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Two-hour glucose is a better risk predictor for incident coronary heart disease and cardiovascular mortality than fasting glucose

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Aims To assess the predictive value of fasting and 2-h glucose after a 75 g glucose load, with regard to incidence of coronary heart disease and cardiovascular mortality.

Methods and Results 6766 subjects from five Finnish cohorts aged 30–89 years were followed up for 7–10 years. Hazards ratios associated with increasing glucose concentrations were homogeneous over studies. Multivariate Cox regression analyses showed that the hazards ratio for one standard deviation increase in 2-h glucose after logarithmic transformation was 1·17 (95% CI 1·05–1·30) for coronary heart disease incidence and 1·22 (1·09–1·37) for cardiovascular mortality. For fasting glucose, they were 1·05 (0·94–1·17) and 1·13 (1·01–1·25), respectively. Inclusion of 2-h glucose in the model based on fasting glucose significantly improved the prediction ($P<0·005$ for coronary heart disease incidence and $P<0·025$ for cardiovascular mortality), whereas fasting glucose did not add significant information to the model initially based on 2-h glucose ($P>0·10$ for both events).

Conclusion In subjects without a prior history of diabetes the association of 2-h glucose with coronary heart disease incidence and cardiovascular morality is graded and independent. The results of our study indicate that 2-h glucose is superior to fasting glucose in assessing the risk of future cardiovascular disease events.
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Introduction

The strong impact of type 2 (non-insulin-dependent) diabetes on the risk of atherosclerotic cardiovascular disease has long been recognised, but more recently interest has also focused on the association of milder abnormalities of glucose homeostasis with the risk of cardiovascular disease. This interest became stimulated in the1980s, when the World Health Organization Expert Committee formulated criteria for diabetes and impaired glucose tolerance based on glucose levels following an oral glucose tolerance test using a 75 g glucose load[1,2]. Coutinho *et al.*[3] in their systematic review of studies on the association between glucose levels and cardiovascular risk reviewed prospective studies on this subject published until 1996. They performed a meta-regression analysis of data from 20 studies and demonstrated a progressive curvilinear increase in the risk of cardiovascular events, which began at fasting and post-load glucose concentrations well below the diabetic glucose levels. In data from the 23-year follow-up of the Paris Prospective Study Balkau *et al.*[4] also found that the relationships of fasting and 2-h post-load glucose with the risk of death from all causes and coronary heart disease were curvilinear and that the increased risk became apparent at the upper levels of the non-diabetic glucose distribution.

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A new surge of interest in the relationship between glucose levels and cardiovascular disease risk has developed following the recent revision of diagnostic criteria for diabetes and milder degrees of hyperglycaemia. This revision process started in 1997, when the American Diabetes Association Expert Committee[5] recommended that the diagnostic threshold for diabetes should be lowered to fasting plasma glucose $\geq 7{\cdot}0$ mmol . l^{-1}, mainly on the basis of new evidence on the relationship between glucose levels and diabetic microvascular disease. Another main point in this recommendation was that in clinical practice the diagnosis of diabetes and milder impairments of glucose homeostasis should be based on fasting glucose. A new diagnostic category, impaired fasting glucose (fasting plasma glucose $\geq 6{\cdot}1$ mmol . l^{-1} but $<7{\cdot}0$ mmol . l^{-1}), was created with the idea that it would be an approximate equivalent for impaired glucose tolerance based on 2-h glucose after a 75 g glucose load. These recommendations have been incorporated in the revised glucose classification for the diagnosis of diabetes and other categories of hyperglycaemia given in the 1999 Report of a World Health Organization Consultation[6], although the former 2-h glucose criteria for diabetes and impaired glucose tolerance were retained.

The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) study[7–9] based on 20 European population- or occupation-based studies with both fasting and 2-h post-challenge glucose concentrations, however, demonstrated substantial discrepancies between the classifications of diabetes category based either on fasting glucose or 2-h glucose. The new diagnostic category of impaired fasting glucose was also found to be far from an equivalent to impaired glucose tolerance based on 2-h glucose[8]. Similar findings were reported from population-based studies from other parts of the world[10,11]. These findings prompted the DECODE Study Group to examine the relationship between glucose tolerance and mortality, in particular cardiovascular mortality, comparing fasting and 2-h glucose criteria for impaired glucose homeostasis in those study populations on which prospective follow-up data were available[12,13]. In subjects without previously diagnosed diabetes, the risk of death from all-cause, cardiovascular and coronary heart disease was found to be significantly increased in subjects with impaired glucose tolerance and newly diagnosed diabetes defined by 2-h glucose criteria, which was independent of the level of fasting glucose[13]. In contrast, the predictive value of fasting glucose largely depended on the level of 2-h glucose. After adjustment for 2-h glucose, only all-cause mortality was significantly increased in subjects with newly diagnosed diabetes by fasting glucose criteria. The impaired fasting glucose category did not incur an increased risk of death compared with the subjects with a normal fasting glucose concentration[13].

In this report we extend the observations of the DECODE study on the predictive value of 2-h glucose vs fasting glucose with regard to the prediction of the risk of serious coronary heart disease events (coronary heart disease death or non-fatal myocardial infarction) based on five Finnish DECODE study cohorts.

Populations and methods

The study includes five Finnish DECODE study cohorts. These cohorts were originally recruited for prospective studies on cardiovascular diseases and their risk factors. Participants in the Helsinki Policemen Study[14] and in the Vantaa Study[15] were from the greater Helsinki area and were recruited in 1966–67 and 1990, respectively. Individuals participating in the FINMONICA study[16,17], a part of the WHO MONICA project in Finland[18], were drawn from the national population register of three geographic areas of Finland (two provinces in eastern Finland and an area in south-western Finland) in 1987 and 1992, respectively. Men from the East and West Finland Study were first recruited in 1959 in connection with the Seven Countries Study[19] and the survivors were given a standard oral glucose tolerance test at the follow-up examination in 1989 that was considered as the baseline in the current analysis[20].

Standard 2-h 75-g oral glucose tolerance tests were administrated to all five cohorts according to the World Health Organization 1985 recommendations[2]. Fasting and 2-h post-load glucose concentrations were determined from plasma samples of participants in the FIN-MONICA 1992 cohort, in the East and West Finland Study and in the Vantaa Study and from whole blood samples in the FIN-MONICA 1987 cohort and the Helsinki Policemen Study. Before the data were analysed, whole blood glucose concentrations were converted to plasma glucose concentrations using the following equation:

$$[\text{plasma glucose (mmol} \cdot l^{-1}) = 0{\cdot}558 + 1{\cdot}119 * \text{whole blood glucose (mmol} \cdot l^{-1})].$$

The equation is based on 294 paired samples of whole blood and plasma glucose concentrations drawn in the Diabetes and Genetic Epidemiology Unit, National Public Health Institute in Finland from a standard 75 g oral glucose tolerance test in 74 individuals at 0, 30, 60 and 120 min. The relationships between glucose concentrations as measured by the different methods used were estimated using a mixed model with random effects of individuals and samples in the Steno Diabetes Centre in Denmark (J.Tuomilehto, B. Carstensen personal communication).

Subjects who had a clinical diagnosis of diabetes before screening were classified as having known diabetes and the data for them were analysed separately. Classification of subjects who had not been diagnosed as diabetic previously was made according to the criteria given in the 1999 Report of a World Health Organization Consultation[6]. On the basis of 2-h plasma glucose alone, individuals were classified into categories of newly

Table 1 Demographic characteristics of subjects at baseline and the number of subjects with incident coronary heart disease and cardiovascular death during follow-up by study cohorts

Study cohort	Number of subjects		Men (%)	Age (years) Mean (SD)	Follow-up (max. years)	Number of subjects with event (%)	
	All	Without prior MI				CHD*	CVD death†
East and West Finland	405	341	100	76 (4·5)	9	72 (21·1)	103 (25·4)
Vantaa	606	572	45	65 (0·4)	9	38 (6·6)	30 (5·0)
Helsinki Policemen Study	1136	1071	100	45 (8·0)	10	50 (4·7)	46 (4·0)
FINMONICA 1992	1918	1862	46	54 (6·0)	7	53 (2·8)	31 (1·6)
FINMONICA 1987	2701	2607	47	54 (5·7)	10	167 (6·4)	119 (4·4)
Total	6766	6453	58	55 (9·5)	10	380 (5·9)	329 (4·9)

CHD=coronary heart disease; CVD=cardiovascular disease; MI=myocardial infarction.
*Among subjects without prior MI.
†Among all subjects.

diagnosed diabetes, impaired glucose tolerance and normal glucose tolerance if their 2-h plasma glucose concentrations were $\geq$11·1, 7·8–11·0 and <7·8 mmol . l^{-1}, respectively. On the basis of fasting plasma glucose alone, individuals were classified into categories of newly diagnosed diabetes, impaired fasting glucose and normal fasting glucose, using cut-off levels of $\geq$7·0, 6·1–6·9 and <6·1 mmol . l^{-1}, respectively.

A total of 6766 subjects (3950 men and 2816 women) aged 30–89 years for whom baseline fasting and 2-h glucose values, as well as measurements of blood pressure, body mass index, serum cholesterol, and information on smoking status were available, were included in the data analysis. The number of participants and the characteristics of these subjects at the time of glucose measurement are presented in Table 1, stratified by the cohort. Of the 6766 subjects, 6453 did not have a history of prior myocardial infarction at baseline. The duration of follow-up was truncated at 10 years to assure comparability between cohorts. The mean duration of follow-up was 8·0 years, with more than 55 000 person-years of follow-up accumulated.

Data on fatal and non-fatal events were collected for all the participants until the end of 1993 in the Helsinki Policemen Study. In the other four cohorts, the follow-up ended at the end of 1997 for fatal events and at the end of 1998 for non-fatal events. Data on events of interest were obtained by computerized record linkage of the unique national ID-numbers of the survey participants to the national Cause-of-Death Register (Statistics Finland) and the national Hospital Discharge Register. Thus the follow-up was complete with no loss. The International Classification of Diseases (ICD), 9th revision (10th revision), was used for the classification of either fatal or non-fatal events: ICD codes 410–414 (I20–I25) for fatal coronary heart disease; 410–411 (I21–I22, I24) for non-fatal acute myocardial infarction; and 401–448 (I10–I79) for all fatal cardiovascular events. The incident coronary heart disease category comprised coronary heart disease death or non-fatal myocardial infarction. Subjects with previous myocardial infarction at baseline were excluded from the calculations of the incidence of coronary heart disease events.

Statistical analysis

SPSS for Windows 10 was used for all statistical analyses. The hazards ratios for coronary heart disease incidence and cardiovascular mortality were estimated using Cox proportional hazards model for each of the five cohorts, adjusted for age, sex, body mass index, systolic blood pressure, cholesterol and smoking status coded as non-smoker, ex-smoker and current smoker. In order to ensure more symmetrical distributions, fasting and 2-h plasma glucose concentrations were logarithmically transformed and used in the models as a continuous variable. The individual β-coefficient, the natural logarithm of the hazards ratio, of each individual Cox model was then combined into an overall β-coefficient by a fixed effects approach according to the method detailed by Fleiss[21]. A fixed rather than a random effects approach was chosen because the statistic Q for measuring study-to-study variations in effect size was not statistically different from zero[21]. The individual and the overall β-coefficients corresponding to a 10% increase in plasma glucose (mmol . l^{-1}) and the 95% confidence intervals are reported. To make the results concerning fasting and 2-h glucose comparable, standardized analyses were made based on a pooled database of the five cohorts. The standardization was performed by calculating hazard ratios for one standard deviation increment in natural-log-transformed fasting and 2-h glucose values.

Cumulative survival curves were estimated for eight glucose categories classified according to both the fasting and the 2-h glucose criteria, based on the combined database. The estimation was performed using Cox proportional hazards model adjusted for age, sex, cohorts, body mass index, systolic blood pressure, cholesterol and smoking status. A Wald test was used to assess whether there was a trend in changes in the risk of events, by coding the eight glucose categories linearly. The same analysis was also made for three glucose categories defined by fasting or 2-h glucose criteria alone.

A chi-squared log-likelihood ratio test was performed to test whether the predictive effect of fasting glucose depended on the levels of 2-h glucose or vice versa.

Results

The number of subjects and the number of events during the first 10-year follow-up for each cohort are presented in Table 1. The crude 10-year incidence rate of coronary heart disease in the whole study population was 5·9% and the crude 10-year cardiovascular mortality rate 4·9%. Subjects with isolated post-load hyperglycaemia (impaired glucose tolerance or newly diagnosed diabetes) were older than those with isolated fasting hyperglycaemia (impaired fasting glucose or newly diagnosed diabetes) (Table 2). The mean body mass index, blood pressure and cholesterol concentrations in diabetic subjects diagnosed by fasting glucose criteria alone did not differ from those in diabetic subjects diagnosed by the 2-h glucose criteria alone. However, subjects with impaired glucose tolerance but normal fasting glucose had higher cholesterol levels than subjects with impaired fasting glucose but normal 2-h glucose.

The individual β-coefficients for each individual cohort corresponding to relative risk increase associated with a 10% increase in 2-h and fasting plasma glucose ($mmol \cdot l^{-1}$) are shown in Fig. 1. The variation of β-coefficients between cohorts was smaller for 2-h glucose, with narrower overall confidence intervals, than for fasting glucose. The statistic for measuring study-to-study variations in effect size showed that the studies were homogeneous, with Q values varying from 5·8 to 6·9, 4 df, all P-values >0·10. There was no statistically significant evidence against pooling the data. The overall β-coefficients for the incidence of coronary heart disease and cardiovascular mortality increased linearly and significantly with increasing 2-h glucose concentration, whereas the overall β-coefficient for the incidence of coronary heart disease with increasing fasting glucose was not significant.

Standardized analyses showed that the hazards ratio corresponding to one standard deviation increase in natural-log-transformed 2-h glucose was 1·17 (95% CI 1·05–1·30) for coronary heart disease incidence and 1·22 (1·09–1·37) for cardiovascular mortality. Corresponding to one standard deviation increase in natural-log-transformed fasting glucose the respective hazard ratios were 1·05 (0·94–1·17) and 1·13 (1·01–1·25).

Multivariate Cox proportional hazards analyses, based on the combined data of the five cohorts, showed that previously diagnosed diabetic subjects had worse survival profiles for coronary heart disease incidence and for cardiovascular mortality than those observed in newly diagnosed diabetic subjects (Fig. 2). Subjects with newly diagnosed diabetes who qualified for this category with both fasting and 2-h glucose criteria had survival profiles between that for subjects with known diabetes and that for subjects with newly diagnosed diabetes by either fasting or 2-h criterion alone. In subjects with impaired glucose tolerance based on 2-h glucose only, the survival profiles for the incidence of coronary heart disease event was worse than and the survival profiles for cardiovascular death and similar to those in subjects with newly diagnosed diabetes by fasting or 2-h criterion alone. Survival in individuals with impaired fasting glucose was apparently better than in individuals with diabetes or impaired glucose tolerance and close to that in normoglycaemic subjects. The trend tests showed that the decrease in survival over the eight lines was statistically significant for both coronary heart disease incidence and cardiovascular mortality ($P<0·001$).

Among subjects without previously diagnosed diabetes, the trends for the increase in the risk of events over the three 2-h glucose categories — normal glucose tolerance, impaired glucose tolerance and newly diagnosed diabetes — were statistically significant ($P=0·001$ for coronary heart disease incidence and $P<0·001$ for cardiovascular mortality) (Fig. 3). For the three fasting glucose categories (normal, impaired fasting glucose and newly diagnosed diabetes) a positive trend was observed only for cardiovascular mortality ($P=0·01$) but not for coronary heart disease incidence ($P=0·68$). Overall, the cumulative survival curves were better separated among the three 2-h glucose categories than among the three fasting glucose categories, indicating that the former classification provided a better discrimination for cardiovascular mortality and morbidity. Comparing nested models, inclusion of the fasting glucose classes did not significantly improve the prediction of the model based on 2-h glucose alone ($\chi^2=2·46$ for coronary heart disease incidence and $\chi^2=2·20$ for cardiovascular mortality, 2 df, both P-values >0·10). In contrast, the addition of the 2-h classes to the fasting glucose classes significantly improved the prediction ($\chi^2=11·39$ for coronary heart disease incidence and $\chi^2=8·86$ for cardiovascular mortality, 2 df, $P<0·005$ and $P<0·025$, respectively).

Discussion

Our study, based on 7–10 years of follow-up of five Finnish population- or occupation-based cohorts, demonstrated that in subjects without previous myocardial infarction 2-h post-load glucose in an oral glucose tolerance test was a stronger predictor of the risk of serious coronary heart disease events (coronary heart disease death or non-fatal myocardial infarction) than fasting glucose. This became evident when standardized hazard ratios for increments in fasting and 2-h glucose concentrations were calculated. Furthermore, when data on subjects without previously diagnosed diabetes was analysed by glycaemic categories defined on the basis of fasting or 2-h glucose concentrations according to the criteria given in the 1999 Report of a World Health Organization Consultation[6], a statistically significant trend in the incidence of coronary heart disease was observed for 2-h glucose categories (normal glucose tolerance, impaired glucose tolerance, newly diagnosed diabetes), whereas the respective trend for fasting glucose categories (normal fasting glucose, impaired fasting glucose, newly diagnosed diabetes) failed to reach significance. The finding that the inclusion of 2-h glucose to the model based on fasting glucose categories

Table 2 Baseline characteristics of the whole study population according to the fasting and 2-h plasma glucose categories

Fasting plasma glucose(mmol . l^{-1}) 2-h plasma glucose (mmol . l^{-1})	<6·1 <7·8 Normal	6·1–6·9 <7·8 IFG&NGT*	<6·1 7·8–11·0 NFG&IGT*	6·1–6·9 7·8–11·0 IFG&IGT	≥7·0 <11·1 New diabetes†	<7·0 ≥11·1 New diabetes†	≥7·0 ≥11·1 New diabetes	Known diabetes	*P*-value*	*P*-value†
No. of subjects (%)	4667 (69)	663 (9·8)	636 (9·4)	211 (3·1)	108 (1·6)	109 (1·6)	57 (0·8)	315 (4·7)		
Age (years)	54 (0·1)	49 (0·4)	59 (0·4)	59 (0·6)	55 (0·9)	61 (0·9)	63 (1·2)	61 (0·5)	<0·001	<0·001
Body mass index (kg . m^{-2})	26·7 (0·06)	27·6 (0·16)	28·1 (0·16)	29·3 (0·27)	29·5 (0·38)	29·2 (0·38)	30·9 (0·53)	29·7 (0·23)	0·13	0·75
Blood pressure (mmHg)										
Systolic	144 (0·3)	148 (0·8)	149 (0·8)	152 (1·4)	152 (1·9)	155 (1·9)	150 (2·6)	150 (1·1)	0·62	0·36
Diastolic	86 (0·2)	87 (0·4)	88 (0·4)	89 (0·8)	92 (1·1)	89 (1·1)	87 (1·5)	87 (0·6)	0·83	0·18
Serum cholesterol (mmol . l^{-1})	6·2 (0·02)	6·1 (0·05)	6·3 (0·05)	6·1 (0·08)	6·2 (0·11)	6·2 (0·11)	6·1 (0·16)	6·1 (0·07)	0·01	0·54

Data are given as age- and cohort-standardized means (SEM).
IFG=impaired fasting glucose; IGT=impaired glucose tolerance; NFG=normal fasting glucose; NGT=normal glucose tolerance.
*†The difference between the two groups with the same marks.

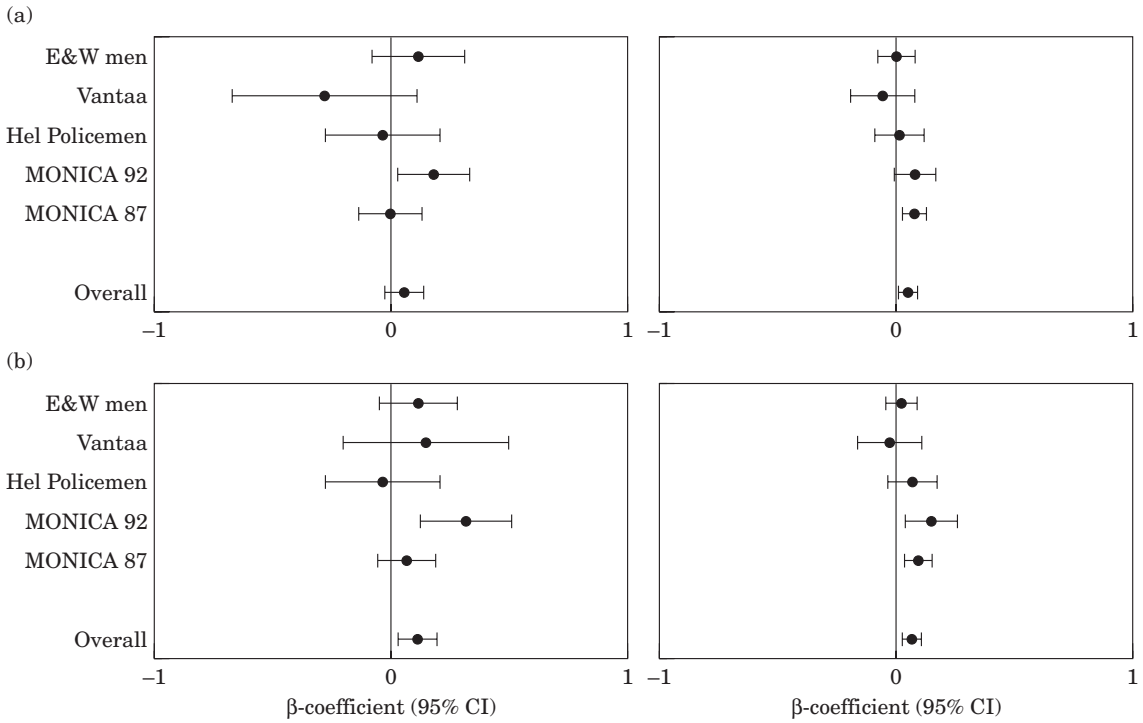

Figure 1 **Individual and overall *β*-coefficients (●) and 95% confidence intervals (——) corresponding to a 10% increase in fasting (left panels) and in 2-h (right panels) plasma glucose concentrations (mmol . l^{-1}) for incidence of coronary heart disease (a) and for cardiovascular mortality (b), adjusted for age, sex, body mass index, systolic blood pressure, cholesterol and smoking.**

significantly improved the prediction suggests that the predictive ability of fasting glucose largely depends on the levels of 2-h glucose.

With regard to cardiovascular mortality, the findings of this study were in accordance with the findings of the DECODE study as a whole[13]; in standardized analyses of fasting and 2-h glucose as continuous variables, as well as in analyses by glycaemic categories, 2-h glucose was a better predictor of the risk of cardiovascular death than fasting glucose. Similar findings have also been reported from population-based prospective studies conducted in the town of Hoorn, the Netherlands[22], and in the area of Funagata, Japan[23]. However, in the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study[24], a prospective cohort study of the adult population of the United States, standardized analyses with regard to cardiovascular mortality gave nearly identical, although statistically non-significant, hazard ratios for one standard deviation increment in fasting and 2-h glucose concentrations.

The 1997 recommendation of the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[5] that in clinical practice the diagnosis of diabetes should be primarily based on fasting glucose determinations was based on the acceptance of the prevailing situation in the United States and worldwide that oral glucose tolerance testing is not widely used for diagnosing diabetes, because many physicians consider that it is unnecessary, and because it is more costly, inconvenient and time-consuming than testing for fasting glucose only. Furthermore, it has been claimed that the measurement reproducibility would be better for fasting glucose than for post-load glucose levels. However, a study on the intra-individual variability of glucose tolerance in an elderly population showed that the reproducibility was not better for fasting glucose than for post-load glucose measurements[25].

If only fasting glucose testing is used in the diagnosis of diabetes and milder degrees of hyperglycaemia, those individuals who have normal fasting glucose but get the diagnosis of diabetes or impaired glucose tolerance on the basis of their 2-h glucose levels will remain undiagnosed. According to the DECODE study[8] and other studies[10,11], using the 1999 World Health Organization criteria[6], these individuals constitute approximately one third of all diabetic subjects, and their proportion appears to increase with increasing age[9]. Furthermore, one third of those subjects who would become classified into the impaired glucose tolerance category on the basis of their 2-h glucose levels have normal fasting glucose[8,10,11]. With regard to the assessment of the risk of mortality and cardiovascular disease events, these discrepancies in the diagnostic classification based on fasting glucose only vs 2-h glucose are of crucial importance. The DECODE study[12] and several other previous studies[23,24,26,27] have already demonstrated that diabetes diagnosis based on 'isolated' elevation of 2-h glucose above the diagnostic threshold for

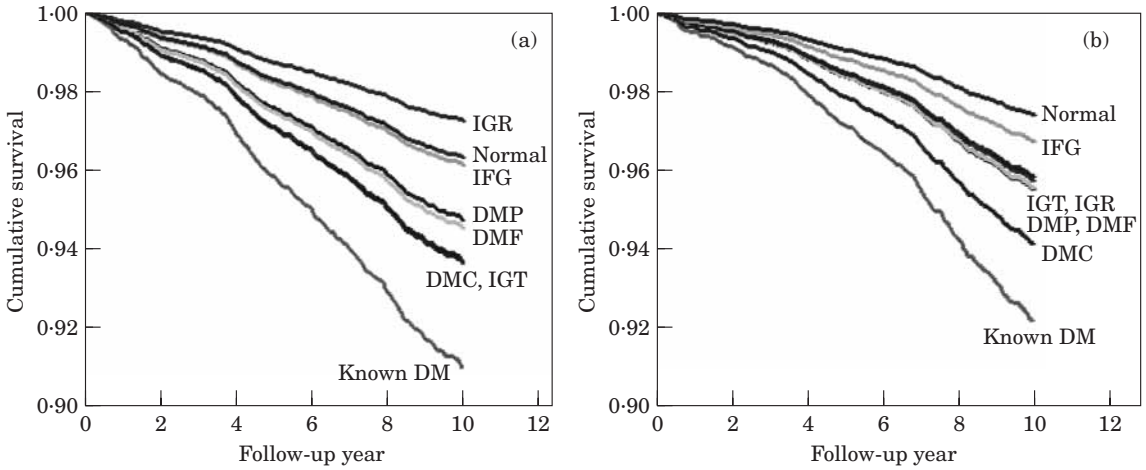

Figure 2 **Cumulative survival curves for incidence of coronary heart disease (a) and for cardiovascular mortality (b) according to the glucose categories defined by both fasting and 2-h plasma glucose criteria. The cumulative survival is estimated from Cox proportional hazards models and adjusted for age, cohorts, sex, body mass index, blood pressure, serum cholesterol and smoking. Normal = fasting plasma glucose $<6{\cdot}1$ mmol . l^{-1} and 2-h plasma glucose $<7{\cdot}8$ mmol . l^{-1}; IFG = impaired fasting glucose only; IGT = impaired glucose tolerance only; IGR = impaired glucose regulation (IFG and IGT); DMF = undiagnosed diabetes by fasting glucose criteria alone (fasting plasma glucose = $\geq 7{\cdot}0$ mmol . l^{-1} and 2 h plasma glucose $<11{\cdot}1$ mmol . l^{-1}); DMP = undiagnosed diabetes by 2-h post-load glucose criteria alone (2 h plasma glucose = $\geq 11{\cdot}1$ mmol . l^{-1} and fasting plasma glucose $<7{\cdot}0$ mmol . l^{-1}); DMC = undiagnosed diabetes by both fasting and 2-h glucose criteria combined (fasting plasma glucose = $\geq 7{\cdot}0$ mmol . l^{-1} and 2-h plasma glucose = $\geq 11{\cdot}1$ mmol . l^{-1}); known DM = previously diagnosed diabetes.**

diabetes ($\geq 11{\cdot}1$ mmol . l^{-1}) is associated with markedly increased risk of mortality from all causes and cardiovascular disease.

In our study population as many as 65% (61/94) of the subjects with newly diagnosed diabetes based on isolated elevation of 2-h glucose (2-h glucose $\geq 11{\cdot}1$ mmol . l^{-1} and fasting glucose $<7{\cdot}0$ mmol . l^{-1}) and 76% (644/845) of the subjects with impaired glucose tolerance were classified as normal according to the fasting glucose criteria. Such individuals could not have been detected if only fasting glucose had been measured, although according to our results they carried as a high risk of cardiovascular disease events as those newly diagnosed diabetic subjects who were detected by the fasting glucose criterion alone. The high risk in newly diagnosed diabetic subjects who obtained their diagnosis on the basis of fasting glucose alone may be in part explained by their 2-h glucose levels which were within impaired glucose tolerance range in two-thirds of them.

Impaired glucose tolerance was the largest glucose abnormality category in our study population, and we found that in subjects with impaired glucose tolerance the risk of cardiovascular disease events was almost as high as in subjects with diabetes. However, we failed to find any significant association between impaired fasting glucose category and the risk of cardiovascular disease events. These findings are in accordance with the findings in the whole DECODE study population[12,13] and the Funagata study[23].

Our study has some limitations. It is a collaborative study combining data from five Finnish cohort studies with baseline examinations at different times over the period from 1966 until 1992 and there were some methodological differences between the studies in the baseline risk factor measurements, including differences in glucose measurements (whole blood or plasma) for which we used a correction equation. It is, however, unlikely that these differences would have had any major influence on the comparison of the predictive values of fasting and 2-h glucose with regard to cardiovascular disease risk. One problem well known in the measurement of fasting glucose in population studies is the difficulty in ensuring that all the participants have complied with the instructions about fasting. Thus, it is possible that due to failure in fasting some participants with completely normal glucose homeostasis may have had falsely elevated fasting glucose levels and been misclassified into impaired fasting glucose category or, more rarely, even into a diabetes category. This may have weakened, to some extent, the association between fasting glucose and the risk of cardiovascular disease. Nevertheless, the excess risk of cardiovascular disease in subjects with impaired glucose tolerance according to their 2-h glucose levels was not confounded by failures in fasting. With regard to the generalizability of our findings, it has to be noted that the study cohorts were from Finland, a country with a high cardiovascular disease rate[28]. The possibility exists that the impact of hyperglycaemia on the risk of cardiovascular disease might become more strongly evident in such a population than in a population with lower cardiovascular disease rate. However, the similarity of the results of

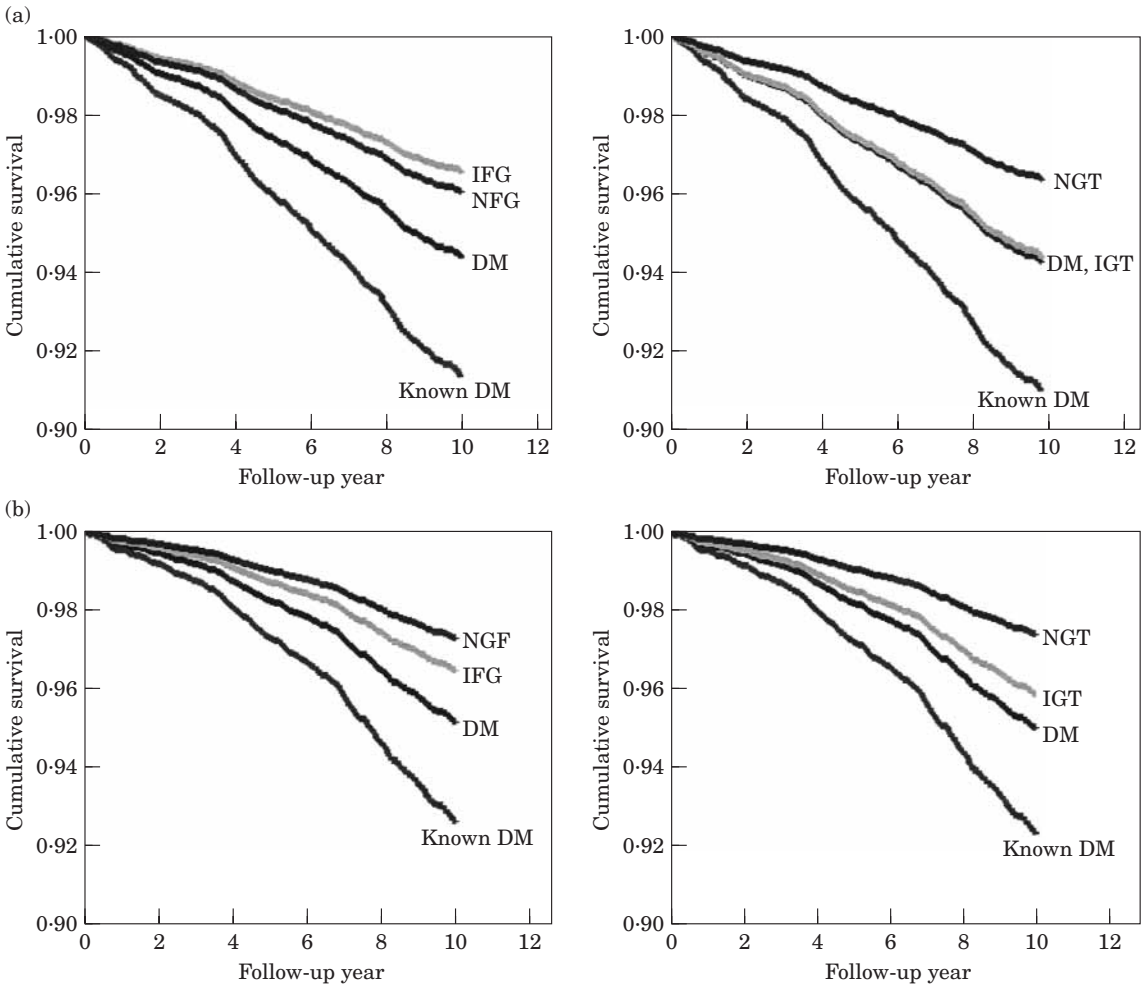

Figure 3 **Cumulative survival curves for incidence of coronary heart disease (a) and for cardiovascular mortality (b) according to the glucose categories defined by fasting (left panel) or 2-h plasma glucose (right panel) criteria alone. The cumulative survival is estimated from Cox proportional hazards models and adjusted for age, cohorts, sex, body mass index, blood pressure, serum cholesterol and smoking. DM=Diabetes; NGT=normal glucose tolerance; NFG=normal fasting glucose; IFG=impaired fasting glucose; IGT=impaired glucose tolerance.**

our study and the Funagata study from Japan[23], a country with a low cardiovascular disease rate, makes this possibility unlikely.

In conclusion, our study demonstrated that in subjects without a prior history of diabetes there is a graded and independent relation between 2-h glucose concentration and incident coronary heart disease events and cardiovascular mortality. Newly diagnosed diabetes and impaired glucose tolerance detected by 2-h glucose criteria were independent risk predictors for these cardiovascular disease events. Newly diagnosed diabetes defined by fasting glucose alone was also associated with an increased risk of these events, but the association between fasting glucose and the risk of cardiovascular disease events depended largely on 2-h glucose levels. Thus, the results of our study indicate that 2-h glucose is superior to fasting glucose measurements in relation to the assessment of the risk of future cardiovascular disease events. Since an oral glucose tolerance test cannot be used in a general screening for cardiovascular risk because of practicalities and costs involved, further research is needed to define the target groups to which it should be applied.

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