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Criteria for previously undiagnosed diabetes and risk of mortality: 15-year follow-up of the Edinburgh Artery Study cohort

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Abstract

Aims To compare risk of all-cause and cardiovascular mortality associated with different criteria for undiagnosed diabetes and glucose tolerance.

Methods A population-based cohort of 758 men and 738 women of 55–74 years of age who had an oral glucose tolerance test or known diabetes at baseline were followed up until death or for 15 years. Mortality outcomes were compared by baseline diabetes status using people with normal glucose tolerance (i.e. those without diabetes, impaired fasting glucose or impaired glucose tolerance) as the reference group.

Results Prevalence of undiagnosed diabetes using World Health Organization (WHO) criteria (fasting glucose of ≥ 7.0 mmol/l and/or a 2-h post-challenge glucose of ≥ 11.1 mmol/l) was 6.6%, of which 81% was associated with fasting glucose ≥ 7.0 mmol/l and 19% was associated with isolated post-challenge hyperglycaemia. Hazard ratios (95% CI) for all-cause mortality adjusted for age and sex were 1.51 (1.09–2.08) for new diabetes by the American Diabetes Association (ADA) criterion (fasting glucose of ≥ 7.0 mmol/l regardless of post-challenge glucose), 1.60 (1.20–2.13) for new diabetes by WHO criteria and 1.98 (1.14–3.44) for isolated post-challenge hyperglycaemia. Hazard ratios (95% CI) for cardiovascular mortality adjusted for age and sex were 1.89 (1.17–3.00), 1.73 (1.12–2.66) and 1.08 (0.34–3.40) for new diabetes by ADA and WHO criteria and for isolated post-challenge hyperglycaemia, respectively.

Conclusions Undiagnosed diabetes was associated with increased risk of all-cause mortality by any criteria but significantly increased cardiovascular disease mortality was only associated with diabetes diagnosed using the fasting glucose criterion. Mortality risks were similar in this population using either ADA or WHO criteria for diagnosis of diabetes.

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Keywords diagnostic criteria, mortality, Type 2 diabetes mellitus

Abbreviations ABPI, ankle brachial pressure index; ADA, American Diabetes Association; BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; WHO, World Health Organization

Introduction

Criteria for the diagnosis of diabetes in epidemiological studies are based upon the glucose level at which risk of complications increases. The levels set by the World Health Organization expert group (WHO) in 1980 were based on fasting and 2-h

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glucose levels after a 75-g glucose tolerance test (OGTT) above which risk of microvascular complications increases [1]. A modification was introduced in 1985 in which the criteria were set at either a fasting glucose level of 7.8 mmol/l and/or a glucose level 2 h after an OGTT of 11.1 mmol/l [2]. In 1997 the American Diabetes Association (ADA) introduced criteria for the diagnosis of diabetes in epidemiological studies based on data solely on fasting glucose using a cut-point of 7.0 mmol regardless of post-load glucose concentrations [3]. A category of impaired fasting glucose was defined for fasting glucose levels of between 6.1 and 6.99 mmol/l inclusive. A fasting glucose of 7.0 mmol/l provides a level that corresponds approximately in diagnostic significance in terms of increased risk of microvascular disease to the 2-h post-load glucose concentration of 11.1 mmol/l [4]. The WHO criteria were modified again in 1999 to incorporate this cut-point for fasting glucose, with the recommendation that an OGTT should be performed and that the 2-h glucose cutpoint of 11.1 mmol/l should continue to be used to identify people with diabetes [4]. WHO criteria include a category of impaired glucose tolerance defined as a fasting glucose level of below 7 mmol/l and a 2-h glucose level of 7.8–11.09 mmol/l. The clinical diagnosis of diabetes in an asymptomatic individual should not be based upon a single abnormal glucose value and repeat measurements should be undertaken in such individuals.

Many studies have compared the prevalence of previously undiagnosed diabetes using the different criteria and the findings differ in different populations, depending to some extent on the distribution of age, sex and body mass index in the study population [5]. Most studies find that the ADA criterion underestimates the prevalence of undiagnosed diabetes compared with WHO 1985 criteria. Fewer studies have compared prevalence of diabetes by the ADA and WHO 1999 criteria. The latter criteria will inevitably identify a larger number of people with diabetes as they include a group with isolated post-challenge hyperglycaemia, i.e. a fasting level below 7.0 mmol/l but a 2-h level ≥ 11.1 mmol/l that are not identified by the fasting criterion.

The risks of mortality and morbidity associated with different criteria for diagnosis of diabetes have been examined in several studies [6–10]. Concerns have been raised that people with diabetes associated with isolated post-challenge hyperglycaemia will not be identified and offered appropriate treatment when the fasting glucose criterion alone is used. The aim of this study was to examine subsequent risk of mortality from all causes, cardiovascular disease and non-cardiovascular disease, including cancers associated with the different criteria for previously undiagnosed diabetes in a UK population.

Subjects and methods

The Edinburgh Artery Study recruited 809 men and 783 women aged 55–74 years in 1988/9 from a general northern European white population sample. Full details of recruitment, data collection at baseline, methods of follow-up and definitions of outcomes have been described previously [11,12]. In summary, the sample population was selected at random in 5-year age bands from 11 general practices, reflecting a range of socio-geographical factors across the city of Edinburgh to provide a population-based sample. The response rate was 65% and respondents appear to have been representative of the wider population—a random sample of 20% of the non-responders did not detect substantial bias [11]. Baseline data were collected during participants' attendance at a university clinic using a combination of questionnaire and examination data, using validated approaches where possible. Complete mortality follow-up was enabled by using flagging at the Information and Statistics Division of NHS Scotland (which also provides notification of emigration, although this was not applicable to this study population) in addition to notification of deaths by general practitioners and family members. Follow-up was undertaken until the date of death or until the end of April 2003. The study was approved by the Lothian Health Board Ethics Committee, and informed consent was obtained from each participant.

Participants completed a self-administered questionnaire at baseline which included the World Health Organization angina and intermittent claudication questionnaires [13]. Height and weight were measured using standard methods and body mass index (BMI) was calculated by dividing weight (in kg) by height (in metres) squared. Participants were asked to indicate whether they had received a diagnosis of diabetes from a doctor. Systolic blood pressure (SBP) was measured in the right arm in the supine position after 10 min rest using a random zero sphygmomanometer. Ankle systolic blood pressures at the posterior tibial artery were measured where possible in both legs using a random zero sphygmomanometer and a Doppler probe. Ankle brachial pressure index (ABPI) was calculated as ankle divided by brachial systolic blood pressures. If the index differed between legs, the lower one was used in the analysis.

A fasting blood sample was collected from the ante-cubital vein using a tourniquet while the subject was recumbent. Glucose, total cholesterol, high-density lipoprotein cholesterol (HDL) and triglycerides were measured using a Cobas Bio analyser (Roche Products, Welwyn Garden City, UK) and standard kits. Participants received an OGTT in the form of 75 g of glucose in 335 ml of Solripe Gluctoza Health Drink (Strathmore Mineral Water Co., Forfar, UK) and a further blood specimen was collected 2 h later for measurement of glucose using the same method as for the fasting sample. Blood samples for analysis of glucose levels were put into fluoride oxalate tubes, were inverted several times, put on a roller for 2 min and then centrifuged for 10 min at 4°C and 1700 g. For each sample, the plasma was then pipetted into a small plastic tube labelled with the subject number, G1 or G2 as appropriate, and kept on ice until analysed.

Previously undiagnosed diabetes was identified on the basis of no known history of diabetes mellitus and the following glucose criteria:

1. a fasting glucose of ≥ 7.0 mmol/l regardless of 2-h post-challenge glucose (ADA criterion);
2. isolated 2-h post-challenge glucose of ≥ 11.1 mmol/l;
3. the combination of a fasting glucose of ≥ 7.0 mmol/l and/or a 2-h post-challenge glucose of ≥ 11.1 mmol/l (WHO criteria).

Criteria used to define cardiovascular outcomes were adapted from international diagnostic criteria developed by the American Heart Association [14] and have been described in detail

elsewhere [12]. In brief, cardiovascular death was defined as post-mortem evidence of acute myocardial infarction, cerebral infarction or haemorrhage, or from death certificates with an underlying cause of death in the range of codes for cardiovascular disease from the ninth (codes 410–414, 430–438, 440–445) and tenth (I21-25, I60-73) revisions of the International Classification of Diseases. Cancer deaths were defined from death certificates with an underlying cause of death in the range of codes reflecting the malignant neoplasm sections from the ninth (codes 140–208) and tenth (C codes) revisions of the International Classification of Diseases.

Analysis was performed using Stata software (Stata Corp., College Station, TX, USA). One-way analysis of variance was used to examine differences in normally distributed continuous variables between categories of glucose tolerance. The chi squared test (or Fisher's exact test, where appropriate) were used to examine associations between two categorical variables. Geometric means and transformed confidence intervals are presented for triglyceride levels which were positively skewed. Hazard ratios for all-cause and cardiovascular disease mortality were estimated using Cox's proportional hazards model for different categories of glucose tolerance with adjustment for age and sex in a basic model and with adjustment for major cardiovascular disease risk factors in the full model. The comparison group was the group with normal glucose tolerance at baseline (i.e. without known or new diabetes, impaired fasting glucose or impaired glucose tolerance).

Results

Prevalence of known diabetes at baseline based on report of doctor-diagnosed diabetes was 2.7% and the 41 people in this category did not receive an OGTT. Of these, eight people reported insulin use and 16 reported taking tablets for diabetes. A further 55 people had missing data for fasting or 2-h glucose and were excluded from further analysis. The subjects for this analysis were therefore 783 men and 754 women (including 25 men and 16 women known to have diabetes).

The prevalence of previously undiagnosed diabetes based on a fasting plasma glucose of ≥ 7.0 mmol/l was 5.3%. Over one-third of people in this category (38%) also had a post-challenge glucose of ≥ 11.1 mmol/l. The prevalence of isolated post-challenge hyperglycaemia was 1.3%, giving a prevalence of previously undiagnosed diabetes by WHO 1999 criteria of 6.6%. Prevalence of impaired fasting glucose alone was 11.6%, prevalence of impaired glucose tolerance was 8.1%, and 3.2% of participants had both impaired fasting glucose and impaired glucose tolerance.

The baseline characteristics of the subpopulations of people by categories of glucose tolerance are summarized in Table 1. People with isolated post-challenge hyperglycaemia formed the oldest subgroup and people with impaired fasting glucose alone had the lowest mean age. Men were more likely to have known diabetes, new diabetes diagnosed using the fasting criterion and impaired fasting glucose alone than women. The highest mean BMI and triglyceride levels together with the lowest HDL levels were recorded among people with new diabetes associated with both fasting and post-challenge hyperglycaemia. The highest mean systolic blood pressures were recorded among people with post-challenge hyperglycaemia. People with known diabetes had the lowest ankle-brachial pressure index and were more likely to have a history of previous vascular disease than other groups.

Among the subgroup of people with newly diagnosed diabetes, the proportion with isolated post-challenge hyperglycaemia (i.e. those who would be missed if only the fasting criterion was used) was 19% overall (15% in men and 27% in women, $P = 0.2$ for sex difference using Fisher's exact test). Isolated post-challenge hyperglycaemia was more common among the subgroup of people with newly diagnosed diabetes who were not overweight (BMI < 25 kg/m^2) than among the overweight (BMI ≥ 25 kg/m^2) group (40 vs. 12%, $P = 0.006$ using Fisher's exact test).

During the follow-up period (mean 12.6 years, median 15 years), there were 589 deaths from all causes (41% of which were due to cardiovascular disease). There were 23 deaths (74% due to cardiovascular disease) among people with known diabetes, 23 deaths (57% due to cardiovascular disease) among people with newly diagnosed diabetes based on isolated fasting hyperglycaemia, 13 deaths (23% due to cardiovascular disease) among people with isolated post-challenge hyperglycaemia, 18 deaths (23% due to cardiovascular disease) among people with combined fasting and post-challenge hyperglycaemia, 87 deaths (44% due to cardiovascular disease) among people with impaired fasting glucose, and 51 deaths (43% due to cardiovascular disease) among people with impaired glucose tolerance and normal fasting glucose ($P = 0.03$ for χ^2 test comparing proportions of deaths due to cardiovascular disease, including people with normal glucose tolerance). All-cause mortality was highest among the group with isolated post-challenge hyperglycaemia at baseline largely as a result of non-cardiovascular disease mortality. Cardiovascular disease mortality was highest among people with known diabetes and was higher among people with new diabetes based on the fasting criterion (either in isolation or in combination with post-challenge hyperglycaemia) than among people with normal glucose tolerance at baseline.

A similar pattern was observed when data for a composite end-point of cardiovascular disease mortality and morbidity (cardiovascular death, myocardial infarction, stroke, intermittent claudication and coronary revascularization) were examined (data available from authors). A higher proportion of cardiovascular events were fatal in the groups with known diabetes and fasting hyperglycaemia (53 and 48%, respectively) than among the groups with normal glucose tolerance, isolated post-challenge hyperglycaemia, impaired fasting glucose alone, impaired glucose tolerance alone and combined impaired fasting glucose and impaired glucoset tolerance (31, 27, 28, 31 and 32%, respectively, $P = 0.06$).

Hazard ratios for all-cause and cardiovascular mortality for different diabetes categories compared with the normal glucose tolerance category adjusted for age and sex and for

Table 1 Characteristics of participants without diabetes, with diabetes defined by the fasting criterion and with diabetes diagnosed by isolated post-challenge hyperglycaemia

Variable	Normal glucose tolerance	Known diabetes	New diabetes (isolated fasting criterion)	New diabetes (isolated post-challenge hyperglycaemia)	New diabetes (combined fasting and post-challenge hyperglycaemia)	Impaired fasting glucose (IGF) alone	Impaired glucose tolerance (IGT) alone	IFG and IGT	*P**
n	1045	41	49	19	30	178	124	51	
Mean age (years)	64.6 [0.18]	66.0 [0.91]	65.9 [0.83]	66.8 [1.33]	65.7 [0.94]	63.9 [0.37]	66.5 [0.53]	65.8 [0.81]	< 0.001
Men (%)	49 [507]	61 [25]	69 [34]	47 [9]	60 [18]	62 [110]	42 [52]	55 [28]	0.001
BMI (kg/m^2)	25.0 [0.1]	27.1 [0.8]	28.3 [0.7]	26.2 [1.3]	28.9 [0.7]	26.4 [0.3]	26.9 [0.4]	27.2 [0.5]	< 0.001
Current smokers (%)	28 [283]	32 [12]	23 [11]	32 [6]	21 [6]	23 [40]	16 [19]	16 [8]	0.03
Systolic blood pressure (mmHg)	141 [0.7]	153 [4.8]	155 [3.5]	161 [6.6]	160 [4.1]	145 [1.7]	150 [2.2]	157 [3.5]	< 0.001
Total cholesterol (mmol/l)	7.00 [0.04]	6.78 [0.23]	7.00 [0.19]	7.23 [0.39]	6.92 [0.24]	6.93 [0.11]	7.23 [0.13]	7.17 [0.19]	0.48
HDL cholesterol (mmol/l)	1.47 [0.01]	1.27 [0.07]	1.37 [0.06]	1.50 [0.14]	1.20 [0.09]	1.42 [0.03]	1.39 [0.03]	1.37 [0.05]	< 0.001
Geometric mean triglyceride (mmol/l)	1.33 [1.30–1.37]	1.75 [1.45–2.12]	1.71 [1.53–1.91]	1.78 [1.36–2.29]	2.26 [1.83–2.79]	1.46 [1.3–1.56]	1.55 [1.43–1.69]	1.66 [1.49–1.84]	< 0.001
History of myocardial infarction, angina, stroke or intermittent claudication at baseline (%)	9.0 [94]	34.2 [14]	14.3 [7]	15.8 [3]	13.3 [4]	9.6 [17]	14.5 [18]	9.8 [5]	< 0.001
Ankle-brachial pressure index	1.04 [0.005]	0.91 [0.04]	1.00 [0.03]	1.06 [0.07]	0.99 [0.03]	1.04 [0.01]	1.03 [0.01]	1.03 [0.02]	< 0.001

Standard errors for means, numerators for percentages and transformed 95% confidence intervals for triglyceride are given in square brackets.
**P*-values refer to chi squared tests for categorical variables described using percentages and one-way analysis of variance for continuous variables described using means.

Table 2 Adjusted hazard ratios for all cause and cardiovascular disease (CV) mortality by glucose tolerance category

	Hazard ratios (95% confidence interval)							
	Known diabetes	Isolated fasting hyperglycaemia	Isolated post-challenge hyperglycaemia	Combined fasting and post-challenge hyperglycaemia	ADA criteria for new diabetes	Impaired fasting glucose	WHO criteria for new diabetes	Impaired glucose tolerance
All-cause mortality	1.75	1.24	1.98	2.07	1.51	1.14	1.60	1.15
Model 1*	(1.15–2.67)	(0.81–1.89)	(1.14–3.44)	(1.29–3.32)	(1.09–2.08)	(0.90–1.45)	(1.20–2.13)	(0.89–1.48)
CV mortality	3.13	1.70	1.08	2.29	1.89	1.09	1.73	1.17
Model 1*	(1.89–5.19)	(0.96–3.01)	(0.34–3.40)	(1.12–4.66)	(1.17–3.00)	(0.74–1.60)	(1.12–2.66)	(0.79–1.75)
CV mortality	2.04	1.36	1.00	1.72	1.49	1.06	1.39	1.14
Model 2**	(1.16–3.59)	(0.75–2.44)	(0.32–3.13)	(0.79–3.72)	(0.90–2.39)	(0.72–1.57)	(0.88–2.20)	(0.75–1.72)

*Model 1: adjusted for age and sex, **Model 2: adjusted for age, sex, hypertension (systolic blood pressure ≥ 140 mmHg), total:HDL cholesterol ratio (≥ 5), triglycerides (≥ 1.7 mmol/l), current smoking, baseline cardiovascular disease.

cardiovascular mortality adjusted for age, sex and major cardiovascular risk factors are given in Table 2. Previously undiagnosed diabetes was associated with significantly increased risk of all-cause mortality by any criteria. A statistically significant excess of cardiovascular mortality was found for diabetes diagnosed using the fasting criterion (with or without the post-challenge criterion) but isolated post-challenge hyperglycaemia was not associated with a significantly increased risk of cardiovascular disease. The excess risk of all-cause and cardiovascular disease mortality associated with previously undiagnosed diabetes was similar using either ADA or WHO criteria for diagnosis of diabetes.

Discussion

In a late middle-aged white Scottish population in 1988/9, the total prevalence of diabetes was 9.2%, of which the majority was undiagnosed (66% by ADA criteria and 71% by WHO 1999 criteria). A large proportion of previously unidentified diabetes was diagnosed on the basis of an elevated fasting glucose level and only 19% was associated with isolated post-challenge hyperglycaemia. New diabetes diagnosed by any criteria was associated with increased all-cause mortality compared with people without diabetes at baseline and the excess risk was similar to that of people with known diabetes. A statistically significant excess of cardiovascular mortality was found among people with known diabetes and people with new diabetes defined by either ADA or WHO criteria, but not among people with isolated post-challenge hyperglycaemia. Isolated post-challenge hyperglycaemia was associated with significantly increased risk of non-cardiovascular disease mortality. Possible explanations for these findings are discussed below and include the limited power of the study. If these findings are confirmed, it would suggest that a post-challenge glucose measurement in people with normal fasting glucose values may not usefully contribute in identifying people at increased risk of cardiovascular disease mortality in this population.

The proportion of undiagnosed diabetes in the Edinburgh Artery Study is higher than in the Third National Health and Nutrition Examination Survey (approximately 35%) [15] and in several other studies, e.g. Bedford 1962 [16], Manchester 2000 [17], AusDiab [18] and southern Germany [19] (approximately 50%), but is similar to that observed in Europeans in the 1990 Coventry study of 65% [20] and in a recent population study in Denmark of 66% [21]. One explanation for higher prevalence of undiagnosed diabetes would be selection bias. The primary aim of the Edinburgh Artery Study was to investigate the epidemiology of peripheral artery disease and it is possible that individuals at higher risk of diabetes chose to take part in the study.

The proportion of people with new diabetes diagnosed by isolated post-challenge hyperglycaemia also differs between populations, e.g. prevalence of isolated post-challenge hyperglycaemia among people with previously undiagnosed diabetes was 72% among women and 48% among men in the Rancho Bernardo study (aged 50–89 years) [6], 54% in the Third National Health and Nutrition Examination Survey (of men and women aged 70–74 years) [15], 52% in the Cardiovascular Health Study (participants aged 65–100 years [7], 36% in the Third National Health and Nutrition Examination Survey (of men and women aged 45–54 years) [15], 32% in DECODE (6140 Europeans aged 60–79 years) [5] and 23% of Parisian policemen aged 45–54 years [9]. Possible explanations for these differences include the distribution by sex, age, ethnicity and body mass index of the populations studied. Women are more likely to have isolated post-challenge hyperglycaemia than men because women tend to have lower fasting glucose levels than men [22]. Elderly and less obese subjects are more likely to have normal fasting glucose levels but 2-h post-challenge glucose levels that are diagnostic for diabetes than younger populations and overweight subjects [4]. The effects of age and sex on proportion of new diabetes associated with isolated post-challenge hyperglycaemia were not statistically significant in the Edinburgh Artery study population but,

consistent with other findings, people with newly diagnosed diabetes who were not overweight were significantly more likely to have isolated post-challenge hyperglycaemia than people who were overweight.

In the Rancho Bernardo Study, the risk of cardiovascular mortality was increased in women with isolated post-challenge hyperglycaemia [age adjusted hazard ratio (HR) 2.6 and 95% confidence intervals (1.5–4.8)] but not in men [HR 0.7 (0.3–1.6)] [6]. The point estimates for Edinburgh Artery Study participants were similar with odds ratios for cardiovascular mortality of 2.7 (0.6–11.6) for women and 0.8 (0.09–6.7) for men. It is possible that the Edinburgh Artery study lacked the power to demonstrate an excess risk of cardiovascular disease mortality among women with isolated post-challenge hyperglycaemia. All-cause mortality data among people with isolated post-challenge hyperglycaemia were not presented for the Rancho Bernardo study.

Cardiovascular disease (including coronary artery disease, stroke and cardiovascular death) among people with newly diagnosed diabetes diagnosed using either the ADA criterion or the WHO 1985 criteria were compared with a reference group that excluded people with impaired fasting glucose or impaired glucose tolerance (i.e. fasting glucose levels < 6.1 mmol/l and 2-h glucose levels < 7.8 mmol/l) in the Cardiovascular Health Study [7]. The authors concluded that ADA criteria are less predictive than WHO criteria for cardiovascular disease in the elderly. The relative risk (95% confidence intervals) of cardiovascular disease among the isolated post-challenge hyperglycaemia group compared with the reference group in this study was 1.35 (0.93–1.96) after adjustment for sex, age and ethnic group. The comparable estimate for the Edinburgh Artery Study (i.e. odds ratio for isolated post-challenge hyperglycaemia for combined cardiovascular disease mortality and morbidity compared with a group without diabetes, impaired fasting glucose or impaired glucose tolerance adjusted for age and sex) was 0.99 (0.38–2.57).

Shaw *et al.* reported significantly increased risks of cardiovascular disease mortality after adjusting for age, ethnicity, smoking, blood pressure and BMI for both men (hazard ratio 2.3, 95% CI 1.2–4.2) and women (hazard ratio 2.6, 95% CI 1.3–5.1) associated with isolated post-challenge hyperglycaemia in a combined analysis of data from longitudinal studies in Mauritius, Fiji and Nauru [8]. An increased risk of cancer mortality associated with isolated post-challenge hyperglycaemia that was significant only for men did not appear to be due to weight loss as it persisted after adjusting for BMI and after excluding deaths in the first 2 years of follow-up.

In the Paris Prospective Study, men with isolated post-challenge hyperglycaemia were found to have a lower cardiovascular risk profile than those with diabetes diagnosed by fasting hyperglycaemia [9]. After 20 years of follow-up, cancer mortality rates were higher in men with diabetes diagnosed by isolated post-challenge hyperglycaemia than in men with diabetes diagnosed by fasting hyperglycaemia (31 vs. 17%, $P = 0.01$), similar to the data from Edinburgh Artery participants (26 vs. 18%, $P = 0.5$). Other similar findings between the studies for comparison between the isolated post-challenge hyperglycaemia group and the elevated fasting plasma glucose group were a non-significant excess of all cause-mortality (55 vs. 44%, $P = 0.1$ in the Paris study, 63 vs. 51%, $P = 0.3$ in the Edinburgh study) and a non-significant reduction of coronary heart disease mortality (5.8 vs. 11.1%, $P = 0.3$ in the Paris Study, 16 vs. 28%, $P = 0.3$ for cardiovascular death in the Edinburgh study). In the Paris study, a high alcohol intake and significantly higher mortality in alcohol-related causes of death among the isolated post-challenge hyperglycaemia group was believed to account for these findings. The authors concluded that screening for isolated post-challenge hyperglycaemia to reduce cardiovascular risk would not be beneficial if people with isolated post-challenge hyperglycaemia die principally because of cancer.

A further potential explanation for differences in effect of isolated post-challenge hyperglycaemia on risk of cardiovascular disease between populations that warrants further investigation is variation in prevalence of features of the metabolic syndrome. Hyperglycaemia is only one component of the metabolic syndrome and it is possible that the relationship between hyperglycaemia and other features of the syndrome differ between populations. Waist measurements were not recorded for Edinburgh Artery study participants but prevalence of the metabolic syndrome (as defined by 3 or more of fasting plasma glucose ≥ 6.1 mmol/l, triglyceride > 1.7 mmol/l, HDL < 1 mmol/l, systolic BP > 130 mmHg, BMI > 30 kg/m^2) was higher among people with fasting hyperglycaemia (regardless of post-challenge level) than among people with isolated post-challenge hyperglycaemia 71 vs. 47%, $P = 0.05$. It is possible that this difference may contribute to the apparent discrepancy in cardiovascular risk between the two groups in this population. The prevalence of the metabolic syndrome was similar in both men and women (25%) although the distribution of prevalence of metabolic syndrome across the glucose tolerance categories differed by sex ranging from 12.5% in men with normal glucose tolerance and 22% in men with isolated post-challenge hyperglycaemia to 70% in women with isolated post-challenge hyperglycaemia and 100% in women with combined fasting and post-challenge hyperglycaemia

The major strengths of this study are the prospective population-based cohort design and the use of standard measures of exposure and outcome. To our knowledge, it is the first attempt to investigate the relationship between isolated post-challenge hyperglycaemia and mortality in a UK population. Limitations of the study include the fact that the hypotheses tested were not the primary research questions of the study, the small number of outcomes in the isolated post-challenge hyperglycaemia group and the single measurement of glucose tolerance.

In summary, WHO 1999 and ADA criteria for newly diagnosed diabetes were associated with similar levels of excess mortality either from all-causes or from cardiovascular disease in the Edinburgh Artery Study population. There was also a modest excess risk of all-cause mortality associated with

impaired fasting glucose and impaired glucose tolerance. People with isolated post-challenge hyperglycaemia were not at a statistically significant increased risk of cardiovascular disease, but were at significantly increased risk of non-cardiovascular disease mortality. Further research is required to establish the value of screening for isolated post-challenge hyperglycaemia in a variety of populations and to investigate the association between isolated post-challenge hyperglycaemia and other features of the metabolic syndrome.

Competing interests

None declared.

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