

# **Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention**

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## **Glossary of abbreviations**

BMI	Body mass index
CHD	Coronary heart disease
CVD	Cardiovascular disease
DECODA	Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia
DECODE	Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe
DPP	Diabetes Prevention Programme
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
HGO	Hepatic glucose output
FDPS	Finnish Diabetes Prevention Study
GDM	Gestational diabetes mellitus
IFG	Impaired fasting glycaemia
IGT	Impaired glucose tolerance
NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research

OGTT Oral glucose tolerance test

RIAD Risk factors in IGT for Atherosclerosis and Diabetes

STOP-NIDDM Study TO Prevent NIDDM

2-HPG 2-h plasma glucose value in an oral glucose tolerance test

TRIPOD Troglitazone in the Prevention of Diabetes

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## Abstract

A workshop was convened by the International Diabetes Federation to review the latest information relating to the risks associated with impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) for future diabetes and cardiovascular disease (CVD). The workshop sought to address three questions: (i) are the current definitions of IGT and IFG appropriate; (ii) are IFG and IGT risk factors, risk markers or diseases; (iii) what interventions (if any) should be recommended for people with IFG and IGT?

- The determinants of elevated fasting glucose and 2-h plasma glucose in an oral glucose tolerance test (2-HPG) levels differ. Raised hepatic glucose output and a defect in early insulin secretion are characteristic of the former, and peripheral insulin resistance is most characteristic of the latter. Therefore, it is not surprising that the concordance between the categories of IFG and IGT is limited.
  - ▶ In all prevalence studies to date only half or less of people with IFG have IGT, and even a lower proportion (20–30%) with IGT also have IFG.
- In the majority of populations studied, IGT is more prevalent than IFG, and there is a difference in phenotype and gender distribution between the two categories.
  - ▶ IFG is substantially more common amongst men and IGT slightly more common amongst women.
  - ▶ The prevalence of IFG tends to plateau in middle age whereas the prevalence of IGT rises into old age.
- Both IFG and IGT are associated with a substantially increased risk of developing diabetes, with the highest risk in people with combined IFG and IGT.
  - ▶ Because IGT is commoner than IFG in most populations it is more sensitive (but slightly less specific) for identifying people who will develop diabetes.
  - ▶ In most populations studied, 60% of people who develop diabetes have either IGT or IFG 5 years or so before, with the other 40% having normal glucose tolerance at that time.
- The limited published data suggest that both isolated IFG (I-IFG) and isolated IGT (I-IGT) are similarly associated with cardiovascular risk factors, such as hypertension and dyslipidaemia, with the highest risk in those with combined IFG and IGT. However, some data have suggested that I-IGT is more strongly associated with hypertension and dyslipidaemia (features of the metabolic syndrome) than I-IFG.
- In unadjusted analyses both IFG and IGT are associated with CVD and total mortality.

In separate analyses for fasting and 2-HPG adjusted for other cardiovascular risk factors (from the DECODE study) there remains a continuous relationship between 2-HPG and mortality, but an independent relationship with fasting glucose is only found above 7.0 mmol/l.

Glycated haemoglobin (HbA<sub>1c</sub>) levels are continuously and positively associated with CVD and total mortality independent of other CVD risk factors.

- Life style interventions, including weight loss and increased physical activity, are highly effective in preventing or delaying the onset of diabetes in people with IGT.

Two randomized controlled trials of individuals with IGT found that life style intervention studies reduce the risk of progressing to diabetes by 58%.

The oral hypoglycaemic drugs metformin and acarbose have also been shown to be effective, but less so than the life style measures.

Similar data do not yet exist for the effectiveness of such interventions in people with I-IFG.

Larger studies are required to evaluate the effects of interventions on cardiovascular outcomes in people with IGT.

Cost effective strategies to identify people with IGT for intervention should be developed and evaluated. The use of simple risk scores to assess who should undergo an oral glucose tolerance test is one promising approach, although these will need to be population-specific.

In conclusion

- IGT and IFG differ in their prevalence, population distribution, phenotype, and risk of total mortality and CVD. The consensus of the workshop was:
  - 1 The diagnostic thresholds for all categories of glucose intolerance should be revisited in the light of the latest evidence. There was no clear consensus (with current evidence) on whether IFG and IGT should be classified as diseases, but they clearly represent risk factors and risk markers for diabetes and CVD, respectively.
  - 2 Both IGT and IFG are similarly associated with an increased risk of diabetes, but IGT is more strongly associated with CVD outcomes.
  - 3 Risks are higher when IGT and IFG coexist.
  - 4 Life style interventions are highly effective in delaying or preventing the onset of diabetes in people with IGT and may reduce CVD and total mortality, but the latter requires formal testing.

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## Introduction

The majority of deaths in persons with diabetes result from accelerated cardiovascular and cerebrovascular atherosclerosis. Mortality attributable to cardiovascular disease (CVD) is increased 1.5–4.5-fold, and all-cause mortality is increased 1.5–2.7-fold. Diabetes has been identified as an independent risk factor for CVD mortality, even though other risk factors such as central obesity, hypertension and dyslipidaemia frequently coexist in persons with diabetes.

Evidence is accumulating that macrovascular disease is associated with lesser degrees of hyperglycaemia than is microvascular disease. The heightened risk of CVD extends to the impaired glucose tolerance (IGT) category, and as with diabetes, IGT is often associated with the metabolic syndrome (insulin resistance syndrome), the components of which explain some, but not all of the excessive CVD risk seen in IGT and diabetes. Both IGT and impaired fasting glycaemia (IFG) are very strong risk markers for the development of diabetes. Both IGT and IFG are associated with increased CVD risk, and the question therefore arises, why they are not considered to be disease states rather than risk factors.

## Aim and objectives of the workshop

The Consensus Workshop was convened by the International Diabetes Federation (IDF) to review information relating to IGT and IFG with the objective of considering:

- Their significance with regard to future risk of both diabetes and CVD; and
- Whether intervention strategies are indicated.

Specifically the workshop participants were set the task of addressing the following questions: (i) are the current definitions of IGT and IFG appropriate? (ii) are IGT and IFG risk factors, risk markers or actually disease states? (iii) are interventions indicated for IGT and IFG and if so, how?

With respect to the second question, the term ‘risk marker’ is used simply to indicate that an association exists between either IGT or IFG and a specified outcome [1]. The term ‘risk factor’ is used where such an association has been found to be independent of known confounders and the evidence suggests that intervention to reduce it will lead to a reduction in the outcomes it is associated with. This is a useful distinction, even though in practice it is often a difficult one to make.

## Structure of the report

The report is divided into two main sections. The first section, the background, provides an overview of the data that were presented and considered by participants at the meeting. The second section summarizes the consensus reached and the recommendations arising.

## Background

### The origin and nature of IGT and IFG categories

IGT was first introduced in 1979 to replace 'borderline' diabetes and other categories of hyperglycaemia that did not appear to carry a risk of microvascular complications [2,3]. It was considered as a clinical class of glucose intolerance in the 1985 WHO classification [4]. It is now, in the latest reports from WHO and the American Diabetes Association (ADA), categorized as a stage in the natural history of disordered carbohydrate metabolism. It was only in the most recent reports that a category of non-diabetic fasting hyperglycaemia was defined and given the name impaired fasting glycaemia (IFG) [5,6]. This indicates glucose concentrations that are clearly above normal but fall short of the diagnostic value for diabetes.

At present neither IFG nor IGT are considered clinical entities in their own right, but as risk categories for the future development of diabetes and CVD. They represent metabolic states intermediate between normal glucose homeostasis and diabetic hyperglycaemia. Individuals who meet the criteria for IGT or IFG usually have HbA<sub>1c</sub> values that are within or only just above the normal range. However, as discussed below, even this degree of hyperglycaemia is clearly associated with other metabolic and cardiovascular abnormalities. IGT and IFG are often components of the metabolic syndrome, thereby heightening the risk of cardiovascular disease.

The metabolic determinants of fasting (FPG) and 2-h plasma glucose (2-HPG) values in an oral glucose tolerance test are somewhat different [7–9]. This means the categorization of an

individual on a fasting value may differ from that on a 2-HPG value. Normal control of fasting glucose depends on the ability to maintain adequate basal insulin secretion, and on appropriate levels of insulin sensitivity in the liver to control hepatic glucose output. Abnormalities of these metabolic functions characterize IFG. During an oral glucose tolerance test (OGTT), the normal response to the absorption of the carbohydrate load is both to suppress hepatic glucose output (HGO) and to enhance glucose uptake in the muscle and liver. This requires a prompt increase in insulin secretion, and adequate hepatic and muscle sensitivity to insulin. In particular, IGT is associated with peripheral insulin resistance, most importantly at the level of skeletal muscle (the main depot for glucose disposal post-prandially). In short, the physiological bases of IFG and IGT are somewhat different.

Finally, it must be remembered that measurement error preceding carbohydrate intake and biological variability can all lead to different classifications of an individual when tested on more than one occasion. An illustration of the effect of random error on the classification of individuals is given using data from the AusDiab (Australian national study [10]). The FPG and 2-HPG results of each individual were changed at random, up to a maximum of  $\pm 5\%$  of the recorded value. When this was done, 22% of the individuals who were classified as IFG on the recorded value, and 10% of those with IGT, were reclassified to another category (J. Shaw, personal communication).

### Definitions

Table 1 shows the plasma and blood glucose values for the categories of diabetes, IFG and IGT [6]. The category in which an individual is placed may depend on whether only fasting glucose is measured or fasting and 2-h glucose values are obtained. For example, an individual falling into the IFG category on the fasting result may also have IGT on the 2-h value, or indeed diabetes. If an individual falls into two different categories, the higher one applies.

**Table 1** Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia [6]

	Glucose concentration, mmol/l (mg/dl)		
	Plasma	Whole blood	
	Venous	Venous	Capillary
Diabetes mellitus			
Fasting and/or	$\geq 7.0$ (126)	$\geq 6.1$ (110)	$\geq 6.1$ (110)
2-h post-glucose load	$\geq 11.1$ (200)	$\geq 10.0$ (180)	$\geq 11.1$ (200)
Impaired glucose tolerance			
Fasting concentration (if measured) and	$< 7.0$ (126)	$< 6.1$ (110)	$< 6.1$ (110)
2-h post-glucose load	7.8–11.0 (140–199)	6.7–9.9 (120–179)	7.8–11.0 (140–199)
Impaired fasting glucose			
Fasting and	6.1–6.9 (110–125)	5.6–6.0 (100–109)	5.6–6.0 (100–109)
2-h (if measured)	$< 7.8$ (140)	$< 6.7$ (120)	$< 7.8$ (140)

	Age (size of study population)	Total IGT	Total IFG	*I-IGT	*I-IFG	IGT/IFG
Mauritius [11]	25–74 (3713)	17.2	7.5	13.9	4.2	3.3
Pima [12]	≥ 15 (5023)	13.2	4.4	10.7	1.9	2.5
Sweden [13]	55–57 (1843)	27.9	17.3	20.3	9.7	7.6
NHANES III [15]	40–74 (2844)	14.9	8.3	11.0	4.4	3.9
Australia [10]	≥ 25 (11 247)	10.6	8.3	8.0	5.7	2.6
Hong Kong [16]	18–66 (1486)	7.2	2.0	6.1	0.9	1.1
DECODE [17]	≥ 30 (25 364)	11.9	10.0	8.8	6.9	3.1

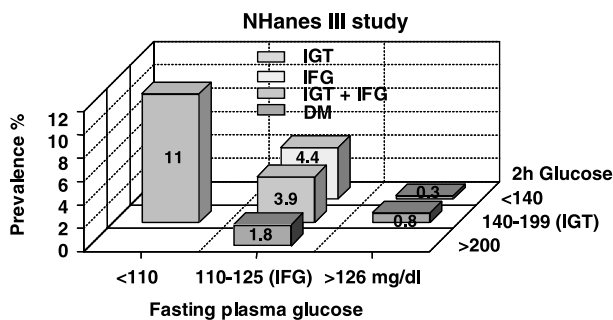
\*Isolated IGT and IFG, respectively.

**Table 2** The prevalence (percentages) of impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) in different adult populations

**Table 3** Summary of the age and sex distribution of impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT) in European and Asian populations aged 30–89 years\*

Age	IFG: Prevalence plateaus in middle age (40–50 years), with the exception of European women where it rises until 70 years IGT: Prevalence rises with age, although exceptions exist in a few populations where it plateaus in middle age
Sex	Men > women for IFG in all age groups with the exception of 70–79 years in Europeans and 80–89 years in Asians Women > men for IGT in all age groups in Europeans (but not Asians) with the exception of 80–89 years
IFG:IGT ratio by age and sex	IGT > IFG in all age groups in Asian men and women and in European women and in European men aged ≥ 70 years IFG > IGT in European men up to the age of 60 years

\*Based on DECODE and DECODA data and analyses.



**Figure 1** Prevalence of impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) in 2662 persons aged 40–74 years without previously diagnosed diabetes by 1985 WHO criteria, NHANES III study. (From Harris MI *et al. Diabetes Care* 1997; 20: 1859–1862.)

### Descriptive epidemiology of IGT and IFG

#### Prevalence and overlap between IGT and IFG

As discussed above, IGT and IFG are not equivalent metabolically, and it is therefore not surprising that there are differences in their prevalence and in the people categorized as having one or the other. In most populations, IGT is considerably more prevalent than IFG. Furthermore, there is limited overlap between the categories—the majority of people with IGT do not have IFG, and the majority with IFG do not have IGT. Hence the terminology of ‘isolated IGT’ and ‘isolated IFG’. Figure 1 shows the different subcategories of IGT and IFG within the American NHANES III study. This demonstrates how little overlap there exists between the categories, and that the largest subgroup is isolated IGT (I-IGT) (FPG < 6.1 mmol/l and 2-HPG 7.8–11.0 mmol/l). Table 2 shows data from a variety of populations demonstrating that this picture of

highest prevalence of I-IGT and limited overlap between IGT and IFG is found in most of them. Thus, IFG and IGT identify substantially different segments of the population with impaired glucose regulation.

#### Age and sex distribution of IGT and IFG

In addition to differences in the overall prevalence between IGT and IFG, there is now clear evidence of differences in phenotype between the two categories. The most robust evidence for this comes from the analyses of the DECODE [18,19] and DECODA [20,21] study groups, which include data from 13 European and 10 Asian studies, respectively. Their findings are summarized in Table 3. The most consistent and statistically significant difference is that IFG is commoner in men than women in virtually all age groups, typically being 1.5–3 times higher, but up to seven or eight times higher in Europeans aged 50–70 years. Conversely, the prevalence of IGT is higher in women than men in all age groups except over the age of 60 in Asian populations and over the age of 80 in the European. However, these findings are less statistically robust than those for IFG, being significant only in Europeans aged 30–39 and 70–79 years. Finally, the prevalence of IGT tends to increase across all age groups, but that of IFG tends to plateau in middle age, and in European men in particular falls in older age groups. In making the generalizations summarized in Table 3 it must be remembered that there are differences between individual studies, particularly in the relationship between age and IFG and IGT prevalence. It can not be determined from these cross-sectional data what these differences represent. For example, the combined effects of age-specific incidence (the rate at which new cases enter the category) and the rate at which people leave the category (through death or progression

to diabetes) will determine current age-specific prevalence. In addition, cross-sectional findings may reflect the differing experience of different age cohorts (likely to be particularly important in populations undergoing rapid lifestyle change), and relationships found cross-sectionally may not apply longitudinally.

### The predictive properties of IFG and IGT—methodological considerations

In common with most other risk factors and risk markers for diabetes and CVD, glucose is usually found to have a continuous relationship with risk of future diabetes, CVD and total mortality [22]. The categories of IFG and IGT therefore represent largely arbitrary sections on the continuum of risk between these outcomes and FPG and 2-HPG, respectively. Inevitably therefore, the findings of studies that quantify the risks associated with IFG or IGT using relative risk or an odds ratio are highly dependent on the reference category that is used, i.e. whether it is: FPG < 6.1 mmol/l; or 2-HPG < 7.8 mmol/l; or FPG < 6.1 mmol/l and 2-HPG < 7.8 mmol/l. Hence, even if fasting and 2-HPG carried equivalent risk of an outcome, the relative risk of IFG compared with FPG < 6.1 mmol/l could be quite different from the relative risk of IGT compared with 2-HPG < 7.8 mmol/l.

Many prospective studies that have examined glucose as an independent risk factor for CVD or total mortality have been under-powered, and this is likely to be a major reason for conflicting findings from different studies. One approach to overcome the low power of individual prospective studies is to combine the data from them. This approach has been taken by the DECODE investigators [17]. While such data sets have considerable power, there is an important limit to their precision with regard to glucose measurements. Differences in the methodology of glucose assessment between studies, such as in the type of blood sample (whole blood vs. plasma or capillary) and glucose assay method, inevitably introduce imprecision into an assessment of the relationship between glucose level or category and outcomes.

Finally, although interest usually focuses on whether a relationship between glucose and outcomes is independent of known or potential confounders (such as other CVD risk factors), both unadjusted and adjusted relationships between glucose and outcomes have utility. For example, glucose may have value as a risk marker for CVD even if this relationship is mediated through its association with other cardiovascular risk factors. A special example of this is whether the relationship between fasting glucose and outcomes is independent of 2-HPG and *vice versa*.

### Predictive properties of IGT and IFG for diabetes

The diagnostic cut-offs for diabetes appear to identify genuine thresholds below which there is virtually no risk of diabetic retinopathy, whilst above it the risk starts to rise substantially

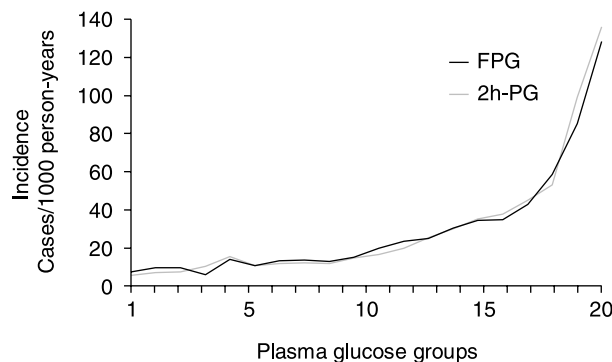


Figure 2 Incidence of diabetes (1999 WHO criteria) in Pima Indians by 5-percentile intervals of baseline fasting plasma glucose (FPG) and 2-h plasma glucose (2-HPG) value in an oral glucose tolerance test. —, FPG; - - -, 2-HPG. (From Gabir MM *et al. Diabetes Care* 2000; 23: 1108–1112.)

[5,6]. The same does not apply to the lower cut-offs of IFG or IGT, which were based on consensus rather than evidence. The risk for CVD or future diabetes appears to be continuous across the glucose range, and the cut-offs merely represent a convenient point at which the risk can be deemed to be 'excessive' and worthy of labelling. This is of undoubted convenience in clinical and public health settings, but has obvious limitations. Indeed, in epidemiological studies, using a single OGTT, a continuous and curvilinear relationship exists between current glucose levels (either fasting or 2 h) and the risk of future diabetes (illustrated in Fig. 2 using data from the Pima Indians [23]). Such data indicate that the predictive abilities for diabetes of fasting and 2-h glucose (when considered as continuous variables) are similar.

A number of studies have recently tried to determine whether IGT or IFG is a better predictor of future diabetes. The findings from six studies are summarized in Table 4. Although there are some differences between the studies, the following general conclusions may be drawn. The incidence of subsequent diabetes is highest in individuals with combined IGT and IFG. It tends to be similar in those with isolated IFG (I-IFG) and I-IGT, although there may be differences in some populations, with data from Pima Indians suggesting a higher incidence in those with I-IFG. However, because in most populations I-IGT is much commoner than I-IFG, it identifies a greater proportion of those who will develop diabetes. A substantial minority, well over a third, of individuals who develop diabetes have normal glucose tolerance at baseline. This latter proportion will be largely dependent on the time interval between glucose measurements. This is probably the main explanation for over 60% of those with diabetes having normal glucose tolerance at baseline in the Italian study, where the follow-up after initial assessment of glucose status was > 11 years. This highlights the fact that the intermittent measurement of FPG and 2-HPG is of limited utility in identifying all those within a population at future risk of developing diabetes.

**Table 4** The predictive power of impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT) for future diabetes

Study	Number, follow-up, definition of diabetes	Glucose tolerance category ( <i>n</i> )	Percentage ( <i>n</i> ) developing diabetes	Percentage of all incident diabetes in population
Hoorn study (white), men and women 50–75 years [14]	1342 without DM. Mean follow up 5.8–6.5 years. WHO 1999	NGT (1125)	4.5 (51)	38.3
		I-IFG (106)	33.0 (35)	26.3
		I-IGT (80)	33.8 (27)	20.3
		IGT and IFG (31)	64.5 (20)	15.0
Pima Indian population, men and women ≥ 15 years [12]	5023 without DM. Five years follow-up*. WHO 1999	NGT (3499)	3.6	40.1
		I-IFG (93)	31.0	9.2
		I-IGT (537)	19.9	34.1
		IGT and IFG (126)	41.2	16.6
Mauritians (multiethnic), men and women 25–74 years [11]	3229 without DM. Five years follow-up. WHO 1999	NGT (2474)	4.7 (117)	39.4
		I-IFG (148)	21.6 (32)	10.8
		I-IGT (489)	20.8 (103)	34.7
		IGT and IFG (118)	38.1 (45)	15.2
Italian (white) men and women, 40–59 years [24]	560 without DM. 11.5 years follow-up. ADA 1997	NGT (500)	7.2 (36)	66.7
		I-IFG (11)	9.1 (1)	1.9
		I-IGT (40)	32.5 (13)	24.1
		IGT and IFG (9)	44.4 (4)	7.4
Ely, UK (white) men and women 40–65 years at baseline [25]†	908 without DM. 4.5 years follow-up. WHO 1999	NGT (604)	0.3 (2)	8.3
		I-IFG (149)	4.7 (7)	29.2
		I-IGT (84)	7.1 (6)	25.0
		IGT and IFG (71)	12.7 (9)	37.5
Brazilian-Japanese, 40–79 years [26]‡	314 without DM. Seven years follow-up. WHO 1999	NGT (252)	20.2 (51)	54.8
		I-IFG (14)	64.3 (9)	9.7
		I-IGT (37)	67.6 (25)	26.9
		IGT and IFG (11)	72.7 (8)	8.6
Paris Prospective Study (white), men, 44–55 years [27]	5139 without DM. 30-month follow-up. WHO 1999	NGT or I-IFG‡ (4615)	2.7 (129)	75.4
		I-IGT	5.4 (14)	8.1
		IGT and IFG	14.9 (28)	16.4

\*Five-year cumulative incidence was calculated using the Kaplan–Meier method.

†The analyses presented here were provided specifically for this report by Dr N. Wareham and Dr L. Franco, respectively.

‡Data were not available for isolated-IFG alone.

Taking into account additional risk factors may improve this, and this is considered later.

A fasting plasma glucose of 5.7 mmol/l has been found to be closer to a 2-h cut-off of 7.8 mmol/l (the lower cut point for IGT) both in terms of the sensitivity for future diabetes and in defining a category of similar prevalence to IGT. This has been shown in the data from Mauritius [11] and Pima Indians [23]. Thus, when looking at each of these populations, reducing the lower limit for IFG to 5.7 mmol/l yielded a group that was approximately the same proportion of the population as the IGT group, and identified a similar number of future cases of diabetes. However, given the differences in the distribution of IFG and IGT by age, sex and ethnicity described above, the ideal lower limit for IFG (ideal at least in terms of equal to IGT in prevalence and risk) will vary by these parameters and thus

be population-specific. There is no *a priori* reason why the prevalence of IGT and IFG should be the same.

### Predictive properties of IGT and IFG for CVD and total mortality

#### Glucose and its association with other CVD risk factors

Both IFG and IGT are associated with CVD risk factors, including hypertension, dyslipidaemia, and other features of the metabolic syndrome (e.g. hyperinsulinaemia, microalbuminuria, inflammatory and haemostatic markers). Given the somewhat different physiological bases of IFG and IGT referred to earlier, differences in their association with other cardiovascular risk factors might be expected. However, published data presenting these associations are limited and often not population-based.

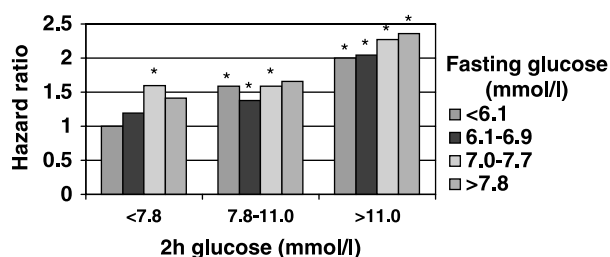


Figure 3 Hazard ratios for all-cause mortality by fasting and 2-h plasma glucose. \*95% CIs do not cross 1. (From DECODE Study Group. *Lancet* 1999; 354: 617–621.)

Further data comparing CVD risk factors across these groups from a variety of populations are desirable. Those that are available suggest little difference between individuals with I-IFG and I-IGT in lipid levels or blood pressure, with higher levels in individuals with both IFG and IGT [9,13,28,29].

The intima-media thickness (IMT) of the common carotid artery is considered a valid marker of atherosclerosis. In the Risk factors in IGT for Atherosclerosis and Diabetes (RIAD) study the IMT in individuals with isolated IFG was no different from controls with normal glucose tolerance (NGT) matched for age, sex and body mass index (BMI). However, IMT was significantly higher in the group with combined IFG–IGT, with the I-IGT group having levels intermediate between the two [29]. Further analyses demonstrated that below a fasting plasma glucose of 7.0 mmol/l fasting glucose level was not related to IMT, but 2-h glucose level was predictive of IMT at fasting glucose levels of both 6.1–7.0 mmol/l, and < 6.1 mmol/l [30].

#### The relationship between glucose and CVD and total mortality

The nature of the relationship between non-diabetic glucose levels and total and CVD mortality has been a subject of investigation for at least the past two decades, but until recently has remained relatively poorly defined. A major part of the reason for this has been the limited statistical power of most studies. In order to overcome this limitation two recent initiatives have pooled results or data from several studies and thus provided much greater statistical power for defining this relationship.

In analyses unadjusted for other risk factors both fasting and 2-HPG are associated with total and CVD mortality. A meta-regression analysis was undertaken in which data relating glucose to CVD events (the vast majority of which were deaths) were combined from 20 studies with a mean follow-up of 12 years [22]. This found a continuous positive relationship between initial fasting and 2-HPG and CVD events that extended below the current thresholds for IFG and IGT. For example, using a reference plasma glucose value of 4.2 mmol/l, a fasting plasma glucose value of 6.1 mmol/l was associated with a relative risk of 1.33 (95% CIs 1.06–1.67), and a 2-HPG value of 7.8 mmol/l was associated with a relative risk of 1.58 (1.19–2.10).

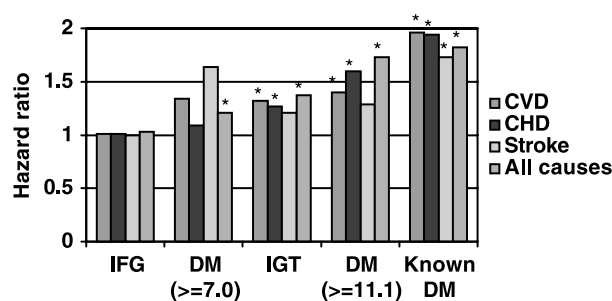
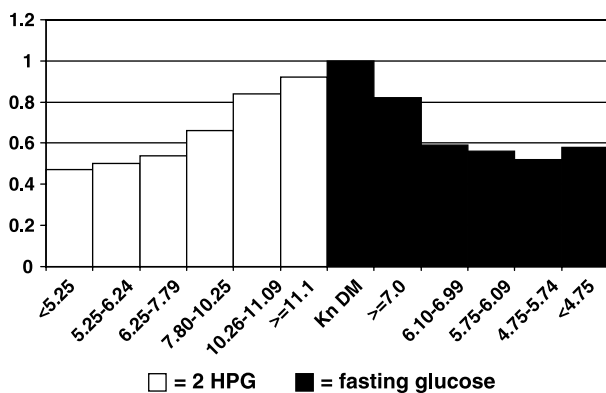


Figure 4 Adjusted† hazard ratios for death with fasting and 2-h glucose categories in the same model. †Adjusted for body mass index, systolic blood pressure, total cholesterol and smoking; reference group for impaired glucose tolerance (IGT) and DM categories is 2-h plasma glucose value in an oral glucose tolerance test < 7.8 mmol/l; for other categories reference is fasting plasma glucose < 6.1. \*95% CIs do not cross 1. (From DECODE Study Group. *AIM* 2001; 161: 397–405.)

Analyses from the DECODE data set have also demonstrated an unadjusted association between both fasting and 2-h glucose and mortality, but with 2-h glucose being more predictive than fasting. Thus, in an analysis combining 13 prospective European studies [17] the hazard ratio for all-cause mortality (adjusted only for age, sex and study centre) compared with the group with normal fasting and 2-h glucose tolerance was 1.20 (95% CI 1.04–1.38) for IFG and 1.50 (1.33–1.69) for IGT. A significant association with fasting glucose categories was found only in those with normal 2-HPG (Fig. 3). Indeed, the relationship between fasting glucose and mortality was not independent of 2-HPG, but the relationship with 2-HPG was independent of fasting glucose.

Further analyses of the DECODE data set have examined the association between glucose tolerance categories and CHD, stroke, all CVD and all-cause mortality when adjusted for other cardiovascular disease risk factors (BMI, systolic blood pressure, total cholesterol and smoking) [31]. Such adjustment greatly attenuated the relationships with IFG, e.g. hazard ratios for death from CVD and all causes were 1.09 (95% CI 0.90–1.30) and 1.11 (1.00–1.23), respectively; but had much less effect on the relationships with IGT, e.g. hazard ratios of 1.34 (1.14–1.57) and 1.40 (1.27–1.54), respectively. When the analyses included both fasting and 2-h glucose in the same model any hint of a relationship with IFG disappeared, but there was little change in the relationship with IGT. There remained, however, a statistically significant relationship for all-cause mortality with fasting plasma glucose levels at or above 7.0 mmol/l (Fig. 4). Further analyses of the DECODE data adjusted for other CVD risk factors demonstrate a continuous relationship with 2-HPG but suggest a possible threshold effect with fasting glucose at 7.0 mmol/l. This is shown in Fig. 5, which compares the hazard ratios for fasting and 2-h glucose levels with that for known diabetes. The hazard ratio associated with a fasting plasma glucose level of  $\geq 7.0$  mmol/l is similar to that associated with a 2-h value of 10.25–11.09 mmol/l.



**Figure 5** Adjusted\* hazard ratios for cardiovascular disease mortality for fasting and 2-h plasma glucose values in an oral glucose tolerance test levels compared with known diabetes. \*Adjusted for body mass index, systolic blood pressure, total cholesterol and smoking. (From DECODE Study Group, provided by J. Tuomilehto.)

The DECODE data therefore support the conclusion that in unadjusted analyses 2-HPG (and IGT) is more strongly associated with both CVD and total mortality than is fasting glucose (and IFG). In addition, the data suggest that the relationship with 2-h glucose is at least partly independent of other CVD risk factors (BMI, total cholesterol, systolic blood pressure and smoking), but that this is only the case for fasting glucose  $> 7.0$  mmol/l. These conclusions apply to European populations. The interrelationships between other cardiovascular risk factors and glucose levels may vary between different populations. Further analyses from other populations are highly desirable. Nonetheless, it is worth emphasizing that irrespective of the extent to which the associations between fasting and 2-HPG with mortality are statistically dependent on their association with other cardiovascular risk factors, hyperglycaemia by either measurement is a marker for premature death.

#### Relative and attributable risks for mortality

Relative risk is used to determine the strength of an association between a risk factor or risk marker, such as 2-HPG, and an outcome. Of greater public health importance is the attributable risk, which is the proportion of outcomes that can be attributed to the risk factor—assuming that the risk factor is causal. A risk factor may have a small relative risk but because it is common have a large attributable risk, an example of what has been termed the ‘prevention paradox’ [32].

This is the case in the DECODE analyses for IGT. By comparison with the mortality rates in those with normal glucose tolerance (both normal fasting and 2-HPG) estimates were derived for the number of excess CVD deaths attributable to higher glucose levels after excluding those with previously diagnosed diabetes and adjustment for other risk factors [31]. Of all the excess deaths associated with hyperglycaemia, none was attributed to I-IFG, 44% were attributed to I-IGT and a further 14% to IGT and IFG combined. The remainder was attributed to people with glucose values in the diabetic range.

#### Associations of cardiovascular mortality with glycated haemoglobin

The limited number of prospective studies describing the relationship between the HbA<sub>1c</sub> level and CVD events have consistently found a positive, continuous relationship. For example, in a recent Dutch study of 2363 non-diabetic individuals aged 50–75 years, CVD mortality rose 51% (95% CI 20–88%) for every 1.4% rise in HbA<sub>1c</sub> (after adjustment for age and sex) [33]. Similar findings were reported in a recent prospective study of 4662 men from the UK that analysed the risk of CV events associated with HbA<sub>1c</sub> levels of  $\ge 5\%$  compared with lower levels [34]. There was a graded relationship between rising HbA<sub>1c</sub> levels  $> 5\%$  and the risk of all causes of mortality, ischaemic heart disease mortality and cardiovascular death; after adjustment for age, CV mortality rose 41% (95% CI 21–64%) for every 1% rise in HbA<sub>1c</sub>. These data were also explored in an attempt to determine the relative contributions of diabetes and HbA<sub>1c</sub>. When either diabetes status or the HbA<sub>1c</sub> were included in separate multivariate analyses, both were independent predictors of CVD death. However, when both were included in the same analysis, only the HbA<sub>1c</sub> and not diabetes status predicted CVD death. The number of deaths in the group with diabetes was small ( $< 20$ ), but these data support the suggestion that it is the HbA<sub>1c</sub>, i.e. hyperglycaemia, and not the presence or absence of diabetes that is related to the risk of CVD death.

Finally, two studies, the Hoorn study [33] and the Finnish studies contributing to DECODE (J. Tuomilehto, personal communication), have investigated whether knowledge of 2-h plasma glucose adds to the predictive power of HbA<sub>1c</sub>. Both found that below a HbA<sub>1c</sub> level of 7.7% 2-h plasma glucose was a significant and independent (of HbA<sub>1c</sub>) predictor of mortality.

#### Predicting CVD and diabetes as outcomes from a ‘common soil’

Non-diabetic hyperglycaemia is just one of several risk factors that CVD and Type 2 diabetes share. This sharing of risk factors has been described as a ‘common soil’ from which both conditions arise [35]. The ‘common soil’ hypothesis easily extends to the level of prevention, with there being much overlap in life style measures for prevention of both conditions [36]. There is preliminary evidence that several pharmacological agents may also be effective in the prevention of both conditions [37]. These include the angiotensin converting enzyme inhibitor ramipril [38] pravastatin [39], and the  $\alpha$ -glucosidase inhibitor acarbose (data presented June 2002, Journal of Hypertension Vol 20; Suppl 4: 55). Metformin has been proven to be effective in certain individuals in the prevention or delay of Type 2 diabetes [40], and although it has not been evaluated in terms of CVD outcomes, has been shown to have beneficial effects on other cardiovascular risk factors [41]. Similarly the insulin sensitizing drugs, the thiazolidinediones, may also lower cardiovascular [42] and diabetes risk. In short, an individual at risk of developing diabetes is also at risk of

**Table 5** Recent intervention studies in people with impaired glucose tolerance (IGT)

Study (year) [ref.]	Study participants ( <i>n</i> for number included in main analysis)	Design, interventions and length of follow-up	Key outcomes
Da Qing study, China (1997) [48]	577 men and women, > 25 years (mean BMI 25.8 kg/m <sup>2</sup> ). IGT based on single OGTT (WHO 1985 criteria). Recruited from 33 health clinics, with 5–33 participants per clinic	Clinics randomized to diet, exercise, diet and exercise, and general advice (control) groups. Six-year follow up. Analysis on 530 participants	Cumulative incidence of diabetes at 6 years: 44%, 41%, 46%, and 68%, respectively, in the four groups. After adjustment for differences in baseline characteristics 31%, 46%, and 42% reduction in diabetes incidence in three intervention groups.
Finnish diabetes prevention study (2001) [45]	522 men and women, 40–64 years. BMI > 25 kg/m <sup>2</sup> . IGT based on means of two OGTTs (WHO 1985 criteria). Recruited from five centres in Finland	Randomization (stratified by 2-HPG, sex and centre) to intensive diet and exercise intervention or general advice (control) group. Mean follow-up 3.2 years, 90% for > 2 years. Intention to treat analysis.	Overall 58% reduction in risk of diabetes in intervention group: 11% vs. 23% at 4 years. Incidence inversely associated with degree of compliance with intervention.
Diabetes Prevention Programme, USA (2002) [40]	3234 men & women (45% non-white), ≥ 25 years, BMI ≥ 22 in Asians, ≥ 24 other groups. Fasting plasma glucose of 5.3–6.9 mmol/l and 2-h post- OGTT level of 7.8–11.0 mmol/l. Recruited from 27 centres in USA.	Randomization, stratified by centre, to placebo or metformin (850 mg twice daily)—both with general life style advice, or intensive life style intervention. Mean follow up 2.8 years, intention to treat analysis.	Compared with placebo: 58% reduction in incidence of diabetes with intensive life style intervention, 31% with metformin. Estimated incidence at 3 years: 28.9%, 14.4% and 21.7%, respectively. No significant difference between sex or minority groups.
STOP-NIDDM, international multicentre (2002, in press) [46]	1368 men and women (97.5% white), aged 40–70 years, BMI 25–40. IGT based on WHO 1985 criteria plus fasting plasma glucose of ≥ 5.6 and < 7.8 mmol/l.	Double blind randomization to placebo or acarbose 100 mg tid. General advice given to all on diet, weight loss (if appropriate) and physical activity. Mean follow-up 3.3 years, intention to treat analysis.	Based on single annual OGTT, using the 2-HPG result, cumulative incidence of 32.4% in acarbose-treated vs. 41.5%. Effect consistent across age, sex and BMI groups. Similar size effects when assessing diabetes incidence using WHO 1999 criteria.

CVD, and effective measures to prevent both conditions have much in common both at the individual and population level.

An argument can be made therefore to consider the prediction and prevention of both outcomes together. This approach has been taken by the San Antonio Heart Study [43] investigators, who used their prospective data to derive a prediction score for one or both outcomes [44]. They used generally readily available data, including medical and family history, blood pressure, BMI, and fasting lipids. Two-hour glucose made little difference to the prognostic value of the prediction equation, hinting at the possibility that such an approach might obviate the need for an OGTT. Although considering diabetes and CVD outcomes together in this way is attractive, it is currently novel. Similar analyses of data from other populations are highly desirable in order to evaluate the potential utility of this approach.

### Intervention studies in people with IGT

The question of whether the onset of diabetes in people with IGT can be prevented or delayed has been adequately addressed only within the past few years. Prior to this, the possibility of prevention by both behavioural and pharmacological means had strong theoretical support. However, the relatively few studies addressing these issues suffered from various flaws, including small sample size, lack of randomization, and low intensity of the interventions. However, with the publication

of results from the four studies summarized in Table 5 there is now strong evidence that the onset of diabetes in people with IGT can be delayed or prevented by both behavioural and pharmacological interventions. It is worth noting that the Finnish Diabetes Prevention Study (FDPS) [45], the Diabetes Prevention Programme (DPP) [40] and STOP-NIDDM [46,47] all recruited individuals with IGT whose average risk of developing diabetes was likely to be greater than those with IGT identified on a single OGTT in population-based studies (such as those shown in Table 3). In the Finnish study participants were recruited on the basis of two OGTT results and all were overweight. In the American study BMI criteria were also applied, and although a single OGTT was used an additional fasting glucose criterion was applied (plasma glucose of 5.3–6.9 mmol/l). Similarly, in the STOP-NIDDM trial BMI criteria were applied plus the criterion that fasting plasma glucose was 5.6–7.7 mmol/l.

In both the FDPS and the DPP, intensive life style measures, which consisted of a package of dietary change, weight loss, and increased physical activity, were associated with a 58% reduction in the incidence of diabetes compared with those who received general advice. In the DPP the effectiveness of metformin was also evaluated and was associated with a reduction in incidence of just under a third—roughly half the reduction achieved through life style measures. Furthermore, while life style measures were equally effective in all subgroups, the efficacy of metformin was variable. Amongst the

over 60s, those with BMI < 35, and those with FPG < 6.1 mmol/l, there was no significant effect of metformin. Neither the FDPS nor the DPP were designed to examine the effectiveness of different components of the life style intervention, although attempts to do this in multivariate analysis may be made. In the Da Qing study [48] the intervention arms that included exercise advice (with or without dietary advice) appeared more effective than dietary advice alone (reductions in incidence of 42%, 46% and 31%, respectively, when adjusted for differences in baseline characteristics). However, the study was not designed to test differences between these groups, but rather between each of them and the control group, and conclusions on the relative effectiveness of different life style interventions requires further study.

The Stop-NIDDM trial [47] evaluated the effectiveness of acarbose, an  $\alpha$ -glucosidase inhibitor, and results [46] indicate a reduction in diabetes incidence of around 25%, all apparent over the first year of intervention. All trial participants completing the study were given placebo for a 3-month period. During this 3-month period those that had been originally taking acarbose had a higher incidence of diabetes than those that had been on placebo throughout the trial [46], suggesting the preventive effect of acarbose may require continued treatment—although further evaluation of this is needed.

Studies on the effectiveness of pharmacological interventions other than metformin and acarbose in the delay or prevention of diabetes are required. Initially the DPP included an intervention arm with troglitazone, but this was discontinued after its uncommon but potentially fatal effects on the liver became apparent [49]. A randomized controlled trial of troglitazone in young Hispanic women with a history of gestational diabetes mellitus (GDM) was reported as showing a 60% reduction in the incidence of Type 2 diabetes over a mean follow-up of 27 months [50,51]. Two further large multicentre studies have recently been established. The DREAM study is investigating the effectiveness of ramipril and rosiglitazone in the prevention of diabetes in over 4000 individuals with IGT. The NAVIGATOR study is investigating the effectiveness of nateglinide, an oral hypoglycaemic agent that enhances early phase insulin secretion [52], and valsartan, an angiotensin II receptor blocker [53], in 7500 individuals with IGT and at high risk of CVD. Primary outcome measures for the NAVIGATOR study are the development of diabetes and CVD.

Finally it must be noted that the effectiveness of the life style and pharmacological interventions evaluated to date in people with IGT have not examined CVD and total mortality. Longer follow-up or larger studies, such as NAVIGATOR, will be required to comment on these outcomes. The FDPS demonstrated favourable changes in blood pressure and lipids in the intervention group after 1 year [45] and it is likely that similar findings will be reported from the life style group in the DPP. There is much evidence to support the notion that life style change leading to change in biological risk factors will

translate into improved CVD outcomes and mortality rates. Greater caution is required in the assumption that long-term pharmacological intervention, particularly because of the possibility of unknown long-term adverse effects, in people with IGT will be associated with reduced CVD events and mortality rates.

### Identifying and prioritizing people with IGT for intervention

#### *Risk prediction scores for screening people for IGT*

It has been demonstrated earlier in this document that fasting glucose is a poor marker for IGT. However, screening large numbers of people with an OGTT is time-consuming and expensive. Targeting individuals at a high likelihood of having IGT for oral glucose tolerance testing is thus desirable. Some analyses of existing data sets have been undertaken in order to determine factors that predict the presence of IGT. Two analyses of data from the San Antonio Heart Study [54], one utilizing fasting glucose and lipid results and the other not, are shown in Table 6. The figures illustrate the performance of the prediction scores using a cut-off at a level for the top 30% of the population by the score. Including data on fasting glucose and triglycerides, this approach identified just under two-thirds of those with IGT, and a slightly lower percentage without fasting blood results. Thus roughly one person with IGT would be identified for every three to four OGTTs performed. Reducing the cut-off level to include the top 40% of the population at risk would identify around 75% of those with IGT, with only slightly less efficiency, i.e. one person identified for every four OGTTs performed. These analyses were also done using simple categorical variables, e.g. with age, blood pressure, BMI, and waist circumference each grouped into two or three categories. The efficiency of such an approach is only slightly less than using variables with greater gradation and has the advantage that the risk prediction score is easier to calculate without a computer or calculator. The figures in Table 6 illustrate that although the percentage of people with IGT identified with or without fasting blood results is similar, the former appears better at distinguishing between those with IGT at high and lower risk of developing diabetes.

The results from the San Antonio Heart Study strongly support the strategy of using other risk factors to determine whether an individual should have an OGTT. These analyses are currently being repeated in data sets from other populations. It is likely that the efficiency of such prediction equations will be population-specific, and that when such equations are used on other populations (i.e. other than that from which the equations were derived) the performances will not be as good. When screening strategies for undiagnosed diabetes have been derived from one population and tested in another, they have identified about half the population as being 'at risk', and have identified about three-quarters of those with undiagnosed diabetes [55,56]. It should be noted that such an approach is not necessarily a 'cheaper' option, particularly if blood tests are involved.

### Prediction of diabetes without the measurement of blood glucose

Finally, blood glucose level is one of several risk factors for the future development of diabetes. The use of cheap, rapid and non-invasive methods (i.e. without glucose tolerance testing) for identifying those who will benefit from preventive measures is clearly an attractive proposition. An example of such an approach is the use of the 'Finnish Diabetes Risk Score' [57]. The items in the score include age, BMI, waist circumference, family history of diabetes and personal history of hypertension. The score performs well within the cohort data set from which it was derived, with a sensitivity of 73%, specificity of 83% and positive predictive value of 16% for the 10-year risk of diabetes. Efforts are underway to evaluate its performance in other data sets and to evaluate its value in identifying individuals for intervention. This type of approach deserves further work and may in the future provide an alternative to the use of IGT and IFG for identifying individuals at high risk of developing diabetes.

### Prioritizing people with IFG and IGT for intervention

The risks of developing diabetes and CVD are not homogeneous within the categories of IFG or IGT, but are heavily influenced by the presence or absence of other risk factors. For example, individuals with both IFG and IGT are at a much higher risk of developing diabetes than individuals with either condition alone (as shown in Table 4). Similarly, the heterogeneity of risk in people with IGT is apparent from the data in Table 6, showing a two to greater than three-fold difference in the incidence of diabetes in people with IGT according to the presence or absence of other factors. There have been a small number of reports of differences in future diabetes risk between people with transient and persistent IGT. In South African Indians transient IGT did not carry an increased risk of diabetes [58], but it did in Pima Indians. Those with transient IGT had a three-fold greater risk of diabetes over 10 years compared

with those with NGT [59]. It is likely that risks associated with IGT and other risk factor combinations will be population-specific, and any scoring system to identify those at high risk ideally should be based on data from within the population in which the scoring system will be used.

Within the context of limited health care resources it is sensible to focus initially on those at highest risk of developing diabetes. Those at highest risk should receive the most effective interventions available. These are life style interventions of the type developed and used in the FDPS and DPP. The option of pharmacological therapy exists for those who do not respond to life style measures (e.g. using the targets set in FDPS or DPP) and for whom such therapy is clearly indicated (e.g. those with a BMI > 35 and < 60 years old for metformin, although acarbose should be suitable for all subgroups). As resources allow, people in lower risk categories may receive similar or less intensive intervention.

In designing strategies to identify and target interventions in people with IGT, consideration of both relative and attributable risk is important. For example, the data in Table 4 illustrate that individuals with combined IGT and IFG tend to be at a much higher risk of diabetes than individuals with IGT alone, but that those with IGT alone account for a greater proportion of those who develop diabetes. This is because IGT alone is much commoner than IGT and IFG combined.

Finally, it is acknowledged that the evidence base for intervening in people with IFG is much less strong than for people with IGT. There have been no diabetes prevention studies specifically addressing people with IFG. It is highly desirable that future studies of interventions for the prevention of diabetes include people with IFG in sufficient numbers to allow firm conclusions to be reached. However, in the meantime it is argued that the risk of developing diabetes associated with IFG, as reviewed earlier, is well enough understood to recommend the same interventions as shown to be effective in people with IGT.

**Table 6** Predicting impaired glucose tolerance—the performance of a risk prediction score in the San Antonio Heart Study derived using logistic regression [54]

Population used in analysis	Variables in model	Percent glucose intolerance identified in top 30% of score		Incidence over 7.5 years of DM in those with IGT	
		IGT	New DM	In top 30% of score	In lower 70% of score
<i>Including fasting blood results</i>					
4194 men and women, FPG < 7 mmol/l, no hx DM, 559 with IGT, 118 DM on 2-h OGTT	Age, sex, FH diabetes, sys BP, anti-hyp med., BMI, FPG, fast trig.	64.9%	89.8%	40.3%	12.0%
<i>Excluding fasting blood results*</i>					
2516 men and women, no hx DM	Age, sex, FH diabetes, sys BP, anti-hyp med., BMI, waist circum.	62.2%	76.3% by 2-HPG only 72.6% by FPG	50.4%	26.7%

\*Including waist circumference—the measurement of this was introduced half way through the baseline survey, hence the smaller numbers included in the analysis.

## Consensus statements and recommendations

The workshop was convened to address three major questions. These were: are the current definitions of IGT and IFG appropriate; are IFG and IGT risk factors, risk markers or diseases; and should we intervene in IGT and IFG, and if so how? After reviewing the evidence summarized above the following consensus was reached and the following recommendations were made.

### The definition and status of IGT and IFG

#### Definition

The definition of IGT as established by WHO appears satisfactory. Since 1979 only one change has been made—lowering the fasting plasma glucose from 7.8 to 7.0 mmol/l. This means that a small number of individuals who previously were classified as IGT would now have diabetes according to the new 1999 WHO criteria. The 2-h range of 7.8–11.0 mmol/l has remained unchanged. The upper value remains secure as the cut-point between risk of microvascular complications and minimal risk. It is possible that the lower value, however, could be modified. Further studies and data analyses are needed to see whether this is worthwhile and whether this also applies to macrovascular risk. For the time being no change is recommended. Clear distinction is needed, however, between IGT with a normal fasting plasma glucose value ('isolated IGT') and IGT with IFG ('combined IGT'), as the risks of both progression to diabetes and macrovascular disease are greater with the latter. Better understanding of the significance of a single abnormal result compared with repeated abnormalities is also needed, particularly in light of the known variability of the OGTT. Finally, there is no agreement at present on whether the terms IGT and IFG should be restricted to those who show the abnormality twice or whether one abnormal test suffices. Most epidemiological studies have been restricted to single tests. A separate category are those who show one abnormal test only whilst undergoing a series of tests over a period of time.

IFG is less certain. As with IGT, the upper limit is clear as the cut-point for risk of microvascular disease, but the lower limit is arguable as there is no clear threshold for macrovascular risk or indeed for risk of diabetes.

It is worth stressing that IGT and IFG are not interchangeable. They represent metabolically distinct abnormalities and it is not surprising that they show a different prevalence. In most populations IGT is more prevalent than IFG, with the former more common on the older age groups and IFG prevalence levelling out at younger ages. Roughly half the people with IFG also have IGT, whilst a much smaller proportion of those with IGT are found to have IFG—although as previously discussed these relationships vary by age and sex.

#### Recommendations

- WHO should re-examine the diagnostic thresholds of IGT and IFG.

- The significance of 'isolated IFG', 'isolated IGT', 'combined IFG and IGT' and 'transient IGT' should be clarified.
- Scoring systems to guide screening for diabetes, IGT and IFG using risk markers such as obesity, hypertension, age, family history and ethnicity should be developed and evaluated.
- All individuals with IFG should have an OGTT, as a significant number (approximately 5%, but up to 20% in some populations) will already have diabetes by 2-h post-challenge criteria.
- The diagnosis of IFG or IGT in an individual should be based on two OGTTs no more than 3 months apart, and the mean values used to classify the individual.

### Diseases, risk factors or risk markers?

There was no clear consensus on whether IFG and IGT should be classified as diseases. It was clear that both IGT and IFG are risk factors for diabetes. Both are certainly risk markers for CVD. Until intervention is shown to delay or reduce the development of CVD it will not be possible to state unequivocally that they are risk factors for CVD.

There are parallels with other CVD risk markers and risk factors such as hypertension, dyslipidaemia and obesity. There is every reason to take IGT and IFG as seriously in relation to diabetes risk and classify them as treatable risk factors. Regardless of nomenclature, they should be treated seriously by health authorities and both screening for and treatment of them should be reimbursable.

#### Recommendations

- IGT and IFG should be considered as major risk factors for Type 2 diabetes, and important risk markers for CVD of similar prognostic importance to the other major CVD risk makers.

### Should we intervene?

#### Diabetes

As stated above, the risk of developing diabetes in IGT and IFG is not homogeneous within these categories but dependent on the levels of other risk factors such as age, BMI and family history of diabetes. The risk may also vary between populations. Both IGT and IFG are strongly associated with other CVD risk factors and the management of these is both important and may impact on the glucose dysregulation. There are currently no data available to evaluate the effectiveness of interventions in the elderly, in people with 'isolated' IFG or people without other CVD risk factors.

Available trial data from IGT trials indicate that the greatest reduction of risk of developing diabetes is achieved through a package of life style measures that include weight reduction, increased physical activity and dietary changes. Interventions with drugs, notably metformin and acarbose, have also been shown to reduce progression to diabetes but in the studies undertaken were less effective than life style intervention.

Metformin was shown to be effective in the subgroup of younger subjects and in the subgroup of more obese subjects.

The use of pharmacological interventions in subjects with IGT raises questions about long-term safety and whether the drugs could ever be stopped. This is no different, however, from long-term treatment of other CVD risk factors except that in the latter case closer to 100% control may be achieved, although in practice often not.

No intervention studies have been performed on subjects with I-IFG.

In view of the above the question must be answered, whether subjects should be screened for IGT and/or IFG. Screening separate from screening for diabetes is probably not justified. Similarly, it is probably not cost-effective to screen entire populations. However, a high-risk strategy as part of a diabetes screening programme using an OGTT would be feasible. If a suitable risk screening scoring system can be developed this would be a useful preliminary to glucose testing. Screening by FPG alone will of course not identify IGT subjects and FPG levels are poor predictors of IGT.

#### Recommendations

- Subjects with IGT and IFG should be given life style advice and reviewed on a regular basis.
- If life style advice fails, drug therapy should be considered.
- Prevention should be targeted at those at highest risk of developing diabetes and CVD.
- Trials are urgently required of life style and drug interventions in subjects with I-IFG.
- The efficacy of different drugs and combinations of drugs in preventing diabetes needs to be established, in addition to metformin and acarbose. The results of the NAVIGATOR and DREAM studies are awaited.

#### Cardiovascular disease

There are no trials specifically targeting people with IGT and IFG with the aim of preventing CVD. Thus it is still not known whether IGT and IFG are risk associations, i.e. markers or genuine modifiable risk factors. The situation is further complicated by subjects with IFG and IGT generally having other features of the metabolic syndrome.

#### Recommendations

- Completed intervention studies in those with IGT should analyse and report data on fatal and non-fatal CVD events.
- Current and future intervention trials should focus on CVD outcomes as well as progression to diabetes.
- Cardiology trials should include baseline glucose tolerance testing.
- The value of taking plasma glucose levels into account as part of overall CVD risk assessment should be explored.

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#### Appendix—Workshop members

##### Co-Chairpersons

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##### Participants

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#### References

- 1 Last JM. *A Dictionary of Epidemiology*, 3rd edn. New York: Oxford University Press, 1995.
- 2 National Diabetes Data Group. Classification and diagnosis of diabetes and other categories of glucose intolerance. *Diabetes* 1979; 28: 1039–1057.
- 3 WHO Expert Committee on Diabetes Mellitus. Technical Report Series 646, Second report. Geneva: World Health Organisation, 1980.
- 4 WHO Study Group. *Diabetes Mellitus*. Technical report Series 727. Geneva: World Health Organisation, 1985.
- 5 The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; 20: 1183–1197.
- 6 World Health Organisation. *Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications*. Report of a WHO consultation. Part 1: *Diagnosis and Classification of Diabetes Mellitus*. Geneva: World Health Organisation, 1999.
- 7 DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131: 281–303.
- 8 Weyer C, Bogardus C, Pratley RE. Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 1999; 48: 2197–2203.
- 9 Davies MJ, Raymond NT, Day JL, Hales CN, Burden AC. Impaired glucose tolerance and fasting hyperglycaemia have different characteristics. *Diabet Med* 2000; 17: 433–440.

- 10 Dunstan D, Zimmet P, Welborn T, de Courten M, Cameron A, Sicree R *et al.* The rising prevalence of diabetes mellitus and impaired glucose tolerance: the Australian diabetes, obesity and lifestyle study. *Diabetes Care* 2002; **25**: 829–834.
- 11 Shaw J, Zimmet P, de Courten M, Dowse G, Chitson P, Gareeboo H *et al.* Impaired fasting glucose or impaired glucose tolerance. What best predicts future diabetes in Mauritius? *Diabetes Care* 1999; **22**: 399–402.
- 12 Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH *et al.* Plasma glucose and prediction of microvascular disease and mortality: evaluation of 1997 American Diabetes Association and 1999 World Health Organization criteria for diagnosis of diabetes. *Diabetes Care* 2000; **23**: 1113–1118.
- 13 Larsson H, Berglund G, Lindgarde F, Ahren B. Comparison of ADA and WHO criteria for diagnosis of diabetes and glucose intolerance. *Diabetologia* 1998; **41**: 1124–1125.
- 14 de Vegt F, Dekker JM, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ. The 1997 American Diabetes Association criteria versus the 1985 World Health Organization criteria for the diagnosis of abnormal glucose tolerance: poor agreement in the Hoorn Study. *Diabetes Care* 1998; **21**: 1686–1690.
- 15 Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–85 World Health Organization diagnostic criteria. *Diabetes Care* 1997; **20**: 1859–1862.
- 16 Ko GT, Chan JC, Woo J, Cockram CS. Use of the 1997 American Diabetes Association diagnostic criteria for diabetes in a Hong Kong Chinese population. *Diabetes Care* 1998; **21**: 2094–2097.
- 17 The DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 1999; **354**: 617–621.
- 18 DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. Will new diagnostic criteria for mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. *Br Med J* 1998; **317**: 371–375.
- 19 Qiao Q, Hu G, Tuomilehto J, Balkau B, Bord-Johnsen K, for the DECODE Study Group. Age and sex specific prevalence of diabetes and impaired glucose regulation in 13 European cohorts. 37th Annual meeting of the European Diabetes Epidemiology Group, Oxford 2002. Abstract 37.
- 20 Qiao QNT, Tuomilehto J, Borch-Johnsen K, Balkau B, Iwamoto Y, Tajima N. Comparison of the fasting and the 2-hour glucose criteria for diabetes in different Asian cohorts. *Diabetologia* 2000; **43**: 2000.
- 21 DECODA Study Group. Age and sex specific prevalence of diabetes and impaired glucose regulation in 10 Asian cohorts. *Diabetes Research & Clinical Practice* 2002; **56**(1): 540.
- 22 Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999; **22**: 233–240.
- 23 Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH *et al.* The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care* 2000; **23**: 1108–1112.
- 24 Vaccaro O, Ruffa G, Imperatore G, Iovino V, Rivellese AA, Riccardi G. Risk of diabetes in the new diagnostic category of impaired fasting glucose: a prospective analysis. *Diabetes Care* 1999; **22**: 1490–1493.
- 25 Wareham N, Byrne C, Williams D, Day N, Hales C. Fasting proinsulin concentrations predict the development of Type 2 diabetes. *Diabetes Care* 1999; **22**: 262–270.
- 26 Gimeno SG, Ferreira SR, Franco LJ, Iunes M. Comparison of glucose tolerance categories according to World Health Organization and American Diabetes Association diagnostic criteria in a population-based study in Brazil. The Japanese-Brazilian Diabetes Study Group. *Diabetes Care* 1998; **21**: 1889–1892.
- 27 Eschwege E, Charles MA, Simon D, Thibault N, Balkau B, Paris Prospective S. Reproducibility of the diagnosis of diabetes over a 30-month follow-up: the Paris Prospective Study. *Diabetes Care* 2001; **24**: 1941–1944.
- 28 Rathmann W, Giani G, Mielck A. Cardiovascular risk factors in newly diagnosed abnormal glucose tolerance: comparison of 1997 ADA and 1985 WHO criteria. *Diabetologia* 1999; **42**: 1268–1269.
- 29 Hanefeld M, Temelkova-Kurktschiev T, Schaper F, Henkel E, Siegert G, Koehler C. Impaired fasting glucose is not a risk factor for atherosclerosis. *Diabet Med* 1999; **16**: 212–218.
- 30 Hanefeld M, Koehler C, Henkel E, Fuecker K, Schaper F, Temelkova-Kurktschiev T. Post-challenge hyperglycaemia relates more strongly than fasting hyperglycaemia with carotid intima-media thickness: the RIAD study. *Diabet Med* 2000; **16**: 212–218.
- 31 Decode Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001; **161**: 397–405.
- 32 Rose G. Sick individuals and sick populations. *Int J Epidemiol* 1985; **14**: 32–38.
- 33 de Vegt F, Dekker JM, Ruhe HG, Stehouwer CD, Nijpels G, Bouter LM *et al.* Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia* 1999; **42**: 926–931.
- 34 Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A *et al.* Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ* 2001; **322**: 15–18.
- 35 Stern MP. Diabetes and cardiovascular disease. The ‘common soil’ hypothesis. *Diabetes* 1995; **44**: 369–374.
- 36 Tuomilehto J. Primary prevention of non-communicable diseases. In: Hitman G, ed. *Type 2 Diabetes. Prediction and Prevention*. Chichester: John Wiley & Sons, 1999; 213–238.
- 37 Thompson WG. Early recognition and treatment of glucose abnormalities to prevent type 2 diabetes mellitus and coronary heart disease. *Mayo Clinic Proc* 2001; **76**: 1137–1143.
- 38 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**: 145–153.
- 39 Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I *et al.* Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001; **103**: 357–362.
- 40 Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.
- 41 Fontbonne A, Charles MA, Juhan-Vague I, Bard JM, Andre P, Isnard F *et al.* The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. BIGPRO Study Group. *Diabetes Care* 1996; **19**: 920–926.
- 42 Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA. Nonhypoglycemic effects of thiazolidinediones. *Ann Intern Med* 2001; **134**: 61–71.
- 43 Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 1990; **263**: 2893–2898.
- 44 Williams K, Davey J, Haffner S, Stern MDSA. Logistic regression model predicting the incidence of either diabetes or cardiovascular disease in the San Antonio Heart Study: a score sheet for risk assessment. *Diabetes* 2001; **50**: A204.

- 45 Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344**: 1343–1350.
- 46 Chiasson J, Josse R, Gomis R, Hanefeld M, Karasik A, Laakso M. *et al.* Acarbose can prevent the progression of impaired glucose tolerance to type 2 diabetes mellitus: results of a randomised clinical trial. The STOP-NIDDM randomised Trial. *Lancet* 2002; **359**: 2072–2077.
- 47 Chiasson J, Gomis R, Hanefeld M, Josse R, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. *Diabetes Care* 1998; **21**: 1720–1725.
- 48 Pan X-R, Li G-W, Hu Y-H, Wang J-X, Yang W-Y, An Z-X *et al.* Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT Diabetes Study. *Diabetes Care* 1997; **20**: 537–544.
- 49 Scheen AJ. Thiazolidinediones and liver toxicity. *Diabetes Metab* 2001; **27**: 305–313.
- 50 Azen SP, Peters RK, Berkowitz K, Kjos S, Xiang A, Buchanan TA. TRIPOD (Troglitazone In the Prevention of Diabetes): a randomized, placebo-controlled trial of troglitazone in women with prior gestational diabetes mellitus. *Controlled Clin Trials* 1998; **19**: 217–231.
- 51 Buchanan T, Xiang A, Peters R, Kjos S, Marroquin A, Goico J *et al.* Protection from type 2 diabetes persists in the TRIPOD cohort eight months after stopping troglitazone. *Diabetes* 2001; **50** (Suppl. 2): A81.
- 52 Uchino H, Niwa M, Shimizu T, Nishiyama K, Kawamori R. Impairment of early insulin response after glucose load, rather than insulin resistance, is responsible for postprandial hyperglycemia seen in obese type 2 diabetes: assessment using nateglinide, a new insulin secretagogue. *Endocrine J* 2000; **47**: 639–641.
- 53 Dina R, Jafari M. Angiotensin II-receptor antagonists: an overview. *Am J Health Sys Pharm* 2000; **57**: 1231–1241.
- 54 Hunt K, Williams K, Haffner S, Stern M. Predicting impaired glucose tolerance (IGT) among individuals with a non-diabetic fasting glucose value. The San Antonio Heart Study. *Diabetes* 2002; **51**: A229.
- 55 Ruige JB, de Neeling JN, Kostense PJ, Bouter LM, Heine RJ. Performance of an NIDDM screening questionnaire based on symptoms and risk factors. *Diabetes Care* 1997; **20**: 491–496.
- 56 Baan CA, Ruige JB, Stolk RP, Witteman JC, Dekker JM, Heine RJ *et al.* Performance of a predictive model to identify undiagnosed diabetes in a health care setting. *Diabetes Care* 1999; **22**: 213–219.
- 57 Lindstrom J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. In: *20th International Symposium on Diabetes and Nutrition, European Association for the Study of Diabetes; June 27–30 2002; Samos, Greece; 2002.*
- 58 Motala AA, Omar MAK, Gouws E. Transient impaired glucose tolerance in South African Indians does not carry a risk for progression to NIDDM. *Diabetes Care* 1997; **20**: 1101–1107.
- 59 Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Bennett PH. Transient impaired glucose tolerance in Pima Indians: is it important? *BMJ* 1988; **297**: 1438–1441.