.96 and 2.58 corresponding to 95% and 99% probability, respectively. The RCVs for FPG and 2-hr PG can be calculated if CV$_A$ and CV$_I$ data are available. There was only one study in this systematic review with this data.$^{29}$ Using a Z score of 1.96 the RCV for FPG was 17.9% or RCV = $2^{\frac{1}{2}} \times 1.96 \times (1.4^2 + 6.3^2)^{1/2}$. For 2-hr PG, the RCV = $2^{\frac{1}{2}} \times 1.96 \times (1.4^2 + 16.6^2)^{1/2}$ or 46.2%. Therefore, the difference between two FPGs would need to be greater than 17.9% to be significantly different. A 95% probability can be described as, to prompt, suggest, advise, and propose. Although other probabilities may fulfill or better represent the clinical need. For example, if the probability sought were to hint, indicate or draw attention to, then a Z score of 80% would be preferable. Another example, considers two repeat FPG concentrations of 6.9 mmol/L and 6.0 mmol/L. The difference between them is 15%. Since this value is less than 17.9%, there is a 95% probability there is no difference between these two glucose results. Another way of expressing this is the 95% CIs which around 6.9 mmol/L (5.7 to 8.1 mmol/L) and 6.0 mmol/L (4.9 to 7.1 mmol/L) overlap. A lower RCV would increase the sensitivity to change, or reduce the variation noise, and could be achieved if the CV$_A$ or CV$_I$ are lowered. Values for CV$_I$ differ somewhat in the literature and depend on the type of participants selected and how closely the pretest protocol was followed. The lowest biological variability for fasting glucose was reported in a study of 12 young, healthy participants where there was strict adherence to a pretest protocol.$^{226}$ The FPG CV$_I$ in this study was 4.8%. If this value is used along with an intra-laboratory imprecision of 1%, the RCV can be reduced to 13.6%. This is the very best or lowest amount of variation possible for an FPG measurement at a 95% probability. The biological variation values used here are for populations and appear to be slightly different among individual diagnostic categories of glycemia.$^{29}$ There is more biological variation in subjects classified as IFG (5.9%) or DM (7.0%) compared to NFG (4.6%), but the opposite is seen for subjects classified as IGT (14.9%) or DM (12.6%) compared to NGT (16.3%).$^{29}$
Repeating a test will also reduce variation. The amount the variation will be reduced by a factor of \( n^{\frac{1}{2}} \). For example, in the best case, if two FPG tests are done the RCV will be reduced by a factor of 2\(^{\frac{1}{2}}\), giving a new RCV of 9.6%. More realistically, the RCV will only be reduced to 12.8% when population CVs are used.\(^{28}\) Repeat testing will reduce the deviation around the homeostatic set-point and have a much greater effect for 2-hr PG than FPG because of the higher individual variation for 2-hr PG. In the above calculation, the 2-hr PG RCV would be reduced to 33%, albeit still about three times higher than for repeat FPG testing.

The new clinical practice recommendations of the American Diabetes Association (ADA) redefined the diagnostic criteria for DM.\(^{227}\) The IFG category has now been widened by 0.5 mmol/L: 5.6 to 6.9 mmol/L from 6.1 to 6.9 mmol/L. This new range will positively impact IFG category reproducibility. There will be a slight increase in reproducibility because of the larger range of glucose values that determine this category.

The changes in criteria were made for fasting glucose only. No changes were made to the 2-hr PG OGTT criteria. Normoglycemia has been lowered to a glucose value of < 5.6 mmol/L from < 6.1 mmol/L. Hence, the IFG category has now been widened by 0.5 mmol/L: 5.6 to 6.9 mmol/L. Diagnosis of DM remains at \( \leq 7.0 \) mmol/L. The new term “prediabetes” was introduced and refers to patients with IFG and/or IGT. This term indicates that patients with this diagnosis have a relatively high risk for the development of DM.

The new recommendations for the diagnosis of IFG will result in an increase in the number of patients diagnosed as IFG. Patients with a fasting glucose value \( \geq 5.6 \) mmol/L, but less than 6.1 mmol/L, will now also be classified as IFG. Previously, these patients would have been categorized as normoglycemia. The impact of this will no doubt be an increase in repeat FPG tests and more OGTTs to confirm the abnormal result. If the ADA guidelines are followed closely, no repeat FPG or OGTT will be done on patients with glucose values < 7.0 mmol/L unless there is a high suspicion for DM. Repeat testing (FPG or OGTT) is only indicated for confirmation of DM and not for confirmation of IFG or IGT. However, the suggestion for patients classified as IFG on the first test is to do an OGTT to determine if they also have IGT. Also, since the diagnostic glucose range for IFG has been changed, there will be slightly better reproducibility in IFG categorization.

The actual increase in the number of OGTTs performed on patients with IFG on the first test will ultimately depend on the physician’s suspicion that a patient may be at risk for DM and their comfort level with a single test result. The potential increase in OGTTs was recently estimated using glucose data from a large regional laboratory.\(^{228}\) A frequency plot of all fasting glucose results showed that 14.8% of FPG concentrations were between 5.6 and 6.9 mmol/L. This percentage is similar to the reference distribution for FPG. A conservative estimate of the potential increase in number of OGTTs based on this percentage is 10-fold, and represents a huge increased economical burden on health care resources.

**Comparison of IFG and IGT Diagnosis**

This review also compared the proportion of participants classified according to the various criteria and categories for IGT and IFG with one test. No confirmation testing was done. As expected, the changing criteria for IGT (FPG < 7.8 mmol/L to < 7.0 mmol/L) decreased the number of participants classified as IGT, although the proportion varied among the different studies (a function of population type). A change of criteria from 7.8 mmol/L to 7.0 mmol/L had greater impact in a high-risk population (previous gestational DM) than in large population-
based studies. A change to the lower cut point of 6.1 mmol/L saw a large negative reduction in IGT for a Caucasian population with no DM compared to the general population of Pima Indians. The population effect was also observed when study data were plotted as a function of IFG or IGT category (Figure 3). In most studies that involved high-risk participants, the proportion of IFG was greater than that of IGT. Overall, there was a wide variation in the proportion of participants classified as IGT (2-hr PG), IGT (FPG and 2-hr PG), I-IGT, IFG, I-IFG, and IGT and IFG (Table 7). Furthermore, comparisons among these various categories were statistically significant except for I-IGT versus IFG and I-IFG versus IGT and IFG. This comparison highlights that the proportion of study subjects differs depending on which criteria are used to classify impaired glucose status. It also exemplifies the importance of clearly distinguishing categories as this can affect the conclusions from prognosis and treatment data. One of the most problematical aspects for this review was in the differentiation of what each study called IFG or IGT. The term IGT was used liberally to refer to the statistically different categories of IGT diagnosed with a) only the 2-hr PG criteria, b) both FPG and the 2h PG criteria and c) I-IGT criteria. A similar but not as profound a problem was seen for IFG and I-IFG nomenclature.

The clinical significance of the difference between IGT diagnosis and IFG diagnosis is not clearly understood, but either condition is a risk factor for DM and its associated outcomes such as CVD. The oral glucose tolerance test and its 2-hr PG value are described as a marker for early insulin resistance, which is a risk for CVD, whereas FPG value is considered a marker of impaired insulin secretion and suppression of hepatic glucose output.

**Prognosis**

The results of this systematic review clearly show that IGT, IFG, I-IGT, I-IFG, and combined IGT and IFG are strong risk factors for future DM. All of the dysglycemic classifications are also modest risk factors for various cardiovascular outcomes.

Most of the relevant data came from epidemiological studies that determined the glycemic status of participants at baseline and follow-up on the basis of a single glucose tolerance test. As this test has poor reproducibility, many participants may have been misclassified at baseline or at follow-up. The misclassification can occur in either direction. The observation that the results of the placebo arm data from RCTs (some of which did repeat testing) and the epidemiological studies are concordant may suggest that such misclassification was not an important determinant of the findings in this systematic review.

**Progression to DM**

The risk for progression to DM for patients within the five dysglycemic categories was consistent across different countries, study populations, study durations, and study designs. There was no evidence of a difference in risk among people with IGT, IFG, I-IGT, or I-IFG. Indeed, the meta-analysis of these groups reveals that the relative risks varied from 4.7 to 7.24 and the CIs for the pooled estimates of risk substantially overlapped. However, the three studies on people with both IFG and IGT yielded a much larger estimate of 12.21 (95% CI 4.32 to 20.10). From a clinical perspective, this is not surprising as individuals within this category likely have a more advanced metabolic disturbance than individuals in any of the other groups.
The estimate of AR was not influenced by study duration, population, or dysglycemic group. The AR varied from 53% to 97%, suggesting that for those with IFG or IGT, up to 97% of their risk for DM could potentially be prevented if the IFG or IGT were successfully treated or eliminated. It also suggests that much of the risk for progressing to DM is associated with the exposure to IFG or IGT rather than to other factors. Thus any public health initiative to prevent DM in society or in a subgroup of individuals necessarily becomes an initiative to treat IFG or IGT. Since DM is associated with progression to several other health outcomes (see analytic framework), such as CVD and retinopathy, both the prevention of DM and the treatment of IFG and IGT may have far reaching health benefits.

Risk for Reversion to NFG or NGT

This review also showed that up to 53% of dysglycemic individuals may revert to “normoglycemia” within one year. This observation does not mean that they have become metabolically normal. First, the poor reproducibility of glucose testing means that this observation may have occurred by chance alone. Second, there is no real biological difference between an individual whose 2-hour plasma glucose is 7.8 mmol/L on one occasion and 7.7 mmol/L on a repeat occasion, despite the fact that she would have been classified as IGT on the first occasion and normal on the second occasion. Indeed, these two numbers are likely just different estimates of the true value, as they are within the measurement and reproducibility error of each other. Nevertheless, these data do suggest that at least some individuals may revert to normal. This supports recommendations to diagnose DM in a clinical (as opposed to epidemiological) setting on the basis of at least two tests on two separate days, and suggests that such a recommendation should also be applied to diagnosing IGT and IFG.

Risk for Nonfatal CVD Outcomes

In the six papers evaluating nonfatal outcomes, CVD was subdivided into atherothrombosis, non-stenotic atherosclerosis, clinical MI, PTCA (some with CABG), stroke, unstable angina, heart failure, and combinations of these (major event and any event). As only one of the included studies comprised people with IGT, the hypothesis that IGT is a stronger risk factor for nonfatal CVD than IFG could not be carefully tested. Nevertheless, the single IGT study had higher risk estimates across all four metrics than any of the IFG studies. The largest unadjusted RR was 2.46 for the single IGT study and 1.41 for the IFG group. Within the IFG group the pooled estimates were not significant for the outcomes of PTCA/CABG and stroke and significant for the outcome of any nonfatal CVD event (RR 1.28, 95% CI 1.15 to 1.41). Similarly, the highest AR was 53% for the single IGT study and 33% for the IFG group. This metric suggests that treatment of IGT or IFG may reduce nonfatal CVD, but the impact of such an approach would be much lower than the impact on preventing DM.

Risk for Fatal CVD Outcomes

Nine studies reported fatal CVD outcomes, which were subdivided into ischemic heart disease, cardiocerebrovascular, and CHD in some studies. These studies varied in duration from five to 18 years and included men only, women only, subjects with a previous MI, a population-based study (the NHANES II cohort), and a clinical trial (the BIP cohort).
annualized risk per 100 persons were relatively low (less than one) with the exception of one study; two studies had significant RR estimates that varied from 1.67 to 3.08. Moreover, the pooled estimates for IGT show an RR of 1.66 (95% CI 1.21 to 2.11) and for IFG are marginally non-significant for ischemic death (RR 1.27, 95% CI 0.106 to 1.54) and CHD death (RR 1.25, 95% CI 0.99 to 1.51). Similar to findings in individuals with nonfatal CVD, these data suggest a greater risk associated with IGT than with IFG.

Risk for Mortality Outcomes

In general, most studies that reported all-cause mortality outcomes had the largest sample sizes and the longest follow-up duration (up to 18 years) of all eligible studies in this systematic review. The pooled analyses supported the hypothesis that both IGT and IFG are risk factors for mortality, with a slightly higher risk for IGT (RR 1.27, 95% CI 1.06 to 1.54) than IFG (RR 1.21, 95% CI 1.05 to 1.36). It is important to note that the category of all-cause mortality contains mortality due to DM. Indeed, much of the risk may be due to the embedded CV mortality risk.

Treatment

Twenty-three reports of 14 RCTs published between 1992 and 2003 evaluated pharmacotherapeutic or behavioral interventions in adults with IFG or IGT. Duration of follow-up ranged from six months to six years. Studies involved a range (14 to 3234) of participants with mean ages from 37.5 to 70 years. The studies included subjects from Europe, North America, Australia, and Asia. The trials evaluated a range of interventions including diet and exercise, oral hypoglycemic agents (metformin, acarbose, and chromium), a statin (pravastatin), and an ACE inhibitor (enalapril).

Prevention of DM: Lifestyle Interventions

This systematic review clearly demonstrates that DM can be prevented or delayed with lifestyle modification. Six RCTs have now evaluated the effect of lifestyle interventions on the risk for progressing to DM, or reverting to NGT, in individuals with IGT. All but one of the five studies that evaluated a combined diet and exercise program found significant benefits. The only trial to show no effect of a combined diet and exercise intervention was of short duration and followed patients for only six months, whereas other trials had follow-up durations of two to six years.

Dietary intervention alone reduced the risk for progressing to DM in one trial but had no effect in a second study. Exercise alone has been evaluated in only one trial to date, which found a significant benefit in terms of reduced risk for progressing to DM.

For individual patients with IGT, these results indicate that making meaningful changes in dietary intake and activity levels can dramatically reduce one’s risk for progressing to DM. The risk for developing DM was reduced by 31% to 55%, compared with participants in the control arms of the trials. The calculated ARDs in the risk per year for progressing to DM ranged from 1.6% to 7.1%, yielding NNT values of 14 to 62.

Two studies undertook subgroup analyses, but the DPP study provided the most detailed evaluation, though this had not been planned. The analysis demonstrated consistent benefits of
combined dietary and exercise intervention regardless of age, sex, ethnic group, BMI, or baseline glucose levels.

Given these findings, and the significant complications associated with established DM, efforts to modify dietary intake and activity levels in individuals at increased risk for DM are clearly warranted. How best to implement such a recommendation, however, remains unclear and is beyond the scope of this review. Public health interventions targeting populations known to be at increased risk would seem appropriate, along with more intensive intervention for individuals especially at risk, such as obese or overweight individuals with IGT or IFG. Development and evaluation of less intensive approaches for effecting lifestyle change will also be very important.

**Prevention of DM: Pharmacotherapeutic Interventions**

Only four trials to date have evaluated the effect of pharmacotherapeutic intervention on the risk for developing DM in individuals with IGT. Two of the studies, one involving acarbose and one involving metformin, demonstrated reduced rates for progression to DM with an RRR in the order of 25%. Two smaller trials with metformin that had a shorter duration of follow-up and a smaller number of participants found no significant effect of intervention on the risk for DM. The effects of pharmacological intervention on cardiovascular disease outcomes for individuals with IGT is an important topic that as yet has only been evaluated in one trial. Given this relative paucity of information, it would seem premature to recommend pharmacological intervention for the prevention of DM at this time.

**Pediatric Population**

Despite the paucity of population-based studies, several cohort studies in high-risk groups suggest that IGT is a significant and potentially growing problem in the pediatric population. Indeed, larger proportions of children may have IFG/IGT than is currently recognized. It is critical to acquire an understanding of the precursors of type 2 DM development in children and youth. However, few conclusions can be made based on the current pediatric literature. The reproducibility of test results and the prognosis of IGT may differ significantly from those characteristics in adult studies. This may be particularly true in the peri-pubertal period when physiological changes in insulin sensitivity are well known. Further investigation of prevalence in children and adolescents is necessary to clarify the magnitude of the problem.

**Diagnosis**

The reproducibility of the diagnosis of IGT with OGTT testing and the clinical significance of IFG versus IGT have not been widely examined in the pediatric literature. Fasting plasma glucose is recommended for the identification of Type 2 diabetes in children. In 2 studies that have compared IFG and IGT, IFG is a very insensitive test for the identification of IGT. Young age has been implicated as a predictor of poor reproducibility of OGTT results in adults, suggesting that reproducibility of classification may be worse again in adolescents and children. However, this was not the experience in one study in children (n = 10).
Clearly, further investigation of the reliability of diagnostic criteria for IFG and IGT is warranted. Furthermore, given the importance of the prevention of type 2 DM, it may be advantageous to identify children who have disturbed glucose metabolism (insulin resistance and/or beta cell dysfunction) before they develop IFG or IGT.

Prognosis

An understanding of how disturbed glucose metabolism progresses to IGT to type 2 DM is key to the primary prevention of DM. Currently, details of this progression are completely lacking in the pediatric population. Although IGT is present in 25% of obese children and adolescents, DM is found almost exclusively in adolescents. Furthermore, although IGT appears to be prevalent in overweight Caucasian, African-American, and Hispanic populations, type 2 DM is seen more commonly in visible minorities. These data suggest that age, pubertal status, and ethnicity may influence the progression from IGT to type 2 DM, but longitudinal studies to examine this are lacking. Family history of DM, exposure to a diabetic environment in utero, fitness and physical activity, fat distribution, and characteristics of nutritional intake may also influence the prognosis of IFG and IGT. Longitudinal studies are required to examine mid- and long-term outcomes of IGT and the determinants of outcome in multiple ethnic groups and across a broad age range. Investigation of other metabolic outcomes in children and adolescents with IFG and IGT would further improve our understanding of disturbance in health in this population.

Understanding the prognosis of IGT in children and adolescents will clarify the need for intervention and the assessment of outcome within future intervention studies.

Treatment

A single study has described the pharmacological treatment of IGT, and no randomly controlled lifestyle intervention has been done in the pediatric age group. Although promising, the single study of the effect of metformin on IGT in 15 girls with PCOS needs to be replicated with larger sample sizes and other at-risk populations. Given the increasing rates of these disorders, research on the optimal approach to the management of these children should be a research priority. This research should compare lifestyle intervention and pharmacotherapy and use optimal methodologies for young populations. Although glycemic status is likely the key outcome variable, other metabolic disturbance and psychosocial outcomes should also be addressed.

Limitations

The results and conclusions of this evidence report are based on the information that was available in published English-language reports. Contact with authors (or industry sponsors of drugs) could have resulted in identifying additional unpublished studies that may have reduced the likelihood of publication bias. Contact with the original authors of studies to supplement missing information from the included papers could have compensated for many of the difficulties in abstracting missing data. Our experience at the McMaster EPC suggests that the
majority of authors do not respond in a timely fashion to such requests, if at all. The budget and timelines available, however, were a limiting factor to accomplishing these tasks.

Many of the citations eligible for review were longitudinal studies and, as such, had multiple publications on the same cohort with different sampling frames (time interval[s] of data analyzed) and group analyses (subgroup versus whole sample). These related studies were not independent of each other, and a representative publication (based on study quality or sample size) was selected to combine in the quantitative meta-analysis when it was possible to do so. It was also noted that related papers on the same study cohort had diverse methodological quality scores. If a citation directed us to a previous publication for further details, attempts were made to attain the cited publication, and the quality score was applied accordingly. Despite this, variations were found in the quality scores for studies on the same cohort, and this likely reflects reporting biases. It was observed that often multiple publications on the same cohort undertook different analyses with different outcomes and even different classification criteria.

Despite these limitations, this AHRQ report provides valuable insight with regards to the level of the evidence that addresses the issues of diagnosis, prognosis, and treatment of IFG or IGT identified in this systematic review.

**Summary and Conclusions**

The reproducibility for both IGT and IFG categorization is poor by both observed and kappa analysis. The uncertainty in glucose measurement is large and therefore the absolute FPG and 2-hr PG measurement may be more informative than categorization into IFG and IGT, respectively. Comparison of IGT and IFG categories shows wide variation among populations. The prevalence of IGT is greater than that of IFG in almost all studies. High-risk populations have an equal or greater proportion of IFG compared to IGT diagnoses. Statistically, the epidemiological criteria (2-hr PG) result in a greater proportion of study participants being classified as IGT than if the diagnostic criteria (2-hr PG and FPG) are used. This will affect the conclusions of prognosis and possibly treatment data in population studies that use epidemiological criteria only.

IFG and IGT are clearly strong risk factors for future DM, and combined IGT and IFG is the strongest risk factor. These observations are not surprising given the fact that the diagnostic threshold for DM is just a farther point along the dysglycemic spectrum than the threshold for either IFG or IGT. Nevertheless, these large risk estimates clearly do suggest that any clinical approach directed at preventing DM should include a policy of detecting IFG and/or IGT. They do not support suggestions that measures of glucose are not necessary to detect individuals at risk for future DM. However, such a policy may be useful to reduce the number of individuals who require a glucose tolerance test.

The reviewed studies provide confirmation that IFG and/or IGT are risk factors for fatal and nonfatal CVD, and are consistent with other studies that were not eligible because plasma was not used to assay glucose levels, such as the DECODE study. Moreover, the suggestion that IGT is a stronger risk factor for CVD than IFG is also supported by this review. This is not surprising given the fact that IGT is detected in response to stressing the physiology with a nonphysiological glucose load, thus exposing a degree of metabolic dysregulation that would not be apparent on the basis of fasting glucose levels alone.
This review also provides further evidence of the relevance of the OGTT as a diagnostic test. Despite the many shortcomings of the OGTT (reviewed herein), it detects a very high-risk group for future DM and may either need to be more accessible to clinicians or replaced by a simpler test that provides comparable predictive information. The OGTT also detects a group at risk for CVD, and if IGT is causally related to CVD, the AR estimates suggest that its treatment may reduce CVD risk by 20% to 40%.

Finally, these studies highlight the relevance of fasting and post-challenge gluco-metabolic abnormalities to clinically relevant outcomes. Intervention studies have already shown that DM can be prevented in these individuals with some interventions (as described herein). Other studies are underway to determine if aggressive treatment of IFG or IGT has cardiovascular benefits.

The following general conclusions can be made:

- **Diagnosis of IFG or IGT**—The reproducibility for both IGT and IFG categorization is poor. Therefore, an absolute FPG and 2-hr PG measurement may be more informative than categorization into IFG and IGT, respectively. The distribution of study participants in the IGT category varies significantly with the diagnostic criteria used. This will affect findings in epidemiological studies evaluating prognosis and treatment.

- **Prognosis of IFG or IGT**—Many studies consistently show that both IFG and IGT are strong risk factors for the development of DM. Fewer studies also show that they are risk factors for future CVD, all-cause mortality, and lipid disturbances.

- **Treatment**—There is evidence that combined diet and exercise, and drug therapy (metformin, acarbose), are effective at preventing progression to DM in IGT subjects.

- **Pediatric population**—Investigation of IGT and IFG in the pediatric population is extremely limited and is largely confined to descriptions of prevalence within varying populations. These studies confirm that IFG and IGT are relatively common in childhood, particularly in children who are overweight. However, no conclusions can be made relating to the reproducibility of testing for IFG or IGT, the progression to type 2 DM, or the optimal interventions for the management of IGT in childhood.

Given the rising rates of obesity in youth and the recognition that disturbed glucose metabolism and other metabolic disturbances are common in these children, further clarification of population-based prevalence and investigation to improve understanding of the diagnosis, clinical significance, and optimal management of IFG and IGT in childhood is urgently required.
References

Note: See Appendix E for excluded studies and Appendix F for complete bibliography.


152. Weyer C, Bogardus C, Pratley RE. Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. Diabetes 1999 Nov;48(11):2197-203.


Figure 1. Analytic framework for IFG or IGT as a risk factor for progression to outcomes of interest.
Figure 2. Flow diagram showing the numbers of included and excluded articles.

Final yield of included articles for each section, showing overlap

Total included in main review (excluding children) = 156
Figure 3. Distribution of IGT and IFG classifications in 16 studies.
Hospital-based populations (----), random populations (---), selected population (- - -).
Figure 4. Passing-Bablok regression equation for IGT versus I-IGT

Passing-Bablok agreement test $N = 16$
Slope: 0.879 [0.759 to 1.035]
Intercept: -1.29 [-4.04 to 0.32]
Figure 5. Passing-Bablok regression equation for IFG versus I-IFG

Intercept : -0.78 [ -4.81 to 1.05 ]
Slope : 0.521 [ 0.313 to 0.968 ]

Passing-Bablok agreement test N = 16
Slope : 0.521 [ 0.313 to 0.968 ]
Intercept : -0.78 [ -4.81 to 1.05 ]
Figure 6: Meta-analysis of annualized RR for progression to DM in IGT group.

Test for heterogeneity: Q = 37.66 on 16 d.f. (p = 0.002)
Pooled estimate = 6.0202 (s.e. 0.6954) (p < 0.0001), 95% confidence interval (CI) 4.6573 to 7.3831

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N</th>
<th>Annual RR</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IGT</td>
<td>NGT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>King, 1984</td>
<td>13</td>
<td>14</td>
<td>4.29</td>
<td>(2.04, 9.04)</td>
</tr>
<tr>
<td>Puavili, 1987</td>
<td>8</td>
<td>1</td>
<td>3.71</td>
<td>(0.48, 28.75)</td>
</tr>
<tr>
<td>Saad, 1988</td>
<td>118</td>
<td>25</td>
<td>10.33</td>
<td>(6.75, 15.82)</td>
</tr>
<tr>
<td>Schranz, 1989</td>
<td>23</td>
<td>54</td>
<td>8.09</td>
<td>(5.01, 13.06)</td>
</tr>
<tr>
<td>Mykkanen, 1993</td>
<td>48</td>
<td>21</td>
<td>8.43</td>
<td>(5.08, 13.97)</td>
</tr>
<tr>
<td>Haffner, 1995</td>
<td>55</td>
<td>44</td>
<td>7.21</td>
<td>(4.88, 10.65)</td>
</tr>
<tr>
<td>Incue, 1996</td>
<td>5</td>
<td>1</td>
<td>3.06</td>
<td>(0.37, 25.51)</td>
</tr>
<tr>
<td>Kahn, 1996</td>
<td>12</td>
<td>4</td>
<td>4.33</td>
<td>(1.42, 13.21)</td>
</tr>
<tr>
<td>Ammari, 1998</td>
<td>10</td>
<td>10</td>
<td>2.16</td>
<td>(0.92, 5.07)</td>
</tr>
<tr>
<td>Chou, 1998</td>
<td>23</td>
<td>16</td>
<td>4.05</td>
<td>(2.16, 7.61)</td>
</tr>
<tr>
<td>Ko, 2000</td>
<td>19</td>
<td>25</td>
<td>3.58</td>
<td>(2.12, 6.06)</td>
</tr>
<tr>
<td>De Vegt, 2001</td>
<td>36</td>
<td>46</td>
<td>10.01</td>
<td>(6.52, 15.39)</td>
</tr>
<tr>
<td>Norman, 2001</td>
<td>7</td>
<td>4</td>
<td>9.50</td>
<td>(2.84, 31.78)</td>
</tr>
<tr>
<td>Wat, 2001</td>
<td>31</td>
<td>4</td>
<td>7.92</td>
<td>(2.81, 22.31)</td>
</tr>
<tr>
<td>Ferrannini, 2004</td>
<td>62</td>
<td>101</td>
<td>5.82</td>
<td>(4.27, 7.94)</td>
</tr>
<tr>
<td>Total</td>
<td>597</td>
<td>605</td>
<td>6.02</td>
<td>(4.66, 7.38)</td>
</tr>
</tbody>
</table>

Less Risk  More Risk
Figure 7. Meta-analysis of annualized RR for progression to DM in I-IGT group.

Test for heterogeneity: $Q = 8.06$ on 2 d.f. (p = 0.018)
Pooled estimate = 5.5458 (s.e. 1.2244) (p = 0.0002), 95% confidence interval 3.1459 to 7.9456

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N</th>
<th>Annual</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IIGT</td>
<td>NGT</td>
<td>RR</td>
<td>95%</td>
</tr>
<tr>
<td>Gabir, 2000</td>
<td>107</td>
<td>537</td>
<td>5.95</td>
<td>(4.61, 7.67)</td>
</tr>
<tr>
<td>De Vegt, 2001</td>
<td>27</td>
<td>80</td>
<td>8.63</td>
<td>(5.46, 13.64)</td>
</tr>
<tr>
<td>Li, 2003</td>
<td>33</td>
<td>118</td>
<td>3.51</td>
<td>(2.22, 5.54)</td>
</tr>
<tr>
<td>Total</td>
<td>167</td>
<td>735</td>
<td>5.55</td>
<td>(3.15, 7.95)</td>
</tr>
</tbody>
</table>

RR(95% CI)
Figure 8. Meta-analysis of annualized RR for progression to DM in IFG group.

Test for heterogeneity: Q = 34.12 on 4 d.f. (p < 0.0001)
Pooled estimate = 4.7028 (s.e. 1.0175) (p = 0.003), 95% confidence interval 2.7085 to 6.6971

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N</th>
<th>Annual</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG</td>
<td>NFG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinneen, 1998</td>
<td>201/521</td>
<td>592/6887</td>
<td>5.31</td>
<td>(4.53, 6.21)</td>
</tr>
<tr>
<td>Ko, 2000</td>
<td>14/55</td>
<td>13/264</td>
<td>5.22</td>
<td>(2.59, 10.54)</td>
</tr>
<tr>
<td>De Vegt, 2001</td>
<td>52/137</td>
<td>60/1205</td>
<td>9.04</td>
<td>(6.28, 13.03)</td>
</tr>
<tr>
<td>Keech, 2003</td>
<td>43/466</td>
<td>138/3501</td>
<td>2.40</td>
<td>(1.71, 3.37)</td>
</tr>
<tr>
<td>Total</td>
<td>322/1204</td>
<td>822/11967</td>
<td>4.70</td>
<td>(2.71, 6.70)</td>
</tr>
</tbody>
</table>
Figure 9. Meta-analysis of annualized RR for progression to DM in the I-IFG group.

Test for heterogeneity: Q = 4.41 on 2 d.f. (p = 0.11)
Pooled estimate = 7.2351 (s.e. 0.9862) (p < 0.0001), 95% confidence interval 5.3021 to 9.168

<table>
<thead>
<tr>
<th>Study</th>
<th>N IIFG</th>
<th>N NFG</th>
<th>Annual RR</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabir, 2000</td>
<td>29/93</td>
<td>126/3499</td>
<td>9.85</td>
<td>(6.65, 14.60)</td>
</tr>
<tr>
<td>De Vegt, 2001</td>
<td>35/106</td>
<td>51/1125</td>
<td>8.40</td>
<td>(5.50, 12.83)</td>
</tr>
<tr>
<td>Li, 2003</td>
<td>16/42</td>
<td>38/435</td>
<td>5.05</td>
<td>(2.86, 8.90)</td>
</tr>
<tr>
<td>Total</td>
<td>80/241</td>
<td>215/5059</td>
<td>7.24</td>
<td>(5.30, 9.17)</td>
</tr>
</tbody>
</table>
Test for heterogeneity: $Q = 15.19$ on 2 d.f. ($p = 0.001$)
Pooled estimate = 12.211 (s.e. 4.0253) ($p = 0.0054$), 95% confidence interval 4.3215 to 20.1005

<table>
<thead>
<tr>
<th>Study</th>
<th>N IMP</th>
<th>N NORM</th>
<th>Annual RR</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabir, 2000</td>
<td>52/126</td>
<td>126/3499</td>
<td>13.82</td>
<td>(10.10, 18.90)</td>
</tr>
<tr>
<td>De Vegt, 2001</td>
<td>20/31</td>
<td>51/1125</td>
<td>20.69</td>
<td>(12.51, 34.22)</td>
</tr>
<tr>
<td>Li, 2003</td>
<td>20/49</td>
<td>38/435</td>
<td>5.50</td>
<td>(3.25, 9.30)</td>
</tr>
<tr>
<td>Total</td>
<td>92/206</td>
<td>215/5059</td>
<td>12.21</td>
<td>(4.32, 20.10)</td>
</tr>
</tbody>
</table>
Meta-analysis of annualized RR for reversion to normal in IGT group.

Test for heterogeneity: $Q = 156.75$ on 9 d.f. ($p < 0.0001$)
Pooled estimate = 0.3297 (s.e. 0.0497) ($p < 0.0001$), 95% confidence interval 0.2324 to 0.4271
Figure 12. Meta-analysis of annualized RR for non-fatal cardiovascular disease for PTCA/CABG in IFG group.

Test for heterogeneity: $Q = 0.16$ on 1 d.f. ($p = 0.69$)
Pooled estimate = 1.0653 (s.e. 0.1157) ($p = 0.5723$), 95% confidence interval 0.8385 to 1.2922
Figure 13. Meta-analysis of annualized RR for non-fatal cardiovascular disease for stroke in IFG group.

Test for heterogeneity: Q = 0.68 on 1 d.f. (p = 0.411)
Pooled estimate = 1.3502 (s.e. 0.2705) (p = 0.1955), 95% confidence interval 0.82 to 1.8805

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N</th>
<th>Annual RR</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFG</td>
<td>NFG</td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>Goldberg, 1998</td>
<td>5/161</td>
<td>47/1549</td>
<td>1.02</td>
<td>(0.41, 2.57)</td>
</tr>
<tr>
<td>Keech, 2003</td>
<td>25/466</td>
<td>126/3501</td>
<td>1.50</td>
<td>(0.98, 2.30)</td>
</tr>
<tr>
<td>Total</td>
<td>30/627</td>
<td>173/5050</td>
<td>1.35</td>
<td>(0.82, 1.88)</td>
</tr>
</tbody>
</table>
Figure 14. Meta-analysis of annualized RR for non-fatal cardiovascular disease (or any major event) in IFG group.

Test for heterogeneity: $Q = 1.60$ on 3 d.f. ($p = 0.659$)
Pooled estimate = 1.2799 (s.e. 0.0673) ($p = 0.0001$), 95% confidence interval 1.1479 to 1.4119

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N</th>
<th>Annual</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFG</td>
<td>NFG</td>
<td>RR</td>
<td>95%</td>
</tr>
<tr>
<td>Goldberg, 1998</td>
<td>21/161</td>
<td>156/1549</td>
<td>1.31</td>
<td>(0.84, 2.06)</td>
</tr>
<tr>
<td>Rubins, 2002</td>
<td>38/160</td>
<td>149/709</td>
<td>1.15</td>
<td>(0.81, 1.62)</td>
</tr>
<tr>
<td>Smith, 2002</td>
<td>141/592</td>
<td>548/3137</td>
<td>1.41</td>
<td>(1.17, 1.69)</td>
</tr>
<tr>
<td>Keech, 2003</td>
<td>213/466</td>
<td>1348/3501</td>
<td>1.24</td>
<td>(1.08, 1.43)</td>
</tr>
<tr>
<td>Total</td>
<td>413/1379</td>
<td>2201/8896</td>
<td>1.28</td>
<td>(1.15, 1.41)</td>
</tr>
</tbody>
</table>
Figure 15. Meta-analysis of annualized RR for cardiovascular disease mortality in IGT group.

Test for heterogeneity: $Q = 1.86$ on 2 d.f. ($p = 0.395$)
Pooled estimate = 1.6617 (s.e. 0.2298) ($p = 0.004$), 95% confidence interval 1.2114 to 2.1121

<table>
<thead>
<tr>
<th>Study</th>
<th>N IGT</th>
<th>N NGT</th>
<th>Annual RR</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balkau, 1991</td>
<td>7/707</td>
<td>46/6175</td>
<td>1.33</td>
<td>(0.60, 2.95)</td>
</tr>
<tr>
<td>Tominaga, 1999</td>
<td>11/382</td>
<td>19/2016</td>
<td>3.08</td>
<td>(1.47, 6.47)</td>
</tr>
<tr>
<td>Saydah, 2001</td>
<td>55/480</td>
<td>159/2263</td>
<td>1.67</td>
<td>(1.23, 2.26)</td>
</tr>
<tr>
<td>Total</td>
<td>73/1569</td>
<td>224/10454</td>
<td>1.66</td>
<td>(1.21, 2.11)</td>
</tr>
</tbody>
</table>

Less Risk → More Risk
Test for heterogeneity: Q = 1.52 on 3 d.f. (p = 0.678)
Pooled estimate = 1.249 (s.e. 0.1333) (p = 0.0618), 95% confidence interval 0.9877 to 1.5103

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>IFG</th>
<th>N</th>
<th>NFG</th>
<th>Annual RR</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg, 1998</td>
<td>12/161</td>
<td>71/1549</td>
<td>1.65</td>
<td>(0.90, 3.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tominaga, 1999</td>
<td>3/155</td>
<td>27/2307</td>
<td>1.66</td>
<td>(0.50, 5.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balkau, 2002</td>
<td>77/1203</td>
<td>307/5582</td>
<td>1.17</td>
<td>(0.91, 1.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenenbaum, 2002</td>
<td>17/228</td>
<td>90/1813</td>
<td>1.52</td>
<td>(0.91, 2.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>109/1747</td>
<td>495/11251</td>
<td>1.25</td>
<td>(0.99, 1.51)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 16. Meta-analysis of annualized RR for cardiovascular disease mortality in IFG group.
Figure 17. Meta-analysis of annualized RR for cardiovascular disease related to Ischemic mortality in IFG group.

Test for heterogeneity: \( Q = 0.33 \) on 1 d.f. \((p = 0.567)\)
Pooled estimate = 1.2722 \((s.e. 0.1384)\) \((p = 0.0492)\), 95 % confidence interval 1.0009 to 1.5435

<table>
<thead>
<tr>
<th>Study</th>
<th>N IFG</th>
<th>N NFG</th>
<th>Annual RR</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisman, 2001</td>
<td>79/1258</td>
<td>469/9774</td>
<td>1.32</td>
<td>(1.04, 1.67)</td>
</tr>
<tr>
<td>Balkau, 2002</td>
<td>21/1235</td>
<td>82/5467</td>
<td>1.13</td>
<td>(0.70, 1.83)</td>
</tr>
<tr>
<td>Total</td>
<td>100/2493</td>
<td>551/15241</td>
<td>1.27</td>
<td>(1.06, 1.54)</td>
</tr>
</tbody>
</table>
Figure 18. Meta-analysis of annualized RR for all-cause mortality in IGT group.

Test for heterogeneity: $Q = 0.33$ on 1 d.f. ($p = 0.567$)
Pooled estimate = 1.2722 (s.e. 0.1384) ($p = 0.0492$), 95% confidence interval 1.0009 to 1.5435

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N</th>
<th>Annual RR</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFG</td>
<td>NFG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisman, 2001</td>
<td>79/1258</td>
<td>469/9774</td>
<td>1.32</td>
<td>(1.04, 1.67)</td>
</tr>
<tr>
<td>Balkau, 2002</td>
<td>21/1235</td>
<td>82/5467</td>
<td>1.13</td>
<td>(0.70, 1.83)</td>
</tr>
<tr>
<td>Total</td>
<td>100/2493</td>
<td>551/15241</td>
<td>1.27</td>
<td>(1.06, 1.54)</td>
</tr>
</tbody>
</table>
Figure 19. Meta-analysis of annualized RR for all-cause mortality in IFG group.

Test for heterogeneity: Q = 1.32 on 2 d.f. (p = 0.516)
Pooled estimate = 1.2072 (s.e. 0.0789) (p = 0.0086), 95% confidence interval 1.0526 to 1.3618

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>N</th>
<th>Annual RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFG</td>
<td>NFG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tominaga, 1999</td>
<td>10/155</td>
<td>91/2307</td>
<td>1.65</td>
<td>(0.86, 3.17)</td>
</tr>
<tr>
<td>Balkau, 2002</td>
<td>252/1206</td>
<td>1003/5572</td>
<td>1.18</td>
<td>(1.03, 1.35)</td>
</tr>
<tr>
<td>Tenenbaum, 2002</td>
<td>27/228</td>
<td>153/1813</td>
<td>1.43</td>
<td>(0.95, 2.14)</td>
</tr>
<tr>
<td>Total</td>
<td>289/1589</td>
<td>1247/9692</td>
<td>1.21</td>
<td>(1.05, 1.36)</td>
</tr>
</tbody>
</table>

RR(95% CI)
Figure 20. Meta-analysis of progression to DM for four studies that evaluated combined exercise and diet interventions. Pooled overall estimate, presented as a RR, 95% CI.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowler, 2002</td>
<td>151/1079</td>
<td>314/1082</td>
<td>0.48 [0.40, 0.57]</td>
<td>40.81</td>
<td></td>
</tr>
<tr>
<td>Tuomilehto, 2001</td>
<td>27/253</td>
<td>59/247</td>
<td>0.45 [0.29, 0.68]</td>
<td>21.54</td>
<td></td>
</tr>
<tr>
<td>Pan, 1997</td>
<td>58/126</td>
<td>89/133</td>
<td>0.69 [0.55, 0.86]</td>
<td>36.47</td>
<td></td>
</tr>
<tr>
<td>Liao, 2002</td>
<td>1/32</td>
<td>2/32</td>
<td>0.50 [0.05, 5.24]</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1490</strong></td>
<td><strong>1494</strong></td>
<td></td>
<td><strong>100.00</strong></td>
<td>0.54 [0.42, 0.70]</td>
</tr>
</tbody>
</table>

Total events: 237 (Treatment), 464 (Control)
Test for heterogeneity: Chi² = 7.36, df = 3 (P = 0.06), I² = 59.3%
Test for overall effect: Z = 4.68 (P < 0.00001)
Figure 21. Schematic diagrams (not to scale) for frequency distributions of a) 2-hr plasma glucose, and b) fasting plasma glucose.

For both curves the shaded areas represent the current glucose concentration range for IGT (7.8 - 11.0 mmol/L) and IFG (5.6 - 6.9 mmol/L) diagnosis.
Table 1. Plasma glucose cutoffs for diagnosis of IGT and IFG and DM for the varying criteria established at different times.

<table>
<thead>
<tr>
<th></th>
<th>FPG</th>
<th>AND/OR</th>
<th>2-hr PG after 75g OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NDDG 79</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>&lt; 7.8 mmol/L</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>DM</td>
<td>≥ 7.8 mmol/L</td>
<td>OR</td>
<td>≥ 11.1 mmol/L (200 mg/dL)</td>
</tr>
<tr>
<td><strong>WHO 80</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>&lt; 8.0 mmol/L</td>
<td>AND</td>
<td>8.0 to 10.9 mmol/L (144 to 196 mg/dL)</td>
</tr>
<tr>
<td>DM</td>
<td>≥ 8.0 mmol/L</td>
<td>OR</td>
<td>≥ 11.0 mmol/L (199 mg/dL)</td>
</tr>
<tr>
<td><strong>WHO 85</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>&lt; 7.8 mmol/L</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>DM</td>
<td>≥ 7.8 mmol/L</td>
<td>OR</td>
<td>≥ 11.1 mmol/L (200 mg/dL)</td>
</tr>
<tr>
<td><strong>WHO 98/99</strong></td>
<td>IFG</td>
<td>6.1 to 6.9 mmol/L (110 to 125 mg/dL)</td>
<td>NA</td>
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<tr>
<td>I-IFG</td>
<td>6.1 to 6.9 mmol/L (110 to 125 mg/dL)</td>
<td>AND</td>
<td>&lt; 7.8 mmol/L (140 mg/dL)</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt; 7.0 mmol/l</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>I-I-IGT</td>
<td>&lt; 6.1 mmol/L</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>Combined IFG/IGT</td>
<td>6.1 to 6.9 mmol/L (110 to 125 mg/dL)</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>DM</td>
<td>≥ 7.0 mmol/L</td>
<td>OR</td>
<td>≥ 11.1 mmol/L (200 mg/dL)</td>
</tr>
<tr>
<td><strong>ADA 97/98</strong></td>
<td>IFG</td>
<td>6.1 to 6.9 mmol/L (110 to 125 mg/dL)</td>
<td>NA</td>
</tr>
<tr>
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<td>6.1 to 6.9 mmol/L (110 to 125 mg/dL)</td>
<td>AND</td>
<td>&lt; 7.8 mmol/L (140 mg/dL)</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt;7.0 mmol/L</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>I-I-IGT</td>
<td>&lt; 6.1 mmol/L</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>Combined IFG/IGT</td>
<td>6.1 to 6.9 mmol/L (110 to 125 mg/dL)</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>DM</td>
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<td>OR</td>
<td>≥ 11.1 mmol/L (200 mg/dL)</td>
</tr>
<tr>
<td><strong>ADA 2003</strong></td>
<td>IFG</td>
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</tr>
<tr>
<td>I-IFG</td>
<td>5.6 to 6.9 mmol/L (100-125 mg/dL)</td>
<td>AND</td>
<td>&lt; 7.8 mmol/L (140 mg/dL)</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt; 7.0 mmol/l</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>I-I-IGT</td>
<td>&lt; 5.6 mmol/L</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>Combined IFG/IGT</td>
<td>5.6 to 6.9 mmol/L (100 to 125 mg/dL)</td>
<td>AND</td>
<td>7.8 to 11.0 mmol/L (140 to 199 mg/dL)</td>
</tr>
<tr>
<td>DM</td>
<td>≥ 7.0 mmol/L</td>
<td>OR</td>
<td>≥ 11.1 mmol/L (200 mg/dL)</td>
</tr>
</tbody>
</table>

Table 2. Databases and dates included in the search for relevant articles.

<table>
<thead>
<tr>
<th>Database searched</th>
<th>Search date</th>
<th>Period searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE and preMEDLINE</td>
<td>February 17, 2004</td>
<td>1979- February 2004</td>
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<tr>
<td>Cochrane Central Register of Controlled Trials</td>
<td>February 12, 2004</td>
<td>1979- February 2004</td>
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<tr>
<td>HealthSTAR</td>
<td>February 20, 2004</td>
<td>1979- January 2004</td>
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<td>CINAHL</td>
<td>February 12, 2004</td>
<td>1979- February 2004</td>
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<tr>
<td>AMED (alternative medicines)</td>
<td>February 11, 2004</td>
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<td>PsycINFO</td>
<td>February 12, 2004</td>
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<td>1979- 2004 week 6</td>
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Table 3. Example of a 2x2 table of binary outcomes for the disease status of DM and the exposure status of IFG or IGT. (Note: Subjects without glycemic disturbance are NFG or NGT.)

<table>
<thead>
<tr>
<th>Exposure Status Outcome status</th>
<th>Baseline IFG or IGT</th>
<th>Baseline NFG or NGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>$a$</td>
<td>$c$</td>
</tr>
<tr>
<td>NO</td>
<td>$b$</td>
<td>$d$</td>
</tr>
<tr>
<td>Total</td>
<td>$n_1 = a + b$</td>
<td>$n_2 = c + d$</td>
</tr>
</tbody>
</table>

**Abbreviations:** IFG=Impaired Fasting Glucose, IGT=Impaired Glucose Tolerance, NFG=Normal Fasting Glucose, NGT=Normal Glucose Tolerance.
Table 4. General study characteristics: Diagnosis.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Author, Year, Country</th>
<th>Study type</th>
<th>Duration</th>
<th>N</th>
<th>Diagnostic Risk Group</th>
<th>Diagnostic criteria</th>
<th>Age, y mean (range)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 National Diabetes Survey</td>
<td>Al-Lawati, 2000, Omani</td>
<td>CS</td>
<td>NA</td>
<td>4682</td>
<td>-</td>
<td>WHO 85 ADA 97</td>
<td>(20+)</td>
<td>-</td>
</tr>
<tr>
<td>ADSS</td>
<td>Smith, 2003, IE</td>
<td>CS</td>
<td>18 m</td>
<td>8286</td>
<td>-</td>
<td>Not specified</td>
<td>(53-75)</td>
<td>White, Black</td>
</tr>
<tr>
<td>Botnia</td>
<td>Tripathy, 2000, FI</td>
<td>CS</td>
<td>NA</td>
<td>5396</td>
<td>-</td>
<td>WHO 98</td>
<td>55.8</td>
<td>Type 2 diabetic patients and their families</td>
</tr>
<tr>
<td>CHS</td>
<td>Barzilay, 1999, US</td>
<td>PC</td>
<td>8 y</td>
<td>4515</td>
<td>IGT; IFG</td>
<td>WHO 85 ADA 97</td>
<td>73 (65+)</td>
<td>White, Black. Ambulatory subjects with no severe illness</td>
</tr>
<tr>
<td>DECODA</td>
<td>Qiao, 2000, BD*</td>
<td>CS</td>
<td>NA</td>
<td>17666</td>
<td>-</td>
<td>WHO 85, 99 ADA 97</td>
<td>61.5</td>
<td>White</td>
</tr>
<tr>
<td>EDIP</td>
<td>Perry, 2001, US</td>
<td>CS</td>
<td>NA</td>
<td>2378</td>
<td>-</td>
<td>WHO 85 ADA 99</td>
<td>61.7</td>
<td>White. Elderly population</td>
</tr>
<tr>
<td>Hoorn</td>
<td>De Vegt, 1998, NL</td>
<td>CS</td>
<td>NA</td>
<td>2468</td>
<td>IGT; I-IGT; IFG; I-IFG</td>
<td>WHO 85 ADA 97</td>
<td>61.7</td>
<td>White (Dutch). Elderly population</td>
</tr>
<tr>
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<td>De Vegt, 2000, NL</td>
<td>PC</td>
<td>9 y</td>
<td>1342</td>
<td>IGT; I-IGT; IFG; I-IFG</td>
<td>WHO 85, 99 ADA 97</td>
<td>(50-75)</td>
<td>White (Dutch). Elderly population</td>
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<tr>
<td>Hoorn</td>
<td>De Vegt, 2001, NL</td>
<td>PC</td>
<td>6.4 y</td>
<td>342</td>
<td>IGT; I-IGT; IFG; I-IFG</td>
<td>WHO 85, 99 ADA 97</td>
<td>(50-75)</td>
<td>White (Dutch). Elderly population</td>
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<tr>
<td>Hoorn</td>
<td>Mooy, 1996, NL</td>
<td>CS</td>
<td>2-6w</td>
<td>9797</td>
<td>-</td>
<td>WHO 85</td>
<td>(50-74)</td>
<td>White</td>
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<td>Kinmen</td>
<td>Li, 2003, TW</td>
<td>PC</td>
<td>5 y</td>
<td>644</td>
<td>I-IGT; I-IFG; IGT-IFG</td>
<td>WHO 99</td>
<td>(30+)</td>
<td>-</td>
</tr>
<tr>
<td>Study group</td>
<td>Author, Year, Country</td>
<td>Study type</td>
<td>Duration</td>
<td>N</td>
<td>Diagnostic Risk Group</td>
<td>Diagnostic criteria</td>
<td>Age, y mean (range)</td>
<td>Population</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------</td>
<td>------------</td>
<td>----------</td>
<td>-----</td>
<td>------------------------</td>
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<td>-------------------</td>
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<tr>
<td>NHANES III</td>
<td>Harris, 1997, US</td>
<td>CS</td>
<td>NA</td>
<td>5984</td>
<td>IGT; IFG; IGT-IFG</td>
<td>WHO 85 ADA 97</td>
<td>(15+)</td>
<td>Pima Indians</td>
</tr>
<tr>
<td>Pima</td>
<td>Gabir, 2000a, US</td>
<td>PC</td>
<td>5,10 y</td>
<td>7018</td>
<td>IGT; IFG</td>
<td>WHO 98 ADA 97</td>
<td>(40-74)</td>
<td>Paris civil service employees</td>
</tr>
<tr>
<td>Pima</td>
<td>Weyer, 1999, US</td>
<td>CS</td>
<td>NA</td>
<td>434</td>
<td>IGT; IFG</td>
<td>WHO 85 ADA 97</td>
<td>NR</td>
<td>Pima Indians</td>
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<tr>
<td>Pima</td>
<td>Weyer, 1999, FR</td>
<td>CCT</td>
<td>NR</td>
<td>208</td>
<td>IGT; IFG</td>
<td>WHO 98 ADA 97</td>
<td>(44-55)</td>
<td>No known diabetes or medication use</td>
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<td>RIAD</td>
<td>Hanefeld, 1999, DE</td>
<td>CS</td>
<td>NA</td>
<td>591</td>
<td>IGT; IFG</td>
<td>WHO 98 ADA 97</td>
<td>(18-69)</td>
<td>European, No known diabetes or medication use</td>
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<td>CS</td>
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<td>1539</td>
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<td>WHO 98 ADA 97</td>
<td>(25-68)</td>
<td>Mexican American, non-Hispanic White</td>
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<td>CS</td>
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<td>44.2</td>
<td>European, Maori Pacific Islands, Asian, Samoan, Rangar, Niuean, Cook Islands</td>
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<td>4636</td>
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<td>WHO 98 ADA 97</td>
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<td>Carnevale Schianca, 2003, IT</td>
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<td>5 y</td>
<td>398</td>
<td>IGT; IFG</td>
<td>WHO 98 ADA 97</td>
<td>(17-66)</td>
<td>-</td>
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<td>CS</td>
<td>NA</td>
<td>1456</td>
<td>IGT; IFG</td>
<td>WHO 98 ADA 97</td>
<td>(60-92)</td>
<td>Korean, Urban community</td>
</tr>
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<td>Study group</td>
<td>Author, Year, Country</td>
<td>Study type</td>
<td>Duration</td>
<td>N</td>
<td>Diagnostic Risk Group</td>
<td>Diagnostic criteria</td>
<td>Age, y mean (range)</td>
<td>Population</td>
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<td>RC</td>
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<td>-</td>
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<td>de Pablos-Velasco162, 2001, ES</td>
<td>CS</td>
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<td>-</td>
<td>WHO 85 ADA 97</td>
<td>(30+)</td>
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<td>CS</td>
<td>NA</td>
<td>17512</td>
<td>-</td>
<td>WHO 99</td>
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<td>Asian</td>
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<td>Drzewska27, 2001, PL</td>
<td>PC</td>
<td>9 y</td>
<td>1360</td>
<td>-</td>
<td>WHO 85, 99 ADA 97</td>
<td>65</td>
<td>All white. Subjects at risk for glucose intolerance</td>
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<td>PC</td>
<td>1 y</td>
<td>353</td>
<td>-</td>
<td>WHO 85</td>
<td>(56-61)</td>
<td>Patients had CABG surgery</td>
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<tr>
<td>None</td>
<td>Flores-Saenz164, 2003, MX</td>
<td>RCT</td>
<td>9 m</td>
<td>40</td>
<td>I-IGT, IFG</td>
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<td>(20-65)</td>
<td>Volunteers. All had IGT and no concurrent illnesses</td>
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<td>1864</td>
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<td>WHO 85</td>
<td>56.1 (15-95)</td>
<td>Non-pregnant individuals</td>
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<td>NA</td>
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<td>WHO 99</td>
<td>(20-79)</td>
<td>Non-pregnant individuals</td>
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<tr>
<td>None</td>
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<td>CS</td>
<td>5 m</td>
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<td>WHO 80, 85 ADA 97</td>
<td>NR</td>
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<td>240</td>
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<td>42.1 (30-64)</td>
<td>Men and non-pregnant women</td>
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<td>4 m</td>
<td>665</td>
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<td>WHO 85 ADA 97</td>
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<td>NA</td>
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<td>37.5 (18-66)</td>
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</tr>
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<td>CS</td>
<td>6 w</td>
<td>212</td>
<td>-</td>
<td>WHO 85</td>
<td>(30-65)</td>
<td>Hong Kong Chinese. No diabetes</td>
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<tr>
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<td>CS</td>
<td>11 m</td>
<td>165</td>
<td>-</td>
<td>WHO 85, 98 ADA 97</td>
<td>36.6</td>
<td>Women. European, South Asian, Afro-Carribean. Previous GDM</td>
</tr>
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</table>
### Table 4. General study characteristics: Diagnosis, continued

<table>
<thead>
<tr>
<th>Study group</th>
<th>Author, Year, Country</th>
<th>Study type</th>
<th>Duration</th>
<th>N</th>
<th>Diagnostic Risk Group</th>
<th>Diagnostic criteria</th>
<th>Age, y mean (range)</th>
<th>Population</th>
</tr>
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<tr>
<td>None</td>
<td>Li170, 1999, TW</td>
<td>CS</td>
<td>3 y</td>
<td>1456</td>
<td>WHO 85 ADA 97 WHO 99</td>
<td>(30+)</td>
<td>Chinese, All considered at high risk for DM</td>
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<td>None</td>
<td>Mannucci171, 1999, IT</td>
<td>PC</td>
<td>10 m</td>
<td>528</td>
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<td>45.2</td>
<td>Obese</td>
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<tr>
<td>None</td>
<td>Mannucci172, 2003, IT</td>
<td>CS</td>
<td>NA</td>
<td>1215</td>
<td>WHO 98</td>
<td>(30-70)</td>
<td></td>
<td></td>
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<td>Puvilai40, 1999, TH</td>
<td>NC</td>
<td>NA</td>
<td>1051</td>
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<td>WHO 85, 98 ADA 97</td>
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<td>Richard173, 2002, FR</td>
<td>PC</td>
<td>3.5</td>
<td>1149</td>
<td>WHO 85 ADA 97</td>
<td>49 (15-84)</td>
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</tr>
<tr>
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<td>Shaw174, 1999, MU</td>
<td>PC</td>
<td>5y</td>
<td>3229</td>
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<td>(25-74)</td>
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<tr>
<td>None</td>
<td>Snelhawatha175, 2003, IN</td>
<td>CS</td>
<td>11 m</td>
<td>289</td>
<td>WHO 98</td>
<td>42</td>
<td>Chinese, Maylay, Indian. Some hypertensive</td>
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</tr>
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<td>Tavintharan49, 2000, SG</td>
<td>CS</td>
<td>NA</td>
<td>111</td>
<td>WHO 80 ADA 97</td>
<td>43.2 (37-50)</td>
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<tr>
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<td>Tominaga83, 1999, JP</td>
<td>PC</td>
<td>7 y</td>
<td>2651</td>
<td>IGT; IFG</td>
<td>WHO 85 ADA 97</td>
<td>64 (41+)</td>
<td>Inhabitants of Funagata</td>
</tr>
</tbody>
</table>

**Abbreviations:** (*)=Modified criteria; ADA=American Diabetes Association; CS=Cross-Sectional study; d=day; DM=Diabetes; GDM=Gestational Diabetes Mellitus; IFG=Impaired Fasting Glucose; IGT=Impaired Glucose Tolerance; I-IFG=Isolated Impaired Fasting Glucose; I-IGT=Isolated Impaired Glucose Tolerance; m=month; NA=Not Applicable; NC=Not Clear; NR=Not Reported; PC=Prospective Cohort study; RC=Retrospective Cohort; RCT=Randomized Controlled Trial; w=week; WHO=World Health Organization; y=Year(s).

**Study Group Abbreviations:** ADSS=Australia Diabetes Screening Study; ARIC=Atherosclerosis Risk in Communities Study; AusDiab=Australian Diabetes; Obesity and Lifestyle Study; CHS=Cardiovascular Health Study; DECODA=Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia; EDIP=Early Diabetes Intervention Program; JACDS=Japanese American Community Diabetes Study; NHANES=National Health and Examination Survey; Pima=Pima Indians Study; PPS=Paris Prospective Study; RIAD=Risk factors in IGT for Atherosclerosis and Diabetes; SAHS=San Antonio Heart Study; SNHS=Singapore National Health Survey.

**Country Abbreviations:** (*)=Additional countries; AU=Australia; BD=Bangladesh; CA=Canada; DE=Germany; ES=Spain; FI=Finland; FR=France; GB=Great Britain; GH=Ghana; IE=Ireland; IN=India; IT=Italy; JP=Japan; KR=Korea; MU=Mauritius; MX=Mexico; NL=Netherlands; NZ=New Zealand; PL=Poland; SE=Sweden; SG=Singapore; TR=Turkey; TW=Taiwan; TZ=Tanzania; US=United States.
Table 5. Reproducibility of IGT and IFG classification upon retesting within 6 weeks.

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<tr>
<th>Author</th>
<th>n</th>
<th>Repeat interval</th>
<th>First test</th>
<th>Second test</th>
<th>Kappa (95% CI)</th>
<th>NFG</th>
<th>IFG</th>
<th>DM</th>
<th>Kappa (95% CI)</th>
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<td>49</td>
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<td>6</td>
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<tr>
<td>Ko, 1998</td>
<td>93</td>
<td>6 w</td>
<td>46.2</td>
<td>4.1</td>
<td>9.7</td>
<td>0.56 (0.39-0.75)</td>
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<td>63.7</td>
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<tr>
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<td>2 – 6 w</td>
<td>39.3</td>
<td>48</td>
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<td>0.38 (0.30-0.47)</td>
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<td>2 – 6 w</td>
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<td>47</td>
<td>12.6</td>
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<td>38.7</td>
<td>51.4</td>
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Note: DM refers to study participant classification and not diagnosis since confirmation testing was not done.

Abbreviations: NGT=normal glucose tolerance; NFG=normal fasting glucose; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; DM=diabetes mellitus; n=number of participants classified as IFG or IGT by the first test; d=days; w=weeks.
Table 6. Comparison of IGT classifications using a 2-h PG range of 7.8–11.0 mmol/L and FPG values of < 6.1 mmol/L, < 7.0 mmol/L or < 7.8 mmol/L.

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<th>FPG &lt; 6.1 mmol/L</th>
<th>Difference (%) &lt; 6.1 vs &lt; 7.0 mmol/L</th>
<th>FPG &lt; 7.0 mmol/L</th>
<th>Difference (%) &lt; 7.0 vs &lt; 7.8 mmol/L</th>
<th>FPG &lt; 7.8 mmol/L</th>
<th>Difference (%) &lt; 6.1 vs &lt; 7.8 mmol/L</th>
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Abbreviations: FPG=fasting plasma glucose; IGT=impaired glucose tolerance; n=number of subjects.
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<th>IFG 6.1-6.9 mmol/L</th>
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<th>IFG and IGT % (n)</th>
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Table 7. Summary of published studies that compared IGT with IFG criteria, continued

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<th>IFG % (n)</th>
<th>2-hr PG 7.8 - 11.0 mmol/L</th>
<th>IGT % (n)</th>
<th>IFG % (n)</th>
<th>2-hr PG 7.8 - 11.0 mmol/L</th>
<th>Ratio IGT/IFG</th>
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<th>Ratio IGT/IFG 2-hr PG only</th>
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* This is a subset of the Hoorn study representing the participants who had repeat OGTT. This subset had a higher prevalence of IGT, IFG and DM.
Table 8. General study characteristics: Prognosis

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<th>Study group</th>
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<th>Study type</th>
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<th>N (with dysglycemia and untreated)</th>
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<th>Diagnostic criteria Age, y mean (range)</th>
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Table 8. General study characteristics: Prognosis, continued

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<td>WHO 98</td>
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**Diagnostic Category: IFG**

- **BIP**
  - Fisman91, 2001, IL
    - PC 9 11853 IFG ADA 97 (45-74) All have coronary artery disease and previous MI
    - Quality Score: - 5 9 0
  - Tenenbaum99, 2002, IL
    - PC 9 3350 IFG ADA 97 (45-74) History of MI, stable angina. Previous radionuclear studies or standard exercise tests.
    - Quality Score: - 5 9 1

- **CARE**
  - Goldberg82, 1998, CA, US
    - RCT 5 171093 IFG ADA 97 (21-75) Post menopausal women. MI 3 to 20 months prior
    - Quality Score: 7 - - -
  - Cooper Clinic Wei211, 1999, US
    - PC 6.1 NR IFG ADA 97 43.5 NR
    - Quality Score: - 5 10 0
  - LIPID Keech93, 2003, NZ
    - RCT 6 363 IFG ADA 97 (31-75) Previous MI, medication use
    - Quality Score: 6 - - -
  - REP Dinneen212, 1998, US
    - PC 9 7567 IFG NDDG 79 ADA 97 61 Minnesota residents from Mayo Clinic database
    - Quality Score: - 5 10 0

74
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<th>Study type</th>
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<th>Diagnostic criteria</th>
<th>Age, y mean (range)</th>
<th>Population</th>
<th>Quality Score</th>
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**Diagnostic Category: Multiple**

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**Abbreviations:**  ADA=American Diabetes Association; CCT=Controlled Clinical Trial; DM=Diabetes Mellitus; FDR=First-degree relatives of type 2 diabetics; (I)=Refers to number of IGT subjects only; IFG=Impaired Fasting Glucose; (IFG)=Refers to number of IFG subjects only; IGT=Impaired Glucose Tolerance; I-IFG=Isolated Impaired Fasting Glucose; I-IGT=Isolated Impaired Glucose Tolerance; (N)=Refers to number of NGT subjects only; NGT=Normal Glucose Tolerance; NR=Not Reported; (P)=Refers to number of placebo subjects only; PC=Prospective Cohort; RCT=Randomized Control Trial; WHO=World Health Organization.

**Study Group Abbreviations:**  4S=Scandinavian Simvastatin Survival Study; BIP=Bezafibrate Infarction Prevention trial; CARE=Cholesterol and Recurrent Events Study; CHS=Cardiovascular Health Study; DECODE=Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe; DPP=Diabetes Prevention Program; FDPS=Finnish Diabetes Prevention Study; HKCRFP=Hong Kong Cardiovascular Risk Factor Prevalence study; IRAS=Insulin Resistance Atherosclerosis Study; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; MCDS=Mexico City Diabetes Survey; NHANES=National Health and Nutrition Examination Survey; Pima=Pima Indians Study; PPS=Paris Prospective Study; REP=Rochester Epidemiology Project; SAHS=San Antonio Heart Study; SA-Ind=South African Indian study; STOP-NIDDM=Study to Prevent Non-Insulin Dependent Diabetes Mellitus.

**Country Abbreviations:**  AU=Australia; CA=Canada; CN=China; DE=Germany; FI=Finland; FR=France; IL=Israel; IN=India; IT=Italy; JO=Jordan; JP=Japan; MT=Malta; MU=Mauritius; MX=Mexico; NL=Netherlands; NZ=New Zealand; SE=Sweden; SG=Singapore; TH=Thailand; TW=Taiwan; US=United States.
Table 9. Progression to DM in subjects with the risk factor of dysglycemia. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

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<th>Baseline (n)</th>
<th>Annualized Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population for study duration</th>
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<td>4.71</td>
<td>4.05</td>
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Table 9. Progression to DM in subjects with the risk factor of dysglycemia—continued. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
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<th>Study Group</th>
<th>Author</th>
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<th>Baseline (n)</th>
<th>Baseline (n)</th>
<th>Annualized Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population for study duration</th>
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<td>11.70 (96.2)</td>
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<td>11.70 (96.2)</td>
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<td>Saad, 198869</td>
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<td>118</td>
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<td>10.33 (6.75-15.82)</td>
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<td>11.22 (83.3)</td>
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<td>Saad, 198871</td>
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<td>100</td>
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<td>Little, 1994188</td>
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<td>23</td>
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<td>54</td>
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<td>8.09 (5.01-13.06)</td>
<td>5.19 (85.9)</td>
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<td>Norman, 200149</td>
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<td>7</td>
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<td>4</td>
<td>11.72</td>
<td>9.50 (2.84-31.78)</td>
<td>10.49 (86.2)</td>
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Table 9. Progression to DM in subjects with the risk factor of dysglycemia—continued. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>Baseline (n)</th>
<th>Baseline Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population for study duration</th>
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<tr>
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<td>27</td>
<td>624</td>
<td>7.02</td>
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<td>King, 1984\textsuperscript{132}</td>
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<td>201</td>
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<td>1185</td>
<td>5.94</td>
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<td>MCDS</td>
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<td>SAHS</td>
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<td>55</td>
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<td>44</td>
<td>545</td>
<td>7.95</td>
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<td>Haffner, 1997\textsuperscript{194}</td>
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<td>62</td>
<td>102</td>
<td>53</td>
<td>1000</td>
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<td>Stern, 1993\textsuperscript{195}</td>
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<td>45</td>
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<td>Wong, 2003\textsuperscript{209}</td>
<td>8</td>
<td>102</td>
<td>189</td>
<td>12</td>
<td>266</td>
<td>5.25</td>
</tr>
</tbody>
</table>

Risk group: IGT (isolated)

| Kinmen  | Li, 2003\textsuperscript{80} | 5   | 33 | 85 | 38 | 397 | 6.35 | 3.51 (2.22-5.54) | 4.54 | 68.8 |
|         | Gabir, 2000\textsuperscript{36} | 5   | 107 | 430 | 126 | 3373 | 4.35 | 5.95 (4.61-7.67) | 3.62 | 81.9 |
Table 9. Progression to DM in subjects with the risk factor of dysglycemia—continued. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>Baseline (n) IGT and/or IFG</th>
<th>Baseline (n) NGT and/or NFG</th>
<th>Outcome: Progression to DM</th>
<th>Outcome: Progression to DM</th>
<th>Annualized Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population for study duration</th>
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<tbody>
<tr>
<td>Hoorn</td>
<td>De Vegt, 2001&lt;sup&gt;35&lt;/sup&gt;</td>
<td>6.4</td>
<td>27</td>
<td>53</td>
<td>51</td>
<td>1074</td>
<td>6.23</td>
<td>8.63 (5.46-13.64)</td>
<td>5.51</td>
<td>86.6</td>
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<td>Risk group: IFG</td>
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<tr>
<td>Ko, 2001&lt;sup&gt;64&lt;/sup&gt;</td>
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<td>1.1</td>
<td>14</td>
<td>41</td>
<td>13</td>
<td>251</td>
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<td>18.95</td>
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<tr>
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<td>RCT</td>
<td>2.9</td>
<td>12</td>
<td>13</td>
<td>19</td>
<td>91</td>
<td>20.19</td>
<td>3.19 (1.63-6.25)</td>
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<td>423</td>
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<td>9</td>
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<td>320</td>
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<td>6295</td>
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</tr>
<tr>
<td>Pima</td>
<td>Gabir, 2000&lt;sup&gt;36&lt;/sup&gt;</td>
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<td>29</td>
<td>64</td>
<td>126</td>
<td>3373</td>
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<td>26</td>
<td>38</td>
<td>397</td>
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<td>5.05 (2.86-8.90)</td>
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<td>77.1</td>
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<td>71</td>
<td>51</td>
<td>1074</td>
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<td>8.40 (5.50-12.83)</td>
<td>5.35</td>
<td>86.3</td>
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</table>
Table 9. Progression to DM in subjects with the risk factor of dysglycemia—continued. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
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<th>Author</th>
<th>Study Duration (y)</th>
<th>Baseline (n) IGT and/or IFG</th>
<th>Baseline (n) NGT and/or NFG</th>
<th>Annualized Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population for study duration</th>
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<tr>
<td>Pima</td>
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<td>52 74</td>
<td>126 3373</td>
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<td>20 29</td>
<td>38 397</td>
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<tr>
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<td>51 1074</td>
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* Correction for zero values in cells: To avoid division by zero 0.5 was added to the value of all cells.

**Abbreviations:** DM=Diabetes Mellitus; HKCRP=Hong Kong Cardiovascular Risk Factor Prevalence Study; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; I-IFG=Isolated impaired fasting glucose; I-IGT=Isolated impaired glucose tolerance; MCDS=Mexico City Diabetes Survey; Pima=Pima Indians Study; PPS=Paris Prospective Study; REP=Rochester Epidemiology Project; SAHS=San Antonio Heart Study; SA-Ind=Study of South African Indians; y=Year(s).
Table 10. Reversion to NGT/NFG in subjects with the risk factor of dysglycemia. (Note: Annualized risk in the exposed group and annualized risk difference are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
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<th>Author</th>
<th>Study Duration (y)</th>
<th>Baseline (n)</th>
<th>Baseline (n)</th>
<th>Annualized Risk per 100 persons in exposed group</th>
<th>Absolute Annualized Risk Difference per 100 persons</th>
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<td>NGT and/or NFG</td>
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<td>Risk group: IFG (isolated)</td>
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</tbody>
</table>

Notation for NGT and NFG Groups: Note that for the outcome of reversion, the IGT group was compared to the NGT/NFG group who did not remain normal; the NGT/NFG subjects who did not retain their normal glycemic status converted to IGT or DM status.

Absolute Annualized Risk Difference: The absolute value for the Annualized Risk Difference was calculated for this table only, as the annualized rates for the NGT group were generally of greater magnitude than the IGT group.

Abbreviations: HKCRP=Hong Kong Cardiovascular Risk Factor Prevalence Study; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; I-IFG=Isolated impaired fasting glucose; I-IGT=Isolated impaired glucose tolerance; MCDS=Mexico City Diabetes Survey; NFG=Normal fasting glucose; NGT=Normal glucose tolerance; Pima=Pima Indians Study; PPS=Paris Prospective Study; SA-Ind=Study of South African Indians; y=Year(s).
Table 11. Non-fatal cardiovascular disease outcomes in subjects with the risk factor of dysglycemia. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—I GT, IFG, I-IGT, I-IFG and combined I GT/IFG).

<table>
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<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>CVD outcome</th>
<th>Baseline IGT and/or IFG</th>
<th>Baseline NGT and/or NFG</th>
<th>Annualized risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Absolute Annual Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population</th>
</tr>
</thead>
<tbody>
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<td></td>
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<tr>
<td>Bruneck</td>
<td>Bonora, 2000&lt;sup&gt;85&lt;/sup&gt;</td>
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<td>54</td>
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<td>Non-stenotic atherosclerosis</td>
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<td>16</td>
<td>103</td>
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<td></td>
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</tr>
<tr>
<td>Risk group: IFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CARE</td>
<td>Goldberg, 1998&lt;sup&gt;52&lt;/sup&gt;</td>
<td>5</td>
<td>Clinical MI</td>
<td>21</td>
<td>140</td>
<td>156</td>
<td>1393</td>
<td>2.76</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PTCA</td>
<td>17</td>
<td>144</td>
<td>167</td>
<td>1382</td>
<td>2.21</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
<td>5</td>
<td>156</td>
<td>47</td>
<td>1502</td>
<td>0.63</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unstable angina</td>
<td>28</td>
<td>133</td>
<td>261</td>
<td>1288</td>
<td>3.75</td>
<td>1.03</td>
</tr>
<tr>
<td>Veterans</td>
<td>Rubins, 2002&lt;sup&gt;64&lt;/sup&gt;</td>
<td>5.1</td>
<td>Major event</td>
<td>38</td>
<td>122</td>
<td>149</td>
<td>560</td>
<td>5.18</td>
<td>1.15</td>
</tr>
</tbody>
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Table 11. Non-fatal cardiovascular disease outcomes in subjects with the risk factor of dysglycemia—continued. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>CVD outcome</th>
<th>Baseline IGT and/or IFG</th>
<th>Baseline NGT and/or NFG</th>
<th>Annualized risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Absolute Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIPID</td>
<td>Keech, 2003&lt;sup&gt;35&lt;/sup&gt; RCT</td>
<td>6</td>
<td>CHD mortality and non-fatal MI</td>
<td>83</td>
<td>383</td>
<td>507</td>
<td>2994</td>
<td>1.25</td>
<td>(0.99-1.57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any event</td>
<td>213</td>
<td>253</td>
<td>134</td>
<td>2153</td>
<td>1.24</td>
<td>(1.08-1.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CABG or PTCA</td>
<td>77</td>
<td>389</td>
<td>534</td>
<td>2967</td>
<td>1.09</td>
<td>(0.86-1.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
<td>25</td>
<td>441</td>
<td>126</td>
<td>3375</td>
<td>1.50</td>
<td>(0.98-2.30)</td>
</tr>
<tr>
<td>CHS</td>
<td>Smith, 2002&lt;sup&gt;86&lt;/sup&gt;</td>
<td>8.5</td>
<td>Any event</td>
<td>141</td>
<td>451</td>
<td>548</td>
<td>2589</td>
<td>1.41</td>
<td>(1.17-1.69)</td>
</tr>
<tr>
<td>BIP</td>
<td>Tenenbaum, 2002&lt;sup&gt;59&lt;/sup&gt;</td>
<td>9</td>
<td>Heart failure</td>
<td>89</td>
<td>139</td>
<td>647</td>
<td>1166</td>
<td>1.12</td>
<td>(0.90-1.39)</td>
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</table>

<table>
<thead>
<tr>
<th>Risk group: IFG (isolated)</th>
</tr>
</thead>
<tbody>
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<table>
<thead>
<tr>
<th>Risk group: Multiple IGT/IFG</th>
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</thead>
<tbody>
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<td>None</td>
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</table>

Abbreviations: BIP=Bezafibrate Infarction Prevention trial; CABG=Cardiac artery bypass graft; CARE=Cholesterol and Recurrent Events Study; CHD=Coronary heart disease; CHS=Cardiovascular Health Study; CVD=Cardiovascular disease; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; I-IFG=Isolated impaired fasting glucose; I-IGT=Isolated impaired glucose tolerance; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; MI=Myocardial infarction; PTCA=Percutaneous transluminal coronary angioplasty; y=Year(s)
Table 12. Cardiovascular disease-related mortality outcomes in subjects with the risk factor of dysglycemia. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>Mortality Type</th>
<th>Baseline (n) IGT and/or IFG</th>
<th>Baseline (n) NGT and/or NFG</th>
<th>Annualized Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population for study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td>Mortality</td>
<td>Mortality</td>
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<td>Yes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tominaga, 1999</td>
<td>7</td>
<td>CVD</td>
<td>11</td>
<td>371</td>
<td>19</td>
<td>1997</td>
<td>0.42</td>
<td>3.08 (1.47-6.47)</td>
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<td></td>
<td>NHANES II</td>
<td>16</td>
<td>CVD</td>
<td>55</td>
<td>425</td>
<td>159</td>
<td>2104</td>
<td>0.76</td>
<td>1.67 (1.23-2.26)</td>
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<tr>
<td></td>
<td>Balkau, 1991</td>
<td>18</td>
<td>Ischemic heart disease</td>
<td>7</td>
<td>700</td>
<td>46</td>
<td>6129</td>
<td>0.06</td>
<td>1.33 (0.60-2.95)</td>
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<tr>
<td>PPS</td>
<td>Balkau, 1992</td>
<td>18</td>
<td>Cardiovascular</td>
<td>40</td>
<td>638</td>
<td>210</td>
<td>5843</td>
<td>0.34</td>
<td>1.72 (1.23-2.41)</td>
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<tr>
<td></td>
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<td>CHD</td>
<td>28</td>
<td>650</td>
<td>158</td>
<td>5895</td>
<td>0.23</td>
<td>1.59 (1.07-2.28)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>CARE</td>
<td>Goldberg, 1998</td>
<td>5</td>
<td>CHD</td>
<td>12</td>
<td>149</td>
<td>71</td>
<td>1478</td>
<td>1.54</td>
<td>1.65 (0.90-3.02)</td>
</tr>
<tr>
<td></td>
<td>Tominaga, 1999</td>
<td>7</td>
<td>CVD – 7yr</td>
<td>3</td>
<td>152</td>
<td>27</td>
<td>2280</td>
<td>0.28</td>
<td>1.66 (0.50-5.46)</td>
</tr>
</tbody>
</table>
Table 12. Cardiovascular disease-related mortality outcomes in subjects with the risk factor of dysglycemia—continued. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
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<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>Mortality Type</th>
<th>Baseline (n)</th>
<th>Baseline (n)</th>
<th>Annualized Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population for study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td>IGT and/or IFG</td>
<td>NGT and/or NFG</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP</td>
<td>Fisman, 2001&lt;sup&gt;91&lt;/sup&gt;</td>
<td>9</td>
<td>CVD – Ischemic</td>
<td>79</td>
<td>1179</td>
<td>469</td>
<td>9305</td>
<td>0.72</td>
<td>1.32 (1.04-1.67)</td>
</tr>
<tr>
<td>BIP</td>
<td>Tenenbaum, 2002&lt;sup&gt;92&lt;/sup&gt;</td>
<td>9</td>
<td>Cardiac</td>
<td>17</td>
<td>211</td>
<td>90</td>
<td>1723</td>
<td>0.86</td>
<td>1.52 (0.91-2.55)</td>
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<tr>
<td>PPS</td>
<td>Balkau, 2002&lt;sup&gt;93&lt;/sup&gt;</td>
<td>17</td>
<td>Coronary</td>
<td>53</td>
<td>1209</td>
<td>193</td>
<td>5321</td>
<td>0.25</td>
<td>1.20 (0.89-1.63)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>CVD</td>
<td>77</td>
<td>1126</td>
<td>307</td>
<td>5275</td>
<td>0.39</td>
<td>1.17 (0.91-1.50)</td>
</tr>
<tr>
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<td></td>
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<td>Ischemic</td>
<td>21</td>
<td>1214</td>
<td>82</td>
<td>5385</td>
<td>0.10</td>
<td>1.13 (0.70-1.83)</td>
</tr>
</tbody>
</table>

Risk group: IFG (isolated)

None

Risk group: Multiple IGT/IFG

None

Abbreviations: BIP=Bezafibrate Infarction Prevention trial; CHD=Cholesterol and Recurrent Events Study; CHD=Coronary heart disease; CVD=Cardiovascular disease; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; I-IFG=Isolated impaired fasting glucose; I-IGT=Isolated impaired glucose tolerance; NHANES=National Health and Nutrition Examination Survey; PPS=Paris Prospective Study; y=Year(s)
Table 13. Mortality outcomes in subjects with the risk factor of dysglycemia. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>Mortality Type</th>
<th>Baseline (n)</th>
<th>Baseline Risk (95% CI)</th>
<th>Annualized Relative Risk</th>
<th>Absolute Risk Difference per 100 persons in exposed population</th>
<th>% Attributable Risk in exposed population for study duration</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td>IGT and/or IFG</td>
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<tr>
<td>IRAS</td>
<td>Wagenknecht, 2003</td>
<td>5.2</td>
<td>All-cause</td>
<td>8</td>
<td>265</td>
<td>0.57</td>
<td>1.81 (0.70-4.68)</td>
<td>0.26</td>
</tr>
<tr>
<td>Malta</td>
<td>Schranz, 1989</td>
<td>6</td>
<td>All-cause</td>
<td>15</td>
<td>94</td>
<td>2.44</td>
<td>3.18 (1.79-5.63)</td>
<td>1.67</td>
</tr>
<tr>
<td>Hoorn</td>
<td>Van Dijk, 2001</td>
<td>6.6</td>
<td>All-cause</td>
<td>5</td>
<td>63</td>
<td>1.15</td>
<td>0.52 (0.13-2.17)</td>
<td>1.05</td>
</tr>
<tr>
<td>Risk group: IGT (isolated)</td>
<td>Tominaga, 1999</td>
<td>7</td>
<td>All-cause</td>
<td>26</td>
<td>356</td>
<td>1.00</td>
<td>1.85 (1.19-2.89)</td>
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</tr>
<tr>
<td>NHANES II</td>
<td>Saydah, 2001</td>
<td>16</td>
<td>All-cause</td>
<td>137</td>
<td>343</td>
<td>2.08</td>
<td>1.68 (1.39-2.04)</td>
<td>0.84</td>
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<tr>
<td>NHANES II</td>
<td>Saydah, 2003</td>
<td>16</td>
<td>All-cause</td>
<td>128</td>
<td>352</td>
<td>1.92</td>
<td>1.36 (1.12-1.66)</td>
<td>0.51</td>
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<tr>
<td></td>
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<td>Cancer</td>
<td>47</td>
<td>430</td>
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<td>1.86 (1.33-2.60)</td>
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<td>Cancer 70 y+</td>
<td>60</td>
<td>420</td>
<td>0.83</td>
<td>1.62 (1.21-2.17)</td>
<td>0.32</td>
</tr>
<tr>
<td>PPS</td>
<td>Balkau, 1991</td>
<td>18</td>
<td>All-cause</td>
<td>11</td>
<td>696</td>
<td>0.09</td>
<td>2.35 (1.21-4.58)</td>
<td>0.05</td>
</tr>
<tr>
<td>Risk group: IGT (isolated)</td>
<td>PPS</td>
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<td>Cerebrovascular</td>
<td>11</td>
<td>696</td>
<td>0.09</td>
<td>2.35 (1.21-4.58)</td>
<td>0.05</td>
</tr>
<tr>
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<td>PPS</td>
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<td>All-cause</td>
<td>137</td>
<td>570</td>
<td>1.19</td>
<td>1.63 (1.36-1.96)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

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Table 13. Mortality outcomes in subjects with the risk factor of dysglycemia—continued. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>Mortality Type</th>
<th>Baseline (n)</th>
<th>Baseline (n)</th>
<th>Outcome: Mortality</th>
<th>Outcome: Mortality</th>
<th>Annualized Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Absolute Annualized Risk Difference per 100 in exposed population</th>
<th>% Attributable Risk in population for study duration</th>
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</thead>
<tbody>
<tr>
<td>PPS</td>
<td>Balkau, 1992&lt;sup&gt;28&lt;/sup&gt;</td>
<td>18</td>
<td>Alcohol</td>
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<td>644</td>
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<td>0.12</td>
<td>2.12 (1.19-3.79)</td>
<td>0.06</td>
<td>52.6</td>
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<td>Cirrhosis</td>
<td>12</td>
<td>666</td>
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<td>86.0</td>
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<td>26</td>
<td>652</td>
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<td>No</td>
<td>0.22</td>
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<td>67.3</td>
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<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Tominaga, 1999&lt;sup&gt;23&lt;/sup&gt;</td>
<td>7</td>
<td>All-cause</td>
<td>10</td>
<td>145</td>
<td>91</td>
<td>2216</td>
<td>0.95</td>
<td>1.65 (0.86-3.17)</td>
<td>0.37</td>
<td>38.9</td>
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<td>BIP</td>
<td>Fisman, 2001&lt;sup&gt;41&lt;/sup&gt;</td>
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<td>All-cause</td>
<td>253</td>
<td>1005</td>
<td>1398</td>
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<td>Tenenbaum, 2002&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>All-cause</td>
<td>27</td>
<td>201</td>
<td>153</td>
<td>1660</td>
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<td>28.7</td>
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<td>Balkau, 2002&lt;sup&gt;43&lt;/sup&gt;</td>
<td>17</td>
<td>All-cause</td>
<td>252</td>
<td>954</td>
<td>1003</td>
<td>4569</td>
<td>1.37</td>
<td>1.18 (1.03-1.35)</td>
<td>0.21</td>
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</tr>
<tr>
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<td>110</td>
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<td>437</td>
<td>5166</td>
<td>0.56</td>
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<td>14.3</td>
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<tr>
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</tbody>
</table>

**Abbreviations:** BIP=Bezafibrate Infarction Prevention trial; CARE=Cholesterol and Recurrent Events Study; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; I-IFG=Isolated impaired fasting glucose; I-IGT=Isolated impaired glucose tolerance; IRAS=Insulin Resistance Atherosclerosis Study; NHANES II=National Health and Nutrition Examination Survey; PPS=Paris Prospective Study; y=Year(s).
Table 14. Lipid and blood pressure disturbance outcomes in subjects with the risk factor of dysglycemia. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories—IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
<th>Study group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>Metabolic Parameter</th>
<th>Baseline IGT and/or IFG</th>
<th>Baseline NGT and/or NFG</th>
<th>Annualized Risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (95% CI)</th>
<th>Absolute Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population for study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAHS</td>
<td>Haffner, 1992&lt;sup&gt;68&lt;/sup&gt;</td>
<td>8</td>
<td>Hypertension (men)</td>
<td>Yes</td>
<td>6</td>
<td>74</td>
<td>43</td>
<td>418</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertension (women)</td>
<td>Yes</td>
<td>15</td>
<td>94</td>
<td>45</td>
<td>590</td>
<td>1.83</td>
</tr>
<tr>
<td></td>
<td>Pfeffer, 2003&lt;sup&gt;66&lt;/sup&gt;</td>
<td>10</td>
<td>Dialysis return</td>
<td>Yes</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>22</td>
<td>4.74</td>
</tr>
</tbody>
</table>

Risk group: IGT

Risk group: IGT (isolated)

None

Risk group: IFG

None

Risk group: IFG (isolated)

None

Risk group: Multiple IGT/IFG

None

Abbreviations: IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; iIFG=Isolated impaired fasting glucose; iIGT=Isolated impaired glucose tolerance; SAHS=San Antonio Heart Study; y=Year(s).
Table 15. Other outcomes in subjects with the risk factor of dysglycemia. (Note: Annualized risk, unadjusted annualized RR, risk difference on annual data and AR for the study duration (%) are presented across the five diagnostic categories (IGT, IFG, I-IGT, I-IFG and combined IGT/IFG.)

<table>
<thead>
<tr>
<th>Study group</th>
<th>Author</th>
<th>Study Duration (y)</th>
<th>Outcome Type</th>
<th>Baseline (n) IGT and/or IFG</th>
<th>Baseline (n) NGT and/or NFG</th>
<th>Annualized risk per 100 persons in exposed population</th>
<th>Annualized Relative Risk (% 95% CI)</th>
<th>Annualized Risk Difference per 100 persons</th>
<th>% Attributable Risk in exposed population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Outcome Present Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>1.22</td>
</tr>
<tr>
<td>Risk group: IGT (isolated)</td>
<td></td>
<td></td>
<td></td>
<td>Retinopathy</td>
<td>31</td>
<td>773</td>
<td>73</td>
<td>2235</td>
<td>0.71</td>
</tr>
<tr>
<td>Risk group: IFG (isolated)</td>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: Multiple IGT/IFG</td>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; I-IFG=Isolated impaired fasting glucose; I-IGT=Isolated impaired glucose tolerance; y=Year(s).
Table 16. Placebo arm of RCTs: Progression to DM. (Note: All subjects in these trials had dysglycemia and only the annualized risk was estimated.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (years)</th>
<th>Baseline (n)</th>
<th>IGT and/or IFG</th>
<th>Annualized risk per 100 persons in IGT and/or IFG population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Risk group: IGT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>Chiasson, 2002</td>
<td>3.3</td>
<td>165 (by two OGGT)</td>
<td>521</td>
<td>15.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>178 (by two FPG)</td>
<td>508</td>
<td>8.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>285 (by one OGGT)</td>
<td>401</td>
<td>8.00</td>
</tr>
<tr>
<td>Shougang</td>
<td>Li, 1999</td>
<td>1.0</td>
<td>6</td>
<td>31</td>
<td>16.22</td>
</tr>
<tr>
<td></td>
<td>Pan, 1999</td>
<td>6.0</td>
<td>42</td>
<td>20</td>
<td>17.19</td>
</tr>
<tr>
<td></td>
<td>Pan, 1997</td>
<td>6.0</td>
<td>88</td>
<td>45</td>
<td>16.84</td>
</tr>
<tr>
<td></td>
<td>Liao, 2002</td>
<td>2.0</td>
<td>2</td>
<td>30</td>
<td>3.18</td>
</tr>
<tr>
<td>FDPS</td>
<td>Main result for this trial: Tuomilehto, 2001</td>
<td>3.0</td>
<td>59</td>
<td>188</td>
<td>8.18</td>
</tr>
<tr>
<td>DPP</td>
<td>Main result for this trial: Molitch, 2003</td>
<td>3.0</td>
<td>314*</td>
<td>768</td>
<td>11.52</td>
</tr>
<tr>
<td></td>
<td>Wein, 1999</td>
<td>4.3</td>
<td>27</td>
<td>69</td>
<td>7.39</td>
</tr>
</tbody>
</table>

Risk group: IGT (Isolated)

Risk group: IFG

Risk group: IFG (isolated)

Risk group: Multiple IGT/IFG

Abbreviations: DM=Diabetes Mellitus; DPP=Diabetes Prevention Program; FDPS=Finnish Diabetes Prevention Study; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance.

* Other results for this trial: Lindi, 2002; Lindstrom, 2003a; Lindstrom, 2003b
++ Other results for this trial: Knowler, 2002
Table 17. Placebo arm of RCTs: Reversion to normal glycemia. (Note: All subjects in these trials had dysglycemia and only the annualized risk was estimated.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Study Duration (years)</th>
<th>Baseline (n)</th>
<th>IGT and/or IFG</th>
<th>Annualized risk per 100 persons in IGT and/or IFG population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Risk group: IGT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>Chiasson, 2002*</td>
<td>3.3</td>
<td>212</td>
<td>474</td>
<td>10.60</td>
</tr>
<tr>
<td>Shougang</td>
<td>Li, 1999†</td>
<td>1.0</td>
<td>19</td>
<td>18</td>
<td>51.35</td>
</tr>
<tr>
<td></td>
<td>Wein, 1999†</td>
<td>4.3</td>
<td>43</td>
<td>53</td>
<td>12.90</td>
</tr>
<tr>
<td>Risk group: IGT (Isolated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: IFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: IFG (isolated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: Multiple IGT/IFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** STOP-NIDDM=Study to Prevent Non-Insulin Dependent Diabetes Mellitus; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance.
Table 18. Placebo arm of RCTs: Mortality. (Note: All subjects in these trials had dysglycemia and only the annualized risk was estimated.)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author / Parameter</th>
<th>Study Duration (years)</th>
<th>Baseline (n)</th>
<th>IGT and/or IFG</th>
<th>Outcome: Mortality</th>
<th>Annualized risk per 100 persons in IGT and/or IFG population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Da Qing</td>
<td>Pan, 1997\cite{77}</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: IGT (Isolated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: IFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: IFG (isolated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: Multiple IGT/IFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance.
Table 19. Placebo arm of RCTs: Lipid and blood pressure. (Note: All subjects in these trials had dysglycemia.*)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author / Parameter</th>
<th>Study Duration (years)</th>
<th>n</th>
<th>Mean change in outcome of interest in control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk group: IGT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Eriksson, 1999†††</td>
<td>1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HDL Cholesterol</td>
<td></td>
<td></td>
<td>0.01 ± 0.15*</td>
</tr>
<tr>
<td></td>
<td>- Total Cholesterol</td>
<td></td>
<td></td>
<td>-0.1 ± 0.7*</td>
</tr>
<tr>
<td></td>
<td>- Triglycerides</td>
<td></td>
<td></td>
<td>0.00 ± 0.69*</td>
</tr>
<tr>
<td></td>
<td>- BP (systolic)</td>
<td></td>
<td></td>
<td>-1.7 ± 12.4*</td>
</tr>
<tr>
<td></td>
<td>- BP (diastolic)</td>
<td></td>
<td></td>
<td>-1.0 ± 9.6*</td>
</tr>
<tr>
<td>Main result: FDPS</td>
<td>Tuomilehto, 2001†††</td>
<td>1</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HDL Cholesterol</td>
<td></td>
<td></td>
<td>1 ± 6*</td>
</tr>
<tr>
<td></td>
<td>- Total Cholesterol</td>
<td></td>
<td></td>
<td>-4 ± 28*</td>
</tr>
<tr>
<td></td>
<td>- Triglycerides</td>
<td></td>
<td></td>
<td>-1 ± 60*</td>
</tr>
<tr>
<td></td>
<td>- BP (systolic)</td>
<td></td>
<td></td>
<td>-1 ± 15*</td>
</tr>
<tr>
<td></td>
<td>- BP (diastolic)</td>
<td></td>
<td></td>
<td>-3 ± 9*</td>
</tr>
<tr>
<td>Other results : FDPS</td>
<td>Lindstrom, 2003†††</td>
<td>2</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HDL Cholesterol</td>
<td></td>
<td></td>
<td>3 ± 7*</td>
</tr>
<tr>
<td></td>
<td>- Total Cholesterol</td>
<td></td>
<td></td>
<td>0 ± 7*</td>
</tr>
<tr>
<td></td>
<td>- Triglycerides</td>
<td></td>
<td></td>
<td>0 ± 7.5*</td>
</tr>
<tr>
<td></td>
<td>- BP (systolic)</td>
<td></td>
<td></td>
<td>0 ± 15*</td>
</tr>
<tr>
<td></td>
<td>- BP (diastolic)</td>
<td></td>
<td></td>
<td>-3 ± 9*</td>
</tr>
<tr>
<td></td>
<td>Lindstrom, 2003†††</td>
<td>3</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Serum Total Cholesterol</td>
<td></td>
<td></td>
<td>0.1 ± 0.8*</td>
</tr>
<tr>
<td></td>
<td>- Serum Triglycerides</td>
<td></td>
<td></td>
<td>-0.0 ± 0.8*</td>
</tr>
<tr>
<td></td>
<td>Uusitupa, 2000†††</td>
<td>1</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HDL Cholesterol</td>
<td></td>
<td></td>
<td>+0.01*</td>
</tr>
<tr>
<td></td>
<td>- Total Cholesterol</td>
<td></td>
<td></td>
<td>-0.13*</td>
</tr>
<tr>
<td></td>
<td>- Triglycerides</td>
<td></td>
<td></td>
<td>-0.03*</td>
</tr>
<tr>
<td></td>
<td>- BP (systolic)</td>
<td></td>
<td></td>
<td>-3*</td>
</tr>
<tr>
<td></td>
<td>- BP (diastolic)</td>
<td></td>
<td></td>
<td>-1*</td>
</tr>
<tr>
<td>Risk group: IGT (Isolated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: IFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: IFG (isolated)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: Multiple IGT/IFG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Because most of these studies provided only change scores, we were unable to estimate risk.
* change scores presented ± SD if given.
Abbreviations:  BP=Blood pressure; FDPS=Finnish Diabetes Prevention Study; HDL=High density lipoprotein; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance.
<table>
<thead>
<tr>
<th>Author</th>
<th>IGT</th>
<th>I-IGT</th>
<th>IFG</th>
<th>I-IFG</th>
<th>IGT &amp; IFG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gabir, 2000</strong>²⁶</td>
<td>NT</td>
<td></td>
<td>NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted annualized estimates</td>
<td>R = 3.91</td>
<td>RR = 5.95</td>
<td>[95% CI 4.61-7.67]</td>
<td>RD = 3.19</td>
<td>AR% = 81.9^</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NT</td>
<td></td>
<td>NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = 6.05</td>
<td>RR = 9.85</td>
<td>[95% CI 6.65-14.60]</td>
<td>RD = 5.33</td>
<td>AR% = 88.5^</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Li, 2003</strong>²⁰</td>
<td>NT</td>
<td></td>
<td>NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted annualized estimates</td>
<td>R = 5.44</td>
<td>RR = 3.51</td>
<td>[95% CI 2.22-5.54]</td>
<td>RD = 3.71</td>
<td>AR% = 68.8^</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NT</td>
<td></td>
<td>NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = 7.34</td>
<td>RR = 5.05</td>
<td>[95% CI 2.86-8.90]</td>
<td>RD = 5.60</td>
<td>AR% = 77.1^</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>De Vegt, 2001</strong>²⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted annualized estimates</td>
<td>R = 4.94</td>
<td>RR = 10.01</td>
<td>[95% CI 6.52-15.39]</td>
<td>RD = 4.36</td>
<td>AR% = 88.5^</td>
</tr>
<tr>
<td></td>
<td>R = 5.14</td>
<td>RR = 8.63</td>
<td>[95% CI 5.46-13.64]</td>
<td>RD = 4.43</td>
<td>AR% = 86.6^</td>
</tr>
<tr>
<td></td>
<td>R = 5.76</td>
<td>RR = 9.04</td>
<td>[95% CI 6.28-13.03]</td>
<td>RD = 4.98</td>
<td>AR% = 86.9^</td>
</tr>
<tr>
<td></td>
<td>R = 5.03</td>
<td>RR = 8.40</td>
<td>[95% CI 5.50-12.83]</td>
<td>RD = 4.32</td>
<td>AR% = 86.3^</td>
</tr>
<tr>
<td></td>
<td>R = 9.59</td>
<td>RR = 20.69</td>
<td>[95% CI 12.51-34.22]</td>
<td>RD = 8.88</td>
<td>AR% = 93.0^</td>
</tr>
<tr>
<td>Adjusted estimates from Proportional Hazard Model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR = 10.9*</td>
<td>[95% CI 6.0-19.9]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR = 10.0*</td>
<td>[95% CI 6.1-16.5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR = 39.5*</td>
<td>[95% CI 17.0-92.1]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:**

- R=annualized risk per 100 persons in the exposed population
- RR=unadjusted annualized relative risk and [95% CI]
- RD=Risk difference per 100 persons per year
- AR%= percent attributable risk in the exposed population
- NT=not tested
- HR=Hazard ratio
- OR=Odds ratio

^ = AR% is based on study duration of 5 years and 6.4 years for the De Vegt study.
* = OR adjusted for age, sex, and follow-up duration.
Table 21. General study characteristics: Treatment.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author, Year, Country</th>
<th>Treatment</th>
<th>Duration (y)</th>
<th>N (IGT)</th>
<th>Treated and untreated Diagnostic Risk Group</th>
<th>Diagnostic Criteria</th>
<th>Age, y Mean (range)</th>
<th>Population</th>
<th>Funding Source</th>
<th>Quality Jadad (mod)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botnia</td>
<td>Lehtovirta 106 2001, SE</td>
<td>Metformin 500 mg bid</td>
<td>1.0</td>
<td>40</td>
<td>IGT WHO 98</td>
<td>85</td>
<td>58</td>
<td>FDR</td>
<td>I, G, Ch</td>
<td>6</td>
</tr>
<tr>
<td>CARE</td>
<td>Goldberg 52 1998, CA</td>
<td>Pravastatin 40 mg/d</td>
<td>5.0</td>
<td>4159</td>
<td>IFG ADA 97</td>
<td>(21-75)</td>
<td>Subjects recruited for dysglycemia.</td>
<td>-</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Da Qing</td>
<td>Li 66 2002, CN</td>
<td>Diet, Exercise, Diet and exercise</td>
<td>6.0</td>
<td>284</td>
<td>IGT WHO 98</td>
<td>44</td>
<td>Subjects recruited for dysglycemia.</td>
<td>-</td>
<td>3</td>
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</tr>
<tr>
<td>Da Qing</td>
<td>Pan 67 1997, CN</td>
<td>Diet, Exercise, Diet and exercise</td>
<td>6.0</td>
<td>530</td>
<td>IGT WHO 85</td>
<td>45.0 +/- 9.1</td>
<td>Subjects recruited for dysglycemia.</td>
<td>WHO, G</td>
<td>4</td>
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</tr>
<tr>
<td>DPP</td>
<td>DPP Research Group 216 2003, US</td>
<td>Metformin withdrawal</td>
<td>2.8+</td>
<td>1274</td>
<td>I-IGT ADA 97</td>
<td>NR</td>
<td>NR</td>
<td>G, Co, I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP</td>
<td>Molitch 176 2003, US</td>
<td>Metformin 850 mg bid, Diet and Exercise</td>
<td>4.6</td>
<td>3234</td>
<td>IGT</td>
<td>(25+)</td>
<td>Aboriginal</td>
<td>I, G</td>
<td>3</td>
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<tr>
<td>FDPS</td>
<td>Eriksson 177 1999, NL</td>
<td>Diet and Exercise</td>
<td>1.0</td>
<td>212</td>
<td>IGT WHO 85</td>
<td>(40-64)</td>
<td>European, FDR, obese</td>
<td>G</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>FDPS</td>
<td>Lind 101 2002, FI</td>
<td>Diet and Exercise</td>
<td>3.0</td>
<td>469</td>
<td>IGT WHO 85</td>
<td>(40-68)</td>
<td>Overweight, Subjects recruited for dysglycemia.</td>
<td>G</td>
<td>3</td>
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</tr>
<tr>
<td>FDPS</td>
<td>Lindstrom 103 2003, FI</td>
<td>Diet and Exercise</td>
<td>3.2</td>
<td>522</td>
<td>IGT WHO 85</td>
<td>55</td>
<td>Overweight. FDR</td>
<td>Ch</td>
<td>3</td>
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</tr>
<tr>
<td>FDPS</td>
<td>Lindstrom 178 2003, FI</td>
<td>Diet and Exercise</td>
<td>3.0</td>
<td>522</td>
<td>IGT WHO 85</td>
<td>(40-64)</td>
<td>High-risk group</td>
<td>I, G, Ch</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>FDPS</td>
<td>Tuomilehto 100 2001, NL</td>
<td>Diet and Exercise</td>
<td>3.2</td>
<td>522</td>
<td>IGT WHO 85</td>
<td>55</td>
<td>Medication use, overweight, FDR</td>
<td>G, Ch</td>
<td>6</td>
<td></td>
</tr>
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</table>
Table 21. General study characteristics: Treatment, continued

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author, Year, Country</th>
<th>Treatment</th>
<th>Duration (y)</th>
<th>N (IGT)</th>
<th>Treated and untreated</th>
<th>Diagnostic Risk Group</th>
<th>Diagnostic Criteria</th>
<th>Age, y Mean (range)</th>
<th>Population</th>
<th>Funding Source</th>
<th>Quality Jadad (mod)</th>
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</thead>
<tbody>
<tr>
<td>FDPS</td>
<td>Uusitupa 2000, FI</td>
<td>Diet and Exercise</td>
<td>2.0</td>
<td>523</td>
<td>IGT</td>
<td>WHO 85</td>
<td>(40-64)</td>
<td>Overweight</td>
<td>G</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>LIPID</td>
<td>Keech 2003, NZ</td>
<td>Pravastain 40 mg/d</td>
<td>6.0</td>
<td>9014</td>
<td>IFG</td>
<td>ADA 97</td>
<td>(31-75)</td>
<td>Previous MI, medication use</td>
<td>I, G</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Shougang</td>
<td>Li 1999, CN</td>
<td>Metformin 250 mg tid</td>
<td>1.0</td>
<td>90</td>
<td>IGT</td>
<td>WHO 85</td>
<td>48.5</td>
<td>Industry workers</td>
<td>I</td>
<td>6</td>
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<tr>
<td>STOP-NIDDM</td>
<td>Chiasson 2002, AT*</td>
<td>Acarbose 100 mg tid</td>
<td>3.3</td>
<td>1429</td>
<td>IGT</td>
<td>WHO 85</td>
<td>(40-70)</td>
<td>FDR</td>
<td>I</td>
<td>8</td>
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</tr>
<tr>
<td>STOP-NIDDM</td>
<td>Chiasson 2003, AT*</td>
<td>Acarbose 100 mg tid</td>
<td>3.0</td>
<td>1429</td>
<td>IGT</td>
<td>WHO 99</td>
<td>54.5</td>
<td>International trial in 9 countries</td>
<td>I</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Eriksson 1998, FI</td>
<td>Aerobic endurance training</td>
<td>0.5</td>
<td>14</td>
<td>IGT</td>
<td>WHO 85</td>
<td>50</td>
<td>FDR</td>
<td>G</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oldroyd 2001, GB</td>
<td>Diet, Exercise</td>
<td>0.5</td>
<td>78</td>
<td>IGT</td>
<td>WHO 85</td>
<td>(24-75)</td>
<td>European</td>
<td>G, P</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>Uusitupa 1992, FI</td>
<td>Chromium supplement 160u/d</td>
<td>0.5</td>
<td>26</td>
<td>IGT</td>
<td>WHO 85</td>
<td>70</td>
<td>European. Medication use</td>
<td>I</td>
<td>4</td>
<td></td>
<td></td>
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<td>Vermes 2003, CA</td>
<td>Enalapril</td>
<td>2.9</td>
<td>291</td>
<td>IFG</td>
<td>ADA 97</td>
<td>56</td>
<td>Previous MI, angina</td>
<td>G</td>
<td>6</td>
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<td>Wein 1999, AU</td>
<td>Diet advice</td>
<td>4.3</td>
<td>200</td>
<td>IGT</td>
<td>WHO 85</td>
<td>(38-40)</td>
<td>Follow-up after GDM</td>
<td>G, Ch</td>
<td>4</td>
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</tr>
</tbody>
</table>

Abbreviations: ADA=American Diabetes Association; bid=two times daily; Ch=Charity; Co=Consumer; FDR=First-degree relatives of type 2 diabetics; G=Government, GDM=Gestational Diabetes Mellitus; I=Industry; IFG=Impaired Fasting Glucose; IGT=Impaired Glucose Tolerance; I-IGT=Isolated Impaired Glucose Tolerance; MI=Myocardial Infarction; P=Professional; tid=three times daily; WHO=World Health Organization; y=Year(s).

Study Abbreviations: CARE=Cholesterol and Recurrent Events Study; DPP=Diabetes Prevention Program; FDPS=Finnish Diabetes Prevention Study; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; STOP-NIDDM=Study to Prevent Non-Insulin Dependent Diabetes Mellitus.

Country Abbreviations: (*)=additional locations; AT=Austria; AU=Australia; CA=Canada; CN=China; FI=Finland; GB=Great Britain; NL=Netherlands, NZ=New Zealand; SE=Sweden; US=United States.
Table 22. Randomized controlled trials: Progression to DM. Estimates of NNT and absolute risk reduction across diagnostic groups for IGT and/or IFG.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Time to endpoint (y)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Number control subjects</th>
<th>Number control subjects with outcome of interest</th>
<th>Annual risk in control subjects (%)</th>
<th>Number treated subjects</th>
<th>Number treated subjects with outcome of interest</th>
<th>Annual risk in treated subjects (%)</th>
<th>P value</th>
<th>NNT per year</th>
<th>Annualized Absolute risk reduction per 100 persons</th>
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</thead>
<tbody>
<tr>
<td>Risk group: IGT</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Lifestyle intervention</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liao, 2002(^{99})</td>
<td></td>
<td>2.0</td>
<td>Diet and Exercise</td>
<td>DM</td>
<td>32</td>
<td>2</td>
<td>3.18</td>
<td>32</td>
<td>1</td>
<td>1.57</td>
<td>NS</td>
<td>62.48</td>
<td>1.60</td>
</tr>
<tr>
<td>FDPS</td>
<td></td>
<td>Tuomilehto, 2001(^{100})</td>
<td>Diet and Exercise</td>
<td>DM</td>
<td>247</td>
<td>59</td>
<td>8.18</td>
<td>253</td>
<td>27</td>
<td>3.47</td>
<td>&lt;0.001</td>
<td>21.23</td>
<td>4.71</td>
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<tr>
<td>Da Qing</td>
<td></td>
<td>6.0</td>
<td>Diet</td>
<td>DM</td>
<td>133</td>
<td>89</td>
<td>16.84</td>
<td>130</td>
<td>62</td>
<td>10.24</td>
<td>&lt;0.05</td>
<td>15.15</td>
<td>6.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.0</td>
<td>Exercise</td>
<td>DM</td>
<td>133</td>
<td>89</td>
<td>16.84</td>
<td>141</td>
<td>58</td>
<td>8.45</td>
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<td>11.93</td>
<td>8.38</td>
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<td>6.0</td>
<td>Diet and Exercise</td>
<td>DM</td>
<td>133</td>
<td>88</td>
<td>16.84</td>
<td>126</td>
<td>58</td>
<td>9.77</td>
<td>&lt;0.05</td>
<td>14.15</td>
<td>7.07</td>
</tr>
<tr>
<td>Wein, 1999(^{50})</td>
<td></td>
<td>4.3 med</td>
<td>Diet</td>
<td>DM</td>
<td>96</td>
<td>27</td>
<td>7.39</td>
<td>97</td>
<td>26</td>
<td>7.00</td>
<td>NS</td>
<td>254.44</td>
<td>0.39</td>
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<tr>
<td><strong>Pharmacotherapeutic intervention</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>Chiasson, 2002(^{68})</td>
<td>3.3</td>
<td>Acarbose(^{a})</td>
<td>DM</td>
<td>686</td>
<td>285</td>
<td>15.02</td>
<td>682</td>
<td>221</td>
<td>11.19</td>
<td>&lt;0.0001</td>
<td>26.14</td>
<td>3.83</td>
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<tr>
<td></td>
<td></td>
<td>3.3</td>
<td>Acarbose(^{b})</td>
<td>DM</td>
<td>686</td>
<td>178</td>
<td>8.70</td>
<td>682</td>
<td>117</td>
<td>5.54</td>
<td>.0010</td>
<td>31.67</td>
<td>3.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.3</td>
<td>Acarbose(^{c})</td>
<td>DM</td>
<td>686</td>
<td>165</td>
<td>8.00</td>
<td>682</td>
<td>105</td>
<td>4.94</td>
<td>.0003</td>
<td>32.69</td>
<td>3.06</td>
</tr>
<tr>
<td>Shougang</td>
<td>Li, 1999(^{82})</td>
<td>1.0</td>
<td>Metformin</td>
<td>DM</td>
<td>37</td>
<td>6</td>
<td>16.22</td>
<td>33</td>
<td>1</td>
<td>3.03</td>
<td>&lt;0.011</td>
<td>7.58</td>
<td>13.19</td>
</tr>
<tr>
<td>Botnia</td>
<td>Lehtovirta, 2001(^{106})</td>
<td>0.5</td>
<td>Metformin</td>
<td>DM</td>
<td>20</td>
<td>1</td>
<td>9.75</td>
<td>20</td>
<td>1</td>
<td>9.75</td>
<td>NS</td>
<td>NA</td>
<td>0</td>
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</tbody>
</table>

\(^{a}\)Acarbose at 100 mg. \(^{b}\)Acarbose at 200 mg. \(^{c}\)Acarbose at 300 mg.
### Table 22. Randomized controlled trials: Progression to DM. Estimates of NNT and absolute risk reduction across diagnostic groups for IGT and/or IFG, continued

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Time to endpoint (y)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Number control subjects</th>
<th>Number control subjects with outcome of interest</th>
<th>Annual risk in control subjects (%)</th>
<th>Number treated subjects</th>
<th>Number treated subjects with outcome of interest</th>
<th>Annual risk in treated subjects (%)</th>
<th>P value</th>
<th>NNT per year</th>
<th>Annualized Absolute risk reduction per 100 persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk group: IGT (Isolated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group: IFG</td>
<td>Vermes, 2003(^{65})</td>
<td>2.9</td>
<td>Enalapril</td>
<td>DM</td>
<td>138</td>
<td>31</td>
<td>8.40</td>
<td>153</td>
<td>9</td>
<td>2.07</td>
<td>&lt;0.0001</td>
<td>15.80</td>
<td>6.33</td>
</tr>
<tr>
<td></td>
<td>LIPID</td>
<td>Keetch, 2003(^{53})</td>
<td>6.0</td>
<td>Pravastatin</td>
<td>DM</td>
<td>363</td>
<td>33</td>
<td>1.58</td>
<td>380</td>
<td>37</td>
<td>1.69</td>
<td>0.32</td>
<td>865.42~</td>
</tr>
<tr>
<td>Risk group: IFG (isolated)</td>
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<tr>
<td>Risk group: Multiple IGT/IFG</td>
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</tr>
</tbody>
</table>

**Abbreviations**: DM=Diabetes Mellitus; DPP=Diabetes Prevention Program; FDPS=Finnish Diabetes Prevention Study; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; NA=Not applicable; NNT=Number needed to treat; NS=Not significant; STOP-NIDDM=Study to Prevent Non-Insulin Dependent Diabetes Mellitus; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; y=Year(s).

* calculated from a percent; \(^a\) diagnosed by two OGTT; \(^b\) diagnosed by two FPG; \(^c\) diagnosed by one OGTT.

~ risk is higher for control subjects than for treated subjects.

* Other reports of this trial: Lindi, 2002\(^{101}\), Lindstrom, 2003\(^{103}\), Lindstrom, 2003\(^{178}\)

** Other reports of this trial: Li, 2002\(^{66}\)

*** Other reports of this trial: Knowler, 2002\(^{102}\), DPP group, 2003\(^{216}\)
Table 23. Randomized controlled trials: Reversion to normal glycemic levels. Estimates of NNT and absolute risk reduction across diagnostic groups for IGT and/or IFG.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Time to endpoint (years)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Number control subjects in analysis</th>
<th>Number control subjects with outcome of interest in analysis</th>
<th>Annual risk in control subjects (%)</th>
<th>Annual risk in treated subjects (%)</th>
<th>Number treated subjects in analysis</th>
<th>Number treated subjects with outcome of interest in analysis</th>
<th>P value</th>
<th>NNT per year</th>
<th>Annualized Absolute risk reduction per 100 persons</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk group: IGT - Lifestyle intervention</td>
<td>Liao, 2002&lt;sup&gt;99&lt;/sup&gt;</td>
<td>2.0</td>
<td>Diet and Exercise</td>
<td>NGT</td>
<td>38</td>
<td>11</td>
<td>15.71</td>
<td>36</td>
<td>24</td>
<td>42.26</td>
<td>0.01</td>
<td>3.77~</td>
<td>26.56~</td>
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</tr>
<tr>
<td></td>
<td>Oldroyd, 2001&lt;sup&gt;64&lt;/sup&gt;</td>
<td>0.5</td>
<td>Diet and Exercise</td>
<td>NGT</td>
<td>32</td>
<td>13</td>
<td>64.75</td>
<td>35</td>
<td>13</td>
<td>60.49</td>
<td>NS</td>
<td>23.49</td>
<td>4.26</td>
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</tr>
<tr>
<td></td>
<td>Wein, 1999&lt;sup&gt;50&lt;/sup&gt;</td>
<td>4.3</td>
<td>Diet</td>
<td>NGT</td>
<td>96</td>
<td>43</td>
<td>12.90</td>
<td>97</td>
<td>43</td>
<td>12.73</td>
<td>NS</td>
<td>592.16~</td>
<td>0.17</td>
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<tr>
<td>Risk group: IGT - Pharmacotherapeutic intervention</td>
<td>STOP-NIDDM</td>
<td>CHIASSON, 2002&lt;sup&gt;58&lt;/sup&gt;</td>
<td>3.3</td>
<td>Acarbose</td>
<td>NGT</td>
<td>686</td>
<td>212</td>
<td>10.60</td>
<td>682</td>
<td>241</td>
<td>12.38</td>
<td>&lt;0.0001</td>
<td>56.22~</td>
<td>1.78~</td>
</tr>
<tr>
<td></td>
<td>Shougang Li, 1999&lt;sup&gt;62&lt;/sup&gt;</td>
<td>1.0</td>
<td>Metformin</td>
<td>NGT</td>
<td>37</td>
<td>19</td>
<td>51.35</td>
<td>33</td>
<td>28</td>
<td>84.85</td>
<td>0.011</td>
<td>2.99~</td>
<td>33.50~</td>
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</tr>
<tr>
<td></td>
<td>Botnia Lehtovirta, 2001&lt;sup&gt;106&lt;/sup&gt;</td>
<td>0.5</td>
<td>Metformin</td>
<td>NGT</td>
<td>20</td>
<td>6</td>
<td>51.00</td>
<td>20</td>
<td>8</td>
<td>64.00</td>
<td>NS</td>
<td>7.69~</td>
<td>13.00~</td>
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</tr>
<tr>
<td>Risk group: IGT (Isolated)</td>
<td></td>
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<tr>
<td>Risk group: IFG</td>
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<tr>
<td>Risk group: IFG (isolated)</td>
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<tr>
<td>Risk group: Multiple IGT/IFG</td>
<td>Liao, 2002&lt;sup&gt;99&lt;/sup&gt;</td>
<td>2.0</td>
<td>Diet and Exercise</td>
<td>NGT</td>
<td>38</td>
<td>11</td>
<td>15.71</td>
<td>36</td>
<td>24</td>
<td>42.26</td>
<td>0.01</td>
<td>3.77~</td>
<td>26.56~</td>
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</tr>
</tbody>
</table>

Abbreviations: IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; NGT=Normal glucose tolerance; NNT=Number needed to treat; NS=Not significant; STOP-NIDDM=Study to Prevent Non-Insulin Dependent Diabetes Mellitus.

~ risk is higher for control subjects than for treated subjects
### Table 24. Randomized controlled trials: Non-fatal cardiovascular disease. Estimates of NNT and absolute risk reduction across diagnostic groups for IGT and/or IFG.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Time to endpoint (years)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Number control subjects</th>
<th>Number control subjects with outcome of interest</th>
<th>Annual risk in control subjects</th>
<th>Number treated subjects</th>
<th>Number treated subjects with outcome of interest</th>
<th>Annual risk in treated subjects</th>
<th>P value</th>
<th>NNT over year</th>
<th>Annualized Absolute risk reduction per 100 persons</th>
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</tr>
<tr>
<td>CARE Goldberg, 1998$^{52}$</td>
<td>Pravastatin</td>
<td>5.0</td>
<td>CABG</td>
<td>161</td>
<td>15</td>
<td>1.94</td>
<td>181</td>
<td>13</td>
<td>1.48</td>
<td>NR</td>
<td>218.65</td>
<td>0.46</td>
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<td></td>
<td>Pravastatin</td>
<td>5.0</td>
<td>PTCA</td>
<td>161</td>
<td>17</td>
<td>2.21</td>
<td>181</td>
<td>16</td>
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<td>NR</td>
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<td>Stroke</td>
<td>161</td>
<td>5</td>
<td>0.63</td>
<td>181</td>
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<td>NR</td>
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<td>5.0</td>
<td>Unstable Angina</td>
<td>161</td>
<td>28</td>
<td>1.35</td>
<td>181</td>
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<td>3.43</td>
<td>NR</td>
<td>315.49</td>
<td>0.32</td>
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<tr>
<td>LIPID Keech, 2003$^{83}$</td>
<td>Pravastatin</td>
<td>6.0</td>
<td>CHD Mortality AND Non-fatal MI</td>
<td>466</td>
<td>83</td>
<td>3.22</td>
<td>474</td>
<td>56</td>
<td>2.07</td>
<td>NR</td>
<td>87.51</td>
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<td>Pravastatin</td>
<td>6.0</td>
<td>CVD</td>
<td>466</td>
<td>213</td>
<td>9.68</td>
<td>474</td>
<td>176</td>
<td>7.44</td>
<td>NS</td>
<td>44.74</td>
<td>2.24</td>
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<td></td>
<td>Pravastatin</td>
<td>6.0</td>
<td>CABG or PTCA</td>
<td>466</td>
<td>77</td>
<td>2.97</td>
<td>474</td>
<td>64</td>
<td>2.39</td>
<td>NS</td>
<td>173.39</td>
<td>0.58</td>
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<td>Pravastatin</td>
<td>6.0</td>
<td>Stroke</td>
<td>466</td>
<td>25</td>
<td>0.91</td>
<td>474</td>
<td>16</td>
<td>0.57</td>
<td>NS</td>
<td>290.58</td>
<td>0.34</td>
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<td>Risk group: Multiple IGT/IFG</td>
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</tbody>
</table>

**Abbreviations:** CABG=Coronary artery bypass graft; CARE=Cholesterol and Recurrent Events Study; CHD=Coronary heart disease; CVD=Cardiovascular disease; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; LIPID=Long-term Intervention with Pravastatin in Ischemic Disease; MI=Myocardial infarction; NR=Not reported; NS=Not significant; NNT=Number needed to treat; PTCA=Percutaneous transluminal coronary angioplasty.
### Table 25. Randomized controlled trials: Mortality. Estimates of NNT and absolute risk reduction across diagnostic groups for IGT and/or IFG.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Time to endpoint (years)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Number control subjects in analysis</th>
<th>Number control subjects with outcome of interest in analysis</th>
<th>Annual risk in control subjects (%)</th>
<th>Number treated subjects in analysis</th>
<th>Number treated subjects with outcome of interest in analysis</th>
<th>Annual risk in treated subjects (%)</th>
<th>Annual risk reduction per 100 persons</th>
<th>P value</th>
<th>NNT per year</th>
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<tr>
<td><strong>Risk group: IGT</strong></td>
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<tr>
<td>Da Qing</td>
<td>Pan, 1997&lt;sup&gt;67&lt;/sup&gt;</td>
<td>6.0</td>
<td>Diet</td>
<td>All cause mortality</td>
<td>133</td>
<td>3</td>
<td>0.38</td>
<td>130</td>
<td>3</td>
<td>0.39</td>
<td>NR</td>
<td>11307.08~</td>
<td>0.01~</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.0</td>
<td>Exercise</td>
<td>All cause mortality</td>
<td>133</td>
<td>3</td>
<td>0.38</td>
<td>141</td>
<td>0</td>
<td>0.00</td>
<td>NR</td>
<td>263.49</td>
<td>0.38</td>
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<td></td>
<td>6.0</td>
<td>Diet and Exercise</td>
<td>All cause mortality</td>
<td>133</td>
<td>3</td>
<td>0.38</td>
<td>126</td>
<td>5</td>
<td>0.67</td>
<td>NR</td>
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<td>0.29~</td>
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<tr>
<td><strong>Risk group: IFG and previous MI</strong></td>
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<tr>
<td>CARE</td>
<td>Goldberg, 1998&lt;sup&gt;52&lt;/sup&gt;</td>
<td>5.0</td>
<td>Pravastatin</td>
<td>CHD mortality</td>
<td>161</td>
<td>12</td>
<td>1.54</td>
<td>171</td>
<td>11</td>
<td>1.32</td>
<td>NR</td>
<td>462.47</td>
<td>0.22</td>
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<tr>
<td><strong>Risk group: IFG (isolated)</strong></td>
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<tr>
<td><strong>Risk group: Multiple IGT/IFG</strong></td>
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</tbody>
</table>

**Abbreviations:** CARE=Cholesterol and Recurrent Events Study; CHD=Coronary heart disease; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; MI=Myocardial infarction; NNT=Number needed to treat; NR=Not reported.  
~ risk is higher for control subjects than for treated subjects.
### Table 26. Randomized controlled trials: Lipid and blood pressure. Effects across diagnostic groups for IGT and/or IFG.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Author</th>
<th>Time to endpoint (years)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Number control subjects</th>
<th>Mean value for control subjects (± SD)</th>
<th>Number treated subjects</th>
<th>Mean value for treated subjects (± SD)</th>
<th>P value</th>
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<td><strong>Risk group IGT</strong></td>
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</tr>
<tr>
<td>FDPS</td>
<td></td>
<td>2</td>
<td>Diet and Exercise</td>
<td>HDL Cholesterol mg/dl</td>
<td>250</td>
<td>3 ± 7°</td>
<td>256</td>
<td>4 ± 7°</td>
<td>0.2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Diet and Exercise</td>
<td>Total Cholesterol mg/dl</td>
<td>250</td>
<td>0 ± 7°</td>
<td>256</td>
<td>-4 ± 31°</td>
<td>0.1834</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Diet and Exercise</td>
<td>Triglycerides mg/dl</td>
<td>250</td>
<td>0 ± .75°</td>
<td>256</td>
<td>-18 ± 53°</td>
<td>0.0026</td>
</tr>
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<td></td>
<td></td>
<td>2</td>
<td>Diet and Exercise</td>
<td>Ratio of TC to HDL</td>
<td>250</td>
<td>-0.3 ± 0.8°</td>
<td>256</td>
<td>-0.6 ± 0.9°</td>
<td>0.0009</td>
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<tr>
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<td>2</td>
<td>Diet and Exercise</td>
<td>BP (systolic) mmHg</td>
<td>250</td>
<td>0 ± 15°</td>
<td>256</td>
<td>-5 ± 14°</td>
<td>0.0005</td>
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<td></td>
<td>2</td>
<td>Diet and Exercise</td>
<td>BP (diastolic) mmHg</td>
<td>250</td>
<td>-3 ± 9°</td>
<td>256</td>
<td>-5 ± 9°</td>
<td>0.0124</td>
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<td>0.5</td>
<td>Diet and Exercise</td>
<td>HDL Cholesterol mmol/l</td>
<td>32</td>
<td>0.06 ± 0.21°</td>
<td>35</td>
<td>0.04 ± 0.19°</td>
<td>NS</td>
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<td></td>
<td>Diet and Exercise</td>
<td>LDL Cholesterol mmol/l</td>
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<td>-0.21 ± 0.61°</td>
<td>35</td>
<td>-0.10 ± 0.54°</td>
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<td>Diet and Exercise</td>
<td>Total Cholesterol mmol/l</td>
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<td>-0.18 ± 0.59°</td>
<td>35</td>
<td>-0.16 ± 0.55°</td>
<td>NS</td>
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<td>Diet and Exercise</td>
<td>Triglycerides mmol/l</td>
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<td>-0.01 ± 0.67°</td>
<td>35</td>
<td>-0.22 ± 0.78°</td>
<td>NS</td>
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<td></td>
<td>Diet and Exercise</td>
<td>BP (systolic) mmHg</td>
<td>32</td>
<td>-0.27 ± 14.3°</td>
<td>35</td>
<td>-0.79 ± 16.7°</td>
<td>0.050</td>
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<td></td>
<td>Diet and Exercise</td>
<td>BP (diastolic) mmHg</td>
<td>32</td>
<td>1.9 ± 10.0°</td>
<td>35</td>
<td>-2.9 ± 9.9°</td>
<td>0.052</td>
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<tr>
<td>Study Group</td>
<td>Author</td>
<td>Time to endpoint (years)</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Number control subjects</td>
<td>Mean value for control subjects (± SD)</td>
<td>Number treated subjects</td>
<td>Mean value for treated subjects (± SD)</td>
<td>P value</td>
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<td>Ericksson, 1997&lt;sup&gt;108&lt;/sup&gt;</td>
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<td>HDL cholesterol mmol/l</td>
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<td>Systolic BP mmHg</td>
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<td>13^</td>
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<td>4^</td>
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<td>-7^</td>
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<td>3^</td>
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<td>-0.01^</td>
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<td>0.33^</td>
<td>20</td>
<td>0.10^</td>
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<td>Systolic BP mmHg</td>
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<td>-5^</td>
<td>20</td>
<td>-8^</td>
<td>NS</td>
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<tr>
<td></td>
<td></td>
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<td>Diastolic BP mmHg</td>
<td>20</td>
<td>-1^</td>
<td>20</td>
<td>-4^</td>
<td>NS</td>
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Table 26. Randomized controlled trials: Lipid and blood pressure. Effects across diagnostic groups for IGT and/or IFG, continued

<table>
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<th>Study Group</th>
<th>Author</th>
<th>Time to endpoint (years)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Number control subjects</th>
<th>Mean value for control subjects (± SD)</th>
<th>Number treated subjects</th>
<th>Mean value for treated subjects (± SD)</th>
<th>P value</th>
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</thead>
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<tr>
<td>Uusitupa, 1992&lt;sup&gt;109&lt;/sup&gt;</td>
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<td>0.5</td>
<td>Chromium</td>
<td>Cholesterol mmol/l</td>
<td>11</td>
<td>0&lt;sup&gt;^&lt;/sup&gt;</td>
<td>13</td>
<td>-0.1&lt;sup&gt;^&lt;/sup&gt;</td>
<td>NS</td>
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<td></td>
<td></td>
<td>HDL cholesterol mmol/l</td>
<td>11</td>
<td>0.06&lt;sup&gt;^&lt;/sup&gt;</td>
<td>13</td>
<td>0.07&lt;sup&gt;^&lt;/sup&gt;</td>
<td>NS</td>
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<td>LDL cholesterol mmol/l</td>
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<td>-0.1&lt;sup&gt;^&lt;/sup&gt;</td>
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<td>-0.2&lt;sup&gt;^&lt;/sup&gt;</td>
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<td>11</td>
<td>0.1&lt;sup&gt;^&lt;/sup&gt;</td>
<td>13</td>
<td>-0.5&lt;sup&gt;^&lt;/sup&gt;</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Risk group: IGT (Isolated)**

**Risk group: IFG**

**Risk group: IFG (isolated)**

**Risk group: Multiple IGT/IFG**

**Abbreviations:** BP=Blood pressure; CHD=Coronary heart disease; FDPS=Finnish Diabetes Prevention Study; HDL=High density lipoprotein; IFG=Impaired fasting glucose; IGT=Impaired glucose tolerance; LDL=Low density lipoprotein; MI=Myocardial infarction; NNT=Number needed to treat; NR=Not reported; NS=Not significant; SD=Standard Deviation; TC=Total cholesterol.

<sup>^</sup> change scores were calculated from pre and post values; no SD was estimated.

<sup>~</sup> change scores presented with SD.

<sup>+</sup> Other results for this trial: Lindstrom, 2003<sup>178</sup>; Tuomilehto, 2001<sup>100</sup>; Uusitupa, 2000<sup>179</sup>; Eriksson, 1999<sup>177</sup>
Table 27. Pediatric studies included in the main review.

<table>
<thead>
<tr>
<th>Author</th>
<th>Inclusion in pediatric review</th>
<th>Study type</th>
<th>Duration</th>
<th># male</th>
<th># female</th>
<th>Age (y)</th>
<th>Ethnic</th>
<th>IGT 75g cut-offs (mmol/L)</th>
<th>Population</th>
<th>Included for Main Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimmet²⁰, 1984, Naura</td>
<td>Included in main review; included in pediatric portion</td>
<td>prospective cohort</td>
<td>6-8 y mean: 6.2 y</td>
<td>118</td>
<td>148</td>
<td>0-60+</td>
<td>Micronesian (Nauruans)</td>
<td>WHO 80: (7.8-11.0)</td>
<td>Micronesian (Nauruans).</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Rosenbloom¹¹, 1982, USA</td>
<td>Included in main review; not included in pediatric portion</td>
<td>prospective cohort</td>
<td>5-12 y</td>
<td>4</td>
<td>13</td>
<td>1.4-20.5</td>
<td>Not Reported</td>
<td>NDDG 79: (7.8-11.0)</td>
<td>37 children with stress hyperglycemia, asymptomatic glucosuria or possible hypoglycemia.</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Pettitt¹⁰, 1996, USA</td>
<td>Included in main review; not included in pediatric portion (15-39 y with no pediatrics distinction)</td>
<td>prospective cohort</td>
<td>0.5-10 y</td>
<td>317</td>
<td></td>
<td>15-39</td>
<td>Pima Indians</td>
<td>WHO 85: (7.8-11.0)</td>
<td>Women of at least half Pima and Tohono O’odham heritage All had IGT at 15-39 yr after at least 1 pregnancy</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Nagi¹⁰, 1995, USA</td>
<td>Included in main review; not included in pediatric portion (13.2-51.4 y with no pediatrics detail)</td>
<td>prospective cohort</td>
<td>1-17.24y median 5 y</td>
<td></td>
<td></td>
<td>mean: 32.6</td>
<td>Pima Indians</td>
<td>WHO 85 (7.8-11.0)</td>
<td>Pima Indians from Gila River Arizona.</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Motala⁶⁵, 1993, Africa</td>
<td>Included in main review; not included in pediatric portion (&gt; 15y with no pediatrics detail)</td>
<td>prospective cohort</td>
<td>4 y</td>
<td>67</td>
<td>61</td>
<td>16+</td>
<td>South African Indians</td>
<td>WHO 85 (7.8-11.0) WHO 80 (8.0-10.9)</td>
<td>South African Indians. Residents of Durban, S. Africa.</td>
<td>Prognosis</td>
</tr>
</tbody>
</table>

Abbreviations: IGT=Impaired glucose tolerance; NDDG= National Diabetes Data Group; WHO=World Health Organization; y=Year(s).
Table 28. Pediatric studies evaluated but not included in the main review.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Duration</th>
<th>Male n</th>
<th>Female n</th>
<th>Population characteristics</th>
<th>Age range, years</th>
<th>Mean age, years (SD)</th>
<th>Ethnicity (n)</th>
<th>Study group</th>
<th>Issue addressed</th>
<th>IGT and/or IFG prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arslanian^{217}</td>
<td>CS</td>
<td>1-2 w</td>
<td>NR</td>
<td>21</td>
<td>PCOS IGT, NGT or DM</td>
<td>NR</td>
<td>IGT: 14.4 (0.9)</td>
<td>B (9), W (12)</td>
<td>NR</td>
<td>PREV</td>
<td>42.9</td>
</tr>
<tr>
<td>Arslanian^{139}</td>
<td>OS</td>
<td>3 m</td>
<td>NR</td>
<td>15</td>
<td>PCOS Metformin treatment</td>
<td>NR</td>
<td>14 (0.8)</td>
<td>B (6), W (9)</td>
<td>NR</td>
<td>RX</td>
<td></td>
</tr>
<tr>
<td>Braun^{131}</td>
<td>PC</td>
<td>5 y</td>
<td>32</td>
<td>42</td>
<td>Aboriginal (Australia)</td>
<td>NR</td>
<td>male: 13.1 (2.5)</td>
<td>Ab</td>
<td>NR</td>
<td>PREV/PROG</td>
<td>Male: 9.39 Female: 4.7</td>
</tr>
<tr>
<td>de Courten^{9}</td>
<td>PC</td>
<td>12.3 y</td>
<td>C: 1318</td>
<td>A: 1830</td>
<td>Aboriginal (Pima)</td>
<td>C: 6-17 A: ≥ 18</td>
<td>C: NR A: 39.5</td>
<td>Ab</td>
<td>Pima</td>
<td>PREV/PROG</td>
<td>4</td>
</tr>
<tr>
<td>Fagot-Campagna^{137}</td>
<td>CS</td>
<td>6 y</td>
<td>NR</td>
<td>NR</td>
<td>US Pop based</td>
<td>12-19</td>
<td>16</td>
<td>NHANES III</td>
<td>PREV/ DIAG</td>
<td>1.76 IFG (CI 0.02 – 3.5)</td>
<td></td>
</tr>
<tr>
<td>Invitti^{134}</td>
<td>CS</td>
<td>2 w</td>
<td>345</td>
<td>365</td>
<td>obese</td>
<td>6-18</td>
<td>14</td>
<td>E</td>
<td>NR</td>
<td>PREV/ DIAG</td>
<td>4.2</td>
</tr>
<tr>
<td>Knowler^{14}</td>
<td>PC</td>
<td>20 y</td>
<td>NR</td>
<td>NR</td>
<td>Aboriginal</td>
<td>≥ 5</td>
<td>NR</td>
<td>Ab, W</td>
<td>Pima</td>
<td>REVIEW</td>
<td></td>
</tr>
<tr>
<td>Silverman^{133}</td>
<td>PC</td>
<td>6 y</td>
<td>90</td>
<td>78</td>
<td>ODM</td>
<td>≥ 1.5</td>
<td>control: 12.8 (1.7)</td>
<td>NR</td>
<td>NR</td>
<td>PREV/PROG</td>
<td>&lt;5 y: 1.2 5-9 y: 5.4 10-16 y: 18.2</td>
</tr>
<tr>
<td>Silverman^{136}</td>
<td>PC</td>
<td>6 y</td>
<td>NR</td>
<td>NR</td>
<td>ODM</td>
<td>NR</td>
<td>B, H, W</td>
<td>NR</td>
<td>PREV/PROG</td>
<td>14-17 y: 36% had at least one test with IGT</td>
<td></td>
</tr>
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</table>
Table 28. Pediatric studies evaluated but not included in the main review, continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Duration</th>
<th>Male n</th>
<th>Female n</th>
<th>Population characteristics</th>
<th>Age range, years</th>
<th>Mean age (SD)</th>
<th>Ethnicity (n)</th>
<th>Study group</th>
<th>Issue addressed</th>
<th>IGT prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinha122002</td>
<td>CS</td>
<td>NR</td>
<td>C: 17 Ad: 54</td>
<td>C: 38 Ad: 58</td>
<td>obese</td>
<td>4-18</td>
<td>C/male: 8 (0.3) C/female: 7 (0.3) Ad/male: 14 (0.2) Ad/female: 14 (0.2)</td>
<td>B (38), H (32), W (97)</td>
<td>NR</td>
<td>PREV/DIAG</td>
<td>4-10 y: 25.4 11-18 y: 20.5</td>
</tr>
<tr>
<td>Zimmet 130 1992</td>
<td>PC</td>
<td>12 y</td>
<td>NR</td>
<td>NR</td>
<td>Aboriginal (Nauruan Tuvalu)</td>
<td>8 -19 10-19</td>
<td>NR</td>
<td>Other</td>
<td>Nauru Tuvalu</td>
<td>PREV</td>
<td>Naura: 5 Tuvalu: 3.5</td>
</tr>
<tr>
<td>Neufeld 218 1997</td>
<td>CS</td>
<td>4 y</td>
<td>4</td>
<td>4</td>
<td>Siblings of children with Type 2 DM</td>
<td>8 - 16</td>
<td>13.25 ± 2.76</td>
<td>Mexican American</td>
<td>NR</td>
<td>PREV</td>
<td>25</td>
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</table>

Abbreviations: A=Adult; Ab=Aboriginal; Ad=Adolescent; B=Black; C=Children; CS=Cross-sectional; DIAG = Diagnosis; DM=Diabetes Mellitus; E=European; H=Hispanic; IGT=Impaired Glucose Tolerance; m=Month; NGT=Normal Glucose Tolerance; NHANES=National Health and Nutrition Examination Survey; NR=Not Reported; ODM=Offspring of women with pre-gestational and gestational Diabetes Mellitus; OS=Observational Study; PC=Prospective Cohort; PCOS=Polycystic Ovary Syndrome; Pima=Pima Indians; PREV = Prevalence. PROG = Prognosis; RX = Treatment; SD=Standard Deviation; w=Week; W=Caucasian; y=Year.
<table>
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</table>
Appendix A. Search Strategies

Medline and HealthStar

1. exp case-control studies/
2. prospective:.tw.
3. case control:.tw.
4. 1 or 2 or 3
5. exp "sensitivity and specificity"/
6. sensitiv:.tw.
7. diagnos:.tw,sh.
8. di.fs.
9. biological variation.mp. [mp=title, abstract, keywords, mesh subject heading]
10. reliability.tw.
11. "reproducibility of results"/
12. mass screening/
13. screen:.tw.
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. glucose intolerance/
16. (impaired glucose or impaired fasting glucose).tw.
17. (igt or ifg).tw.
18. blood glucose/
19. limit 18 to yr=1996-2004
20. glucose tolerance test/
21. prediabetic state/
22. prediabet:.tw.
23. pre-diabet:.tw.
24. fasting plasma glucose.tw.
25. 15 or 16 or 17 or 19 or 20 or 21 or 22 or 23 or 24
26. exp epidemiologic studies/
27. predict:.mp.
28. ep.xs.
29. exp prognosis/
30. 26 or 27 or 28 or 29
31. randomized-controlled-trial.pt.
32. controlled-clinical-trial.pt.
33. randomized-controlled-trials/
34. random-allocation/
35. double-blind-method/
36. single-blind-method/
37. clinical trial.pt.
38. exp clinical trials/
39. (clin: adj trial:).ti,ab.
40. ((singl: or doubl: or tripl: or trebl:) adj (mask: or blind:)).ti,ab.
41. placebos.sh.
42. placebo:.ti,ab.
43. random:.ti,ab.
44. research design/
45. exp cohort studies/
46. ((control: adj3 (group: or condition:)) or (control: adj2 (trial: or study or studies))).tw.
47. (cohort adj (study or studies or trial or trials)).tw.
48. multivariate analysis/
49. intervention studies/
50. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. animal/ not (animal/ and human/)
52. 50 not 51
53. 25 and 14 and 4
54. 25 and 30 and 4
55. 25 and 50
56. 53 or 54 or 55
57. 56 not 51
58. (addresses or analytic or bibliography or biography or classical article or comment or consensus development conference or consensus development conference nih or current biog obit or dictionary or directory or duplicate publication or editorial or festschrift or historical article or interview or lectures or legal cases or letter or news or newspaper article or review of reported cases or review tutorial or meeting abstracts or meeting report or meeting paper).pt.
59. 57 not 58
60. limit 59 to (english language and yr=1979-2004)
Cochrane

1. ((glucose next blood next level)
2. or (glucose next tolerance next test)
3. or prediabetes
4. or pre-diabetes
5. or prediabetic
6. or pre-diabetic
7. or igt
8. or ifg
9. or (glucose next intolerance)
10. or (impaired next glucose)
11. or (impaired next fasting next glucose)
12. or (fasting next plasma next glucose))
Embase

1. "sensitivity and specificity"/
2. sensitiv:.tw.
3. exp diagnosis/
4. diagnos:.tw.
5. di.fs.
6. biological variation.tw.
7. reliability.tw.
8. reproducibility/
9. screening/ or screening test/ or exp mass screening/
10. screen:.tw.
11. or/1-10
12. case control study/
13. prospective:.tw.
14. case control.tw.
15. or/12-14
16. exp methodology/
17. predict:.mp.
18. prognosis/
19. ep.fs.
20. or/16-19
21. exp Practice Guideline/
22. abstract report/ or editorial/ or letter/ or note/ or exp conference paper/
23. 21 or 22
24. double blind procedure/ or experimental design/ or latin square design/ or parallel design/ or single blind procedure/
25. randomization/
26. (clin: adj trial:).ti,ab.
27. (((singl: or doubl: or tripl: or trebl:) adj (mask: or blind:))).ti,ab.
28. Placebo/
29. placebo:.ti,ab.
30. random:.ti,ab.
31. ((control: adj3 (group: or condition:)) or (control: adj2 (trial: or study or studies))).tw.
32. (cohort adj (study or studies or trial or trials)).tw.
33. exp multivariate analysis/
34. clinical study/ or case control study/ or clinical article/ or longitudinal study/ or major clinical study/ or open study/ or prospective study/ or retrospective study/ or clinical trial/ or multicenter study/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or randomized controlled trial/ or postmarketing surveillance/ or drug surveillance program/ or methodology/ or case finding/ or cohort analysis/ or contingent valuation/ or crossover procedure/ or double blind procedure/ or experimental design/ or intermethod comparison/ or latin square design/ or parallel design/ or pilot study/ or questionnaire/ or sample size/ or single blind procedure/ or evidence based medicine/ or meta analysis/ or outcomes research/ or quality control/ or good laboratory practice/ or medical audit/ or total quality management/ or validation process/
35. or/24-34
36. Glucose Intolerance/
37. (impaired glucose or impaired fasting glucose).tw.
38. (igt or ifg).tw.
39. glucose blood level/
40. exp glucose tolerance test/
41. prediabet:.tw.
42. pre-diabet:.tw.
43. fasting plasma glucose.tw.
44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. 44 and 11 and 15
46. 44 and 20 and 15
47. 44 and 35
48. 45 or 46 or 47
49. 48 not 23
50. animal/ not (human/ and animal/)
51. 49 not 50
52. limit 51 to (english and yr=1979-2004)
CINAHL

1. Glucose Intolerance/
2. (impaired glucose or impaired fasting glucose).tw.
3. (igt or ifg).tw.
4. Blood Glucose/
5. glucose/ or metabolism/ or metabolic diseases/
6. limit 5 to yr=1982-1998
7. Glucose Tolerance Test/
8. pre-diabet:.tw.
9. fasting plasma glucose.tw.
10. exp Clinical Trials/
11. Random Assignment/
12. clinical trial.pt.
13. (clin: adj trial:).ti,ab.
14. ((singl: or doubl: or tripl: or trebl:) adj (mask: or blind:)).ti,ab.
15. Placebos/
16. placebo:.ti,ab.
17. random:.ti,ab.
18. meta analysis/ or exp study design/
19. ((control: adj3 (group: or condition:)) or (control: adj2 (trial: or study or studies))).tw.
20. (cohort adj (study or studies or trial or trials)).tw.
21. Multivariate Analysis/
22. or/12-23
23. Case Control Studies/
24. prospective:.tw.
25. case control:.tw.
26. or/25-27
27. "Sensitivity and Specificity"/
28. sensitiv:.tw.
29. di.fs.
30. biological variation.tw.
31. reliability.tw.
32. Reproducibility of Results/
33. screen:.tw.
34. or/29-37
35. book preservation/ or book reviews/ or allied health literature/ or nursing literature/ or pamphlets/ or "policy and procedure manuals"/ or reports/ or incident reports/ or report writing/ or serial publications/ or newsletters/ or newspapers/ or "theses and dissertations"/
36. Epidemiological Research/
42. predict:.mp.
43. prognosis/ or treatment outcomes/
44. or/41-43
45. 11 and 38 and 28
46. 11 and 44 and 28
47. 11 and 24
48. 45 or 46 or 47
49. 48 not 40
50. animal/ not (animal/ and human/)
51. 49 not 50
52. limit 51 to (english and yr=1979-2003)
AMED

1. exp glucose/ or blood glucose/
2. (impaired glucose or impaired fasting glucose).tw.
3. (igt or ifg).tw.
4. glucose tolerance test.tw.
5. prediabet:.tw.
6. fasting plasma glucose.tw.
7. or/1-6
8. exp clinical trials/ or randomized controlled trials/
9. exp research design/ or clinical trials/ or randomized controlled trials/ or comparative study/ or double blind method/ or random allocation/
10. (clin: adj trial:).ti,ab.
11. (((singl: or doubl: or tripl: or trebl:) adj (mask: or blind:)).ti,ab.
12. placebos/
13. placebo:.ti,ab.
14. random:.ti,ab.
15. (((control: adj3 (group: or condition:)) or (control: adj2 (trial: or study or studies))).tw.
16. (cohort adj (study or studies or trial or trials)).tw.
17. or/8-16
18. predict:.mp.
19. exp prognosis/
20. 18 or 19
21. prospective:.tw.
22. case control:.tw.
23. 21 or 22
24. sensitiv:.tw.
25. diagnos:.tw.
26. diagnosis/ or diagnosis computer assisted/ or diagnosis differential/ or diagnostic errors/ or "diagnostic techniques and procedures"/ or mass screening/
27. biological variation.tw.
28. reliability.tw.
29. reproducibility of results/
30. screen:.tw.
31. or/24-30
32. 7 and 31 and 23
33. 7 and 20 and 23
34. 7 and 17
35. 32 or 33 or 34
36. animal/ not (animal/ and human/)
37. 35 not 36
38. limit 37 to (english and yr=1979-2004)
PsycINFO

1. glucose intolerance
2. impaired glucose
3. impaired fasting glucose
4. igt or ifg
5. prediabetic or prediabetes or pre-diabetic or pre-diabetes
6. fasting plasma glucose
7. glucose blood level/
8. glucose tolerance test/
9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10. #10 #9 and (LA=ENGLISH) and (PO=HUMAN) and (PY=1979-2004)
## Appendix B. Forms

**IGT FULLTEXT SCREENING FORM**

<table>
<thead>
<tr>
<th>AREA</th>
<th>GENERAL</th>
<th>NO</th>
<th>YES/MAYBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) GENERAL</td>
<td>Is article published in English language?</td>
<td>Exclude from review □ Don</td>
<td>Continue to next line □</td>
</tr>
<tr>
<td>(b) GENERAL</td>
<td>Is article a fulltext publication?</td>
<td>Exclude from review □ Don</td>
<td>Continue to next line □</td>
</tr>
<tr>
<td>(c) GENERAL</td>
<td>Was the article published in or after 1979?</td>
<td>Exclude from review □ Don</td>
<td>Continue to next line □</td>
</tr>
<tr>
<td>(d) DESIGN</td>
<td>Does the report describe any type of study or survey?</td>
<td>Exclude from review □ Don</td>
<td>Continue to next line □</td>
</tr>
<tr>
<td>(e) POPULATION</td>
<td>Are results for subjects with IGT or IFG analyzed separately from any others in the study population?</td>
<td>Exclude from review □ Don</td>
<td>Continue to next line □</td>
</tr>
<tr>
<td>(f) POPULATION</td>
<td>Does the study include children with IGT or IFG?</td>
<td>Go to Diagnosis □ Include for children □</td>
<td>Go to diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AREA</th>
<th>DIAGNOSIS</th>
<th>NO</th>
<th>YES/MAYBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) OUTCOME</td>
<td>Does the article examine the variability in repeated measurements (within 8 weeks) of glucose tolerance or fasting glucose in a single subject?</td>
<td>Continue to next line □</td>
<td>Include for diagnosis □</td>
</tr>
<tr>
<td>(b) OUTCOME</td>
<td>Does the article compare the result of diagnosis by application of IGT criteria with the result of diagnosis by application of IFG criteria?</td>
<td>Exclude for diagnosis □ Go to prognosis</td>
<td>Include for diagnosis □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AREA</th>
<th>PROGNOSIS</th>
<th>NO</th>
<th>YES/MAYBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) DESIGN</td>
<td>Does the study use a prospective cohort or case control design?</td>
<td>Exclude for prognosis □ Go to treatment</td>
<td>Continue to next line □</td>
</tr>
<tr>
<td>(b) OUTCOME</td>
<td>Does the article describe the risk of developing diabetes type 2 (by our definition) or reversion towards normal glucose tolerance or fasting glucose?</td>
<td>Continue to next line □</td>
<td>Include for prognosis □ Go to treatment</td>
</tr>
<tr>
<td>(c) OUTCOME</td>
<td>Does the article describe the risk of the development of acute coronary events or coronary mortality as defined for our review?</td>
<td>Continue to next line □</td>
<td>Include for prognosis □ Go to treatment</td>
</tr>
<tr>
<td>(d) OUTCOME</td>
<td>Does the article describe the risk of developing retinal or nephropathy outcomes as defined for our review?</td>
<td>Continue to next line □</td>
<td>Include for prognosis □ Go to treatment</td>
</tr>
<tr>
<td>(e) OUTCOME</td>
<td>Does the article describe the risk of effects on blood pressure, lipid levels, amputation or all cause mortality?</td>
<td>Exclude for prognosis □ Go to treatment</td>
<td>Include for prognosis □ Go to treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AREA</th>
<th>TREATMENT</th>
<th>NO</th>
<th>YES/MAYBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) DESIGN</td>
<td>Is the study design an RCT for any treatment or a controlled clinical trial or concurrent cohort trial for behavioral or lifestyle or surgical treatment?</td>
<td>Exclude for treatment □ Done</td>
<td>Continue to next line □</td>
</tr>
<tr>
<td>(b) INTERVENTION</td>
<td>Does the study evaluate the effect of a therapeutic agent, lifestyle intervention, behavioral intervention or surgical intervention for IGT or IFG?</td>
<td>Exclude for treatment □ Done</td>
<td>Continue to next line □</td>
</tr>
<tr>
<td>(c) OUTCOME</td>
<td>Does the study evaluate the effect of therapy on the development or time to development of diabetes type 2 (by our definition) or reversion towards normal glucose tolerance or fasting glucose?</td>
<td>Continue to next line □</td>
<td>Include for treatment □ Done</td>
</tr>
<tr>
<td>(d) OUTCOME</td>
<td>Does the study evaluate the effect of therapy on the development of acute coronary events or coronary mortality as defined for our review?</td>
<td>Continue to next line □</td>
<td>Include for treatment □ Done</td>
</tr>
<tr>
<td>(e) OUTCOME</td>
<td>Does the study evaluate the effect of therapy on the</td>
<td>Continue to next line □</td>
<td>Include for treatment</td>
</tr>
<tr>
<td>OUTCOME</td>
<td>Does the study evaluate the effect of therapy on blood pressure, lipid levels, amputation or all cause mortality?</td>
<td>Exclude for treatment</td>
<td>Include for treatment</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td></td>
<td>development of retinal or nephropathy outcomes as defined for our review?</td>
<td>Done</td>
<td>Done</td>
</tr>
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</table>
## QUALITY SCORE FOR JADAD SCALE AND FOR MODIFIED JADAD SCALE

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>RESULT</th>
<th>SCORING</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported as randomized</td>
<td>□ YES □ NO</td>
<td>1 point for YES</td>
<td></td>
</tr>
<tr>
<td>Randomization is appropriate</td>
<td>□ YES □ NO □ NOT DESCRIBED</td>
<td>1 point for YES -1 point for NO</td>
<td></td>
</tr>
<tr>
<td>Double blinding is reported</td>
<td>□ YES □ NO</td>
<td>1 point for YES</td>
<td></td>
</tr>
<tr>
<td>Double blinding is appropriate</td>
<td>□ YES □ NO □ NOT DESCRIBED</td>
<td>1 point for YES -1 point for NO</td>
<td></td>
</tr>
<tr>
<td>Withdrawals are reported by number and reason per arm</td>
<td>□ YES □ NO</td>
<td>1 point for YES</td>
<td></td>
</tr>
</tbody>
</table>

**JADAD SCORE**

Method used to assess adverse events is described □ YES □ NO 1 point for YES

Methods of statistical analysis are described □ YES □ NO 1 point for YES

Inclusion criteria reported □ YES □ NO 1 point for YES in at least one of two criteria

Exclusion criteria reported □ YES □ NO

**MODIFIED JADAD SCORE**

TOTAL SCORE (out of 8)

Intended allocation to tx group concealed from investigator □ YES □ NO □ NOT REPORTED

Source of population (circle):
- sampled
- convenience
- clinic
- industry
- volunteer

Other (specify):
**COHORT DESIGN QUALITY ASSESSMENT**

<table>
<thead>
<tr>
<th>Reference ID/RM #</th>
<th>Date of Review</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**REPORTING**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1. Is the hypothesis/aim/objective of the study clearly described?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Q2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Q3. Are the criteria for inclusion in and exclusion from the study clearly described?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Q4. Are the exposures of interest (interventions) clearly described?</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Q5. Are the main findings of the study clearly described?</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.

**INTERNAL VALIDITY**

**Confounding/Selection Bias**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q6. Are the exposed and non-exposed cohorts comparable on the basis of the design or analysis?</td>
<td>An analysis has been done to check comparability of exposed and non-exposed cohorts and the most obvious confounders and other factors are controlled for in the design or analysis</td>
<td>Study controls for some factors, but does not control all of the most obvious factors</td>
</tr>
<tr>
<td></td>
<td>SCORE: 1</td>
<td>SCORE: 1/2</td>
</tr>
</tbody>
</table>

**Confounding/Selection Bias (cont)…**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q7. Is the selection of the non-exposed cohort appropriate?</td>
<td>Drawn from the same community as the exposed cohort</td>
<td>Drawn from a different source or no description of the derivation of the non-exposed cohort</td>
</tr>
<tr>
<td></td>
<td>SCORE: 1</td>
<td>SCORE: 0</td>
</tr>
<tr>
<td>Q8. Is the follow-up of cohorts adequate?</td>
<td>Complete follow up – all subjects accounted for</td>
<td>There is not an adequate description of those lost to follow-up</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Subjects lost to follow up unlikely to introduce bias – small number lost (number reported and an adequate discussion of why unlikely to introduce bias)</td>
<td>Unable to determine</td>
</tr>
<tr>
<td></td>
<td>SCORE: 1</td>
<td>SCORE: 0</td>
</tr>
</tbody>
</table>
### Assessment Bias

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q9. Was the outcome of interest demonstrated to be <strong>not</strong> present at start of the study?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
| Q10. Was the intervention/exposure assessment appropriate and demonstrated to be valid?  
   *Answer Yes if the outcome is assessed by either independent assessment or self-report that has been demonstrated to be valid.* | 1   | 0  | 0       |
| Q11. Was the intervention/exposure assessment appropriate and demonstrated to be reliable?  
   *Answer Yes if the outcome is assessed by either independent assessment or self-report that has been demonstrated to be reliable.* | 1   | 0  | 0       |
| Q12. Was the outcome assessment appropriate and demonstrated to be valid?  
   *Answer Yes if the outcome is assessed by either independent assessment or self-report that has been demonstrated to be valid. A valid assessment would include an accepted diagnostic test (e.g. an X-ray).* | 1   | 0  | 0       |
| Q13. Was the outcome assessment appropriate and demonstrated to be reliable?  
   *Answer Yes if the outcome is assessed by either independent assessment or self-report that has been demonstrated to be reliable.* | 1   | 0  | 0       |
| Q14. Was the outcome assessor blinded appropriately to the intervention status?  
   *To receive a Yes, the assessor must have been blinded to the intervention and the blinding must be appropriate for the situation. For independent assessment the assessor must be blind to the intervention status. In case of self-report, the interviewer or person administering the questionnaire must be blind to intervention status.* | 1   | 0  | 0       |
| Q15. Was follow up long enough for outcomes to occur?  
   *This would be of particular concern when looking at overuse injuries or extremely rare injuries. One season would typically be long enough for outcome to occur.* | 1   | 0  |         |

### Intervention Integrity

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unable to Determine</th>
</tr>
</thead>
</table>
| Q16. Was the consistency of the intervention measured?  
   *This refers to whether the authors described measuring if the intervention was provided to all participants the same way.* | 1   | 0  | 0                   |
| Q17. Has the possibility of participants having received an unintended intervention (contamination or co-intervention) that may influence the results been reported and ruled out?  
   *Co-intervention occurs when the study group receives an additional intervention other than that intended. In this case, it is possible that the effect of the intervention may be over-estimated. Contamination refers to situations where the control group accidentally receives the study intervention. This could result in an underestimation of the impact of the intervention. Answer Yes if potential contamination or co-intervention is reported and demonstrated to be unlikely to have had an effect.* | 1   | 0  | 0                   |

**Internal Validity Score = ____ / 12**

**Total Score = ____ / 17**

### External Validity/ Generalizability

**EXTERNAL VALIDITY/ GENERALIZABILITY**

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Randomly selected from target population with high response and low loss to follow-up (gold standard)</td>
<td>1</td>
</tr>
<tr>
<td>Somewhat representative of the target population – misses the gold standard</td>
<td>½</td>
</tr>
<tr>
<td>Convenience sample – e.g. teams at one centre, volunteers</td>
<td>0</td>
</tr>
<tr>
<td>No description of how the cohort was selected</td>
<td>0</td>
</tr>
</tbody>
</table>

**External Validity Score = ____ / 1**
### Appendix B. Forms – Data Extraction

REFID # _____________  1ST AUTHOR ______________ EXTRACTOR ____________

<table>
<thead>
<tr>
<th>GENERAL</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Answer</td>
<td>Mark</td>
</tr>
<tr>
<td>Type of study</td>
<td>□ RCT □ Controlled clinical trial □ Other (specify)</td>
<td>One</td>
</tr>
<tr>
<td>Publication year</td>
<td></td>
<td>Date</td>
</tr>
<tr>
<td>Location of study reported on</td>
<td>□ USA □ Canada □ Germany □ Italy □ France □ Britain □ Netherlands □ China □ Africa □ Australia □ S. America □ Other</td>
<td>All</td>
</tr>
<tr>
<td>Funding source</td>
<td>□ Industry □ Government □ Consumer □ Charity □ Professional □ NR □ Other</td>
<td>All</td>
</tr>
<tr>
<td>Association with industry reported</td>
<td>□ YES □ NO</td>
<td>One</td>
</tr>
<tr>
<td>If yes, company mentioned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of authors</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>Study duration (day week month year) reported on</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Gender of subjects</td>
<td>□ Male □ Female □ NR</td>
<td>All</td>
</tr>
<tr>
<td>Age of subjects</td>
<td>□&lt;10 □ 10-18 □19-40 □ 41-60 □ 61-80 □&gt;80</td>
<td>All</td>
</tr>
<tr>
<td>Ethnic groups mentioned</td>
<td>□ NO □ YES (specify groups)</td>
<td>All</td>
</tr>
<tr>
<td>Diagnostic criteria used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75g OGTT 2 hr cutoffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG cutoffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFG:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75g OGTT 2 hr cutoffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG cutoffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (specify)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal characteristics described</td>
<td>□ Family history □ Socioeconomic □ Education □ Diet history □ Weight □ Gestational diabetes □ Medical history □ Other □ NR</td>
<td>All</td>
</tr>
<tr>
<td>Other specific population characteristics for all included (not necessarily inclusion criteria, but may be a requirement) (e.g. all subjects had MS or all subjects were Japanese)</td>
<td></td>
<td>Text</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td>Mark</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Number of subjects included</td>
<td>_______</td>
<td>#</td>
</tr>
</tbody>
</table>
| Diagnosis comparisons reported               | □ IFG vs IGT  
□ WHO vs ADA criteria  
□ Repeat testing  
□ YEAR vs YEAR criteria | All    |
<p>| Units compared for IFG vs IGT                | Text   |
| Results of IFG vs IGT                        | Text   |
| Units compared for ADA vs WHO                | Text   |
| Results of ADA vs WHO                        | Text   |
| Units compared for repeat testing within 8 weeks | Text   |
| Results of repeat testing within 8 weeks     | Text   |
| Units compared for year vs year criteria     | Text   |
| Results of year vs year criteria             | Text   |
| Outcome(1) compared for one diagnosis vs another | Text   |
| Units used for outcome (1) comparison between diagnoses | Text   |
| Results of outcome(1) comparison between diagnoses | Text   |
| Outcome(2) compared for one diagnosis vs another | Text   |
| Units used for outcome (2) comparison between diagnoses | Text   |
| Results of outcome(2) comparison between diagnoses | Text   |
| Outcome(3) compared for one diagnosis vs another | Text   |
| Units used for outcome (3) comparison between diagnoses | Text   |
| Results of outcome(3) comparison between diagnoses | Text   |
| Outcome(4) compared for one diagnosis vs another | Text   |
| Units used for outcome (4) comparison between diagnoses | Text   |
| Results of outcome(4) comparison between diagnoses | Text   |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Mark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of untreated IGT subjects included</td>
<td></td>
<td>#</td>
</tr>
<tr>
<td>Outcome reported on (1)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Units used for outcome (1)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Results of outcome (1)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Outcome reported on (2)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Units used for outcome (2)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Results of outcome (2)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Outcome reported on (3)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Units used for outcome (3)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Results of outcome (3)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Outcome reported on (4)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Units used for outcome (4)</td>
<td>Text</td>
<td></td>
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<tr>
<td>Results of outcome (4)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Outcome reported on (5)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Units used for outcome (5)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Results of outcome (5)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
<td>Mark</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Total number of subjects included</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>#</td>
<td></td>
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<tr>
<td>Number of control subjects included</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>Number of control subjects reported on</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>Number of treated subjects reported on</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>Adverse events reported</td>
<td>☐ YES ☐ NO (specify how)</td>
<td>One/text</td>
</tr>
<tr>
<td>Number of treatment arms</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>Treatment 1 (control)</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Treatment 2</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Treatment 3</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Treatment 4</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Intervention duration (day week month)</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>One outcome identified as primary</td>
<td>☐ YES ☐ NO (specify)</td>
<td>One/text</td>
</tr>
<tr>
<td>Treatment compliance monitoring reported</td>
<td>☐ YES ☐ NO</td>
<td>One</td>
</tr>
<tr>
<td>Double blinding is reported</td>
<td>☐ YES ☐ NO</td>
<td>One</td>
</tr>
<tr>
<td>Withdrawals are reported by number and reason per arm</td>
<td>☐ YES ☐ NO</td>
<td>One</td>
</tr>
<tr>
<td>Outcome (1) reported on</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Units used for outcome (1)</td>
<td>Text</td>
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THIS IS A CONSENSUS FORM ☐
Appendix C. Lifestyle Studies

Studies describing lifestyle or behavioral interventions but were excluded because they are not randomized trials.


Appendix D. Peer Reviewers

Dr. Nathaniel Clark, American Diabetes Association, Alexandria, VA, USA
Dr. Michael Engelgau, Centers for Disease Control and Prevention, Atlanta, GA, USA
Dr. Rita Goodman, CQI Branch, Health Resources and Services Admin., Bethesda, MD, USA
Dr. Steven Haffner, University of Texas, San Antonio, TX, USA
Dr. Mary Hager, American Dietetic Association, Washington, DC, USA
Dr. Markolf Hanefeld, Centre for Clinical Studies, Technical University, Dresden, Germany
Dr. Rodney Hornbake, (ACP representative), Hadlyme, CT, USA
Dr. Belinda Ireland – AAFP, Leawood, KS, USA
Dr. Francine Ratner Kaufman, Childrens Hospital Los Angeles, Los Angeles, CA, USA
Dr. Matthew McQueen, Hamilton Health Sciences Corporation, Hamilton, ON, Canada
Drs. Kelly Moore, Steve Rith-Najarian and Charlton Wilson, Indian Health Services, Albuquerque, NM, USA
Dr. Robert Ratner, MedStar Research Institute, Hyattsville, MD, USA

AHRQ representatives:
Dr. David Atkins – AHRQ, Gaithersburg, MD, USA
Dr. Steven Fox – AHRQ, Gaithersburg, MD, USA

Criticism editor:
Dr. Patricia Huston, Ottawa, ON
Appendix E. Excluded Studies

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Angelopoulos, T. J., Schultz, R. M., Denton, J. C., and Jamurtas, A. Z. Significant enhancements in glucose tolerance and insulin action in centrally obese subjects...
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Beasley, C. M., Berg, P. H., Dananberg, J., Kwong, K. C., Taylor, C. C. M., and Breier, A. Treatment-emergent potential impaired glucose tolerance and potential diabetes with olanzapine compared to other antipsychotic agents and placebo. Biol Psychiatry 2001; 49:121S

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Bluher, M., Unger, R., Rassouli, F., Richter, V., and Paschke, R. Relation between glycaemic control, hyperinsulinaemia and plasma concentrations of soluble adhesion molecules in patients with impaired glucose tolerance or Type II diabetes. Diabetologia 2002; 45:210-216.
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Bourn, D. M. and Mann, J. I. The 3-yr follow-up of subjects with impaired glucose tolerance or non-insulin dependent diabetes mellitus in a diet and exercise intervention programme. Diabetes Nutr Metab 1996; 9:240-246.

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Colman, E., Katzel, L. I., Rogus, E., Coon, P., Muller, D., and Goldberg, A. P. Weight loss reduces abdominal fat and improves insulin action in middle-aged and older men with impaired glucose tolerance. Metabolism 1995; 44:1502-1508.

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Cononie, C. C., Goldberg, A. P., Rogus, E., and Hagberg, J. M. Seven consecutive days of exercise lowers plasma insulin responses to an oral glucose challenge in sedentary elderly.


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Excluded Studies

Appendix E – Page 10
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Erenus, M., Gurler, A. D., and Elter, K. Should we consider performing oral glucose tolerance tests more frequently in postmenopausal women for optimal screening of impaired glucose tolerance? *Menopause* 2002; 9:296-301.

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Ginsberg, H. N. Treatment for Patients with the Metabolic Syndrome. Am J Cardiol 2003; 91:Suppl 29E-39E.

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Goetz, F. C., French, L. R., Thomas, W., Gingerich, R. L., and Clements, J. P. Are specific serum insulin levels low in impaired glucose tolerance and type II diabetes?: measurement with a radioimmunoassay blind to proinsulin, in the population of Wadena, Minnesota. Metabolism 1995; 44:1371-1376.

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Gonzalez, Villalpando C., Stern, M. P., Haffner, S., Arredondo, Perez B., Martinez, Diaz S., and Islas, Andrade S. The insulin resistance syndrome in Mexico. Prevalence and

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**Status:** Not included for diagnosis because article does not compare IGT and IFG criteria. Not included for prognosis because of case-control design. Not included for treatment because intervention was not relevant to review


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Status: Not included for diagnosis because article does not compare IGT and IFG criteria. Not included for prognosis and treatment because no extractable data was relevant to review.


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Excluded Studies

Appendix E – Page 25

**Status:** Not included because article is not a full text publication.


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**Excluded Studies**

**Appendix E – Page 26**

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Kanigur-Sultuybek, G., Hatemi, H., Guven, M., Ulutin, T., Tezcan, Y., and Ulutin, O. N. The effect of metformin and gliclazide on platelets and red blood cell glucose transport mechanisms in impaired glucose tolerance and type II diabetic patients with vasculopathy. Thrombotic & Haemorrhagic Disorders 1993; 7:17-21. **Status:** Excluded because no subjects diagnosed by included criteria were analyzed

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Legro, R. S., Kunselman, A. R., Dodson, W. C., and Dunai, A. Prevalence and predictors of risk for type 2 diabetes
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**Status:** Not included for diagnosis because article does not compare IGT and IFG criteria. Not included for prognosis because no extractable data was relevant to review. Not included for treatment because of study design


**Status:** Not included for diagnosis because article does not compare IGT and IFG criteria. Not included for prognosis and treatment because of study design (case-control)


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Status: Not included for diagnosis because article does not compare IGT and IFG criteria. Not included for prognosis and treatment because of study design (case-control)


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Montori, V. M. A lifestyle intervention or metformin prevented or delayed the onset of type 2 diabetes in persons at risk. ACP Journal Club 2002; 137:55

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TO:=Effet de la Metformine sur la résistance à l'insuline chez des patients obèses avec intolérance au glucose. Schweiz Med Wochenschr 1996; 126:12

**Status:** Not included because article was not published in English


**Status:** Not included for diagnosis because article does not compare IGT and IFG criteria. Not included for prognosis and treatment because follow-up was less than 6 months


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Muller, S., Martin, S., Koenig, W., Hanifi-Moghadam, P., Rathmann, W., Haastert, B., Giani, G., Illig, T., Thorand, B., and Kolb, H. Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-alpha or its receptors. Diabetologia 2002; 45:805-812.

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**Status:** Excluded because no subjects diagnosed by included criteria were analyzed.

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Status: Not included for diagnosis because article does not compare IGT and IFG criteria. Not included for prognosis because no extractable data was relevant to review. Not included for treatment because of study design


Status: Excluded because no subjects diagnosed by included criteria were analyzed


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Status: Excluded because no subjects diagnosed by included criteria were analyzed


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Status: Excluded because no subjects diagnosed by included criteria were analyzed


Status: Not included for diagnosis because article does not compare IGT and IFG criteria. Not included for prognosis because no extractable data was relevant to review. Not included for treatment because the intervention was not relevant to review


Status: Excluded because no subjects diagnosed by included criteria were analyzed


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Appendix G. Calculations

Section A: Calculation of kappa coefficient and confidence intervals (CI)

The simple kappa coefficient is calculated as:

$$\hat{\kappa} = \frac{P_o - P_e}{1 - P_e}$$

where

$$P_o = \sum_i p_{ii}$$

and

$$P_e = \sum_i p_{i.} p_{.i}$$

The Variance and CI are calculated as follows:

$$\text{var}( \hat{\kappa} ) = \left[ \left( A + B - C \right)/(1 - p_e^2)^2 n \right]$$

where

$$A = \sum_i p_{ii} \left[ 1 - (p_{i.} + p_{.i})(1 - \hat{\kappa}) \right]^2$$

$$B = (1 - \hat{\kappa})^2 \sum_{i \neq j} \sum_i p_{ij}(p_{i.} + p_{.j})^2$$

and

$$C = \left[ \hat{\kappa} - P_e(1 - \hat{\kappa}) \right]^2$$
\[ \hat{\kappa} = \pm \frac{z_{\alpha/2} \cdot \sqrt{\text{var}}}{\text{estimate}} \]

**Section B: Calculation of annualized relative risk, annualized risk for the exposed (IFG or IGT) and the normal glucose groups**

Calculation of relative risk \( (\hat{RR}_t) \) at time \( t \) would be as follows:

\[
\hat{RR}_t = \frac{\hat{R}_{E_t}}{\hat{R}_{C_t}}
\]

where

\( \hat{R}_{E_t} \) = Calculated Risk in Exposed Group at time \( t \) (or i.e. in Male) and calculated as:

\[
\hat{R}_{E_t} = 1 - e^{-\hat{\lambda}_E t}
\]

\( \hat{R}_{C_t} \) = Calculated Risk in Control Group at time \( t \) (or i.e. in Female)

\[
\hat{R}_{C_t} = 1 - e^{-\hat{\lambda}_C t}
\]

\( \hat{\lambda}_E \) and \( \hat{\lambda}_C \) can be calculated as:

\[
\hat{R}_{E_T} = 1 - e^{-\hat{\lambda}_E T} \text{ is Observed Risk after T period in Exposed Group}
\]

\[
\hat{R}_{C_T} = 1 - e^{-\hat{\lambda}_C T} \text{ is Observed Risk after T period in Control Group}
\]

thus

\[
\hat{\lambda}_E = -\frac{\ln(1 - \hat{R}_{E_T})}{T}
\]

\[
\hat{\lambda}_C = -\frac{\ln(1 - \hat{R}_{C_T})}{T}
\]

where

\[
\hat{R}_{E_T} = \frac{a}{a + b}, \quad \hat{R}_{C_T} = \frac{c}{c + d}
\]
\[ T = \text{Observed duration of study (0.5 to 18 years).} \]
\[ t = \text{Up to one year study duration.} \]
Section C: Calculation of 95% confidence intervals (CI) for the unadjusted annualized RR

\[ Var(\hat{RR}_t) = \frac{\hat{R}_{C_t}^2}{R_{C_t}^4} Var(\hat{R}_{E_t}) + \frac{\hat{R}_{E_t}^2}{R_{C_t}^4} Var(\hat{R}_{C_t}) \]

\[ = \frac{1}{R_{C_t}^4} \left[ \hat{R}_{C_t}^2 Var(\hat{R}_{E_t}) + \hat{R}_{E_t}^2 Var(\hat{R}_{C_t}) \right] \]

\[ LL\left(0.95(\hat{RR}_t)\right) = EXP\left\{ \ln\hat{RR}_t - 1.96 \sqrt{Var\left(\ln\hat{RR}_t\right)} \right\} \]

\[ UL\left(0.95(\hat{RR}_t)\right) = EXP\left\{ \ln\hat{RR}_t + 1.96 \sqrt{Var\left(\ln\hat{RR}_t\right)} \right\} \]

Where:

\[ Var(\hat{\lambda}_E) = \frac{1}{T^2} Var\left[\ln\left(1 - R_{E_t}\right)\right] \]

\[ = \frac{1}{T^2} \frac{1}{\left(1 - R_{E_t}\right)^2} Var\left(R_{E_t}\right) \]

\[ = \frac{1}{T^2} \frac{1}{\left(e^{-\hat{\lambda}_ET}\right)^2} Var\left(R_{E_t}\right) \]

\[ Var(\hat{\lambda}_E) = \frac{1}{\left(TE^{-\hat{\lambda}_ET}\right)^2} Var\left(R_{E_t}\right) \]

\[ Var(\hat{\lambda}_C) = \frac{1}{T^2} Var\left[\ln\left(1 - R_{C_t}\right)\right] \]

\[ = \frac{1}{T^2} \frac{1}{\left(1 - R_{C_t}\right)^2} Var\left(R_{C_t}\right) \]

\[ = \frac{1}{T^2} \frac{1}{\left(e^{-\hat{\lambda}_CT}\right)^2} Var\left(R_{C_t}\right) \]

\[ Var(\hat{\lambda}_C) = \frac{1}{\left(TE^{-\hat{\lambda}_CT}\right)^2} Var\left(R_{C_t}\right) \]
\[
\text{Var}(\hat{R}_{E_t}) = \left( te^{-\hat{\lambda}_{E_t}} \right)^2 \text{Var}(\hat{\lambda}_{E_t}) \\
= \left( \frac{te^{-\hat{\lambda}_{E_t}}}{Te^{-\hat{\lambda}_{ET}}} \right)^2 \text{Var}(R_{E_T}) \\
\text{Var}(\hat{R}_{C_t}) = \left( te^{-\hat{\lambda}_{C_t}} \right)^2 \text{Var}(\hat{\lambda}_{C_t}) \\
= \left( \frac{te^{-\hat{\lambda}_{C_t}}}{Te^{-\hat{\lambda}_{CT}}} \right)^2 \text{Var}(R_{C_T}) \\
\text{Var}(\hat{R}_{C_t}) = \left( \frac{t}{T} \right)^2 (e^{-\hat{\lambda}_{C(t-T)}})^2 \text{Var}(R_{C_T}) \\
\text{Var}(R_{E_T}) = \frac{p_E(1 - p_E)}{n_E} \\
\text{Var}(R_{C_T}) = \frac{p_C(1 - p_C)}{n_C}
\]
Section D: Calculation and test of heterogeneity (Q) and the pooled estimate of RR:

\[ Q = \sum_{i=1}^{k} w_i \left( RR_i - \bar{RR} \right)^2 \]

Where k is the number of studies being combined, \( RR_i \) is the relative risk estimate in \( i^{th} \) Study,

\[ \bar{RR} = \frac{\sum_i w_i RR_i}{\sum_i w_i} \]

is the weighted estimator of relative risk, and \( w_i \) is the weight attached to that study (the reciprocal of the variance of the \( i^{th} \) study, \( \text{var}(RR_i) \)).

\( Q \) is approximately distributed as a \( \chi^2 \) distribution with \( k - 1 \) degrees of freedom under \( H_0 \).

Fixed effects model

\[ \text{var} \left( \bar{RR} \right) = \frac{1}{\sum_i w_i} \cdot \]

\[ \bar{RR} \leq z_{\alpha/2} \sqrt{\frac{1}{\sum_i w_i}} \leq \theta \leq \bar{RR} + z_{\alpha/2} \sqrt{\frac{1}{\sum_i w_i}} \]

Random effect model

\[ \bar{w} = \frac{\sum_{i=1}^{k} w_i}{k}, \]

and

\[ s_w^2 = \frac{1}{k-1} \left( \sum_{i=1}^{k} w_i^2 - k \bar{w}^2 \right). \]

Further, define

\[ U = (k-1) \left( \bar{w} - \frac{s_w^2}{k \bar{w}} \right). \]
The estimated component of variance due to inter-study variation in effect size, $\hat{\tau}^2$, is calculated as:

$$\hat{\tau}^2 = 0 \text{ if } Q \leq k - 1$$

and

$$\hat{\tau}^2 = (Q - (k - 1))/U \text{ if } Q > k - 1.$$

Adjusted weights $w_i^*$ for each of the studies is calculated as:

$$w_i^* = \frac{1}{(1/w_i) + \hat{\tau}^2}.$$

The mean relative risk estimate of all studies $\bar{\theta}$ can then be computed by:

$$\bar{RR}_{RND} = \frac{\sum_i w_i^* RR_i}{\sum_i w_i^*}.$$

The variance of this estimate is calculated as:

$$\text{var} \left( \bar{RR}_{RND} \right) = \frac{1}{\sum_i w_i^*}.$$

$$\bar{RR}_{RND} - z_{a/2} \sqrt{\frac{1}{\sum_i w_i^*}} \leq \bar{\theta} \leq \bar{RR}_{RND} + z_{a/2} \sqrt{\frac{1}{\sum_i w_i^*}}.$$
U.S. Department of Health and Human Services
Mike Leavitt, Secretary

Office of Public Health and Science

Agency for Healthcare Research and Quality
Carolyn M. Clancy, M.D., Director