ARTICLE

Association of impaired fasting glucose and coronary artery calcification as a marker of subclinical atherosclerosis in a population-based cohort—results of the Heinz Nixdorf Recall Study

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Abstract

Aims/hypothesis Atherosclerosis and cardiovascular diseases are often present at the time of diagnosis of type 2 diabetes mellitus. Whether subclinical atherosclerosis can be detected in the pre-diabetic (borderline fasting hyperglycemia) state is not clear. This study investigated the association of impaired fasting glucose (IFG) and coronary artery calcification (CAC), a marker of subclinical atherosclerosis, among participants without a history of coronary heart disease or manifest diabetes mellitus.

Methods Study participants (aged 45–75 years) of the population-based Heinz Nixdorf Recall Study were categorised into those with normal fasting glucose (glucose <6.1 mmol/l) and those with IFG (glucose ≥6.1 to <7.0 mmol/l), excluding participants with a history of CHD or diabetes mellitus. CAC was assessed by electron-beam computed tomography, and risk factors were assessed by extended interviews, anthropometric measurements and laboratory tests. Various CAC cut-off points were used in multiple logistic and ordinal logistic regression models to estimate ORs and 95% CIs.

Results Of the 2,184 participants, more men had IFG than did women (37% vs 22%). Participants with IFG showed a higher prevalence of CAC >0 (men OR 1.90, 95% CI 1.33–2.70; women 1.63, 1.23–2.15). Risk factor adjustment weakened this association in both sexes (men 1.63, 1.12–1.36; women 1.26, 0.93–1.70). When the age- and sex-specific 75th percentile was used as the cut-off point for CAC, the association further decreased in men (1.10, 0.81–1.50), but became stronger in women (1.41, 1.02–1.94).

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Conclusions/interpretation These data support the hypothesis that CAC is already present in the pre-diabetic state and that IFG has a modest and independent impact on the atherosclerotic process. Biological sex appears to modify the association between IFG and CAC.

Keywords Atherosclerosis · Cardiovascular disease · Coronary artery calcification · Electron-beam computed tomography · Impaired fasting glucose

Abbreviations

CAC	coronary artery calcification
CVD	cardiovascular disease
EBCT	electron-beam computed tomography
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
NFG	normal fasting glucose
POM	proportional odds model

Introduction

Diabetes mellitus is a major risk factor for cardiovascular diseases (CVD) [1]. With the repeatedly predicted worldwide increase of type 2 diabetes mellitus [2] a concomitant increase of CVD might be expected. Diabetes mellitus and CVD are two closely related chronic disease entities. The underlying causes of both diseases, insulin resistance and atherosclerosis, are characterised by a long asymptomatic developmental period, starting early in life.

Since the incidence of CVD apparently does not depend on the duration of diabetes mellitus [3], one may speculate that an impaired glucose homeostasis occurs many years before a clinical diagnosis of diabetes mellitus. The World Health Organization has recently summarised the developments in and the reasoning behind changes in classification to include impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) as states occurring before the diagnosis of diabetes [4].

In a meta-analysis a pooled relative risk for incident diabetes mellitus of 4.7 was found in participants with IFG [5]. However, for non-fatal and fatal CVD among participants with IFG the evidence is less consistent, with relative risks ranging between 1.2 and 1.3 compared with participants with normal fasting glucose (NFG) [6].

Several concepts have been developed to explain the observation of higher CVD risk in participants with elevated fasting blood glucose. Some suggest that hyperglycaemia induces a large number of alterations in vascular tissue that potentially promote atherosclerosis [7]; others support the idea that glucose itself is not directly involved in the pathogenesis of cardiovascular disease but correlates with other risk factors that potentially contribute to macrovascular complication [8].

A number of clinical investigations have shown that coronary artery calcification (CAC) is a valid indicator for subclinical atherosclerosis [9]. Previous studies using non-invasive electron-beam computed tomography (EBCT) as a method for the detection and quantification of CAC have found a higher plaque burden in participants with diabetes mellitus [10–14]. However, uncertainty remains regarding the relationship between IFG and CAC in the general population without diabetes mellitus.

The aim of this study was to investigate the association of IFG with the extent of coronary artery calcification in middle aged men and women without overt coronary artery disease (CAD) or diabetes mellitus. For this purpose, we analysed cross-sectional data of a large ongoing population-based cohort of EBCT-screened participants with NFG or IFG.

Methods

Study population The study base of the ongoing Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcium and Lifestyle) Study are men and women of the general German population living in three adjacent cities of the densely populated Ruhr metropolitan area in Germany. The rationale and design of the study have been described in detail [15]. Briefly, 4,814 participants aged 45–75 years, randomly selected from mandatory lists of residents of Essen, Bochum and Mülheim, were recruited between 2000 and 2003. The baseline response was 56% [16]. The study was approved by the institutional local ethics committees and comprises extended quality management procedures, including a certification according to DIN ISO 9001:2000. Informed consent was obtained from all participants.

Blood analysis Standardised enzymatic methods were used to determine total cholesterol, HDL-cholesterol, LDL-cholesterol and triacylglycerol. Serum for glucose determination was immediately centrifuged at the research centre and analysed enzymatically by the hexokinase method. All analyses were done within 12 h at the central laboratory of the University Hospital of Essen, Germany.

Glucose status NFG was defined as fasting plasma glucose <6.1 mmol/l, IFG as fasting plasma glucose ≥6.1 but <7.0 mmol/l [17]. Fasting was defined as no energy intake for at least 8 h.

CAC CAC was assessed by non-enhanced electron-beam CT scans (C-150 scanner, GE Imatron, San Francisco, CA, USA), as previously described in detail [15]. CAC was defined as a hyperattenuating focus of at least four

contiguous pixels with a CT density ≥130 Hounsfield units. The area of each focus was measured and the CAC score was determined using the methods of Agatston et al. [18].

Risk factor assessment Smoking, medical history and socioeconomic status were assessed by trained personnel with standardised computer-assisted face-to-face interviews. Assessment of current use of medication was performed by asking participants to bring along all medication (including packages) taken in the last 7 days. Blood pressure was measured using an automated oscillometric blood pressure device (HEM-705CP-E, Omron Healthcare Europe, Hoofdorp, the Netherlands) with participants in sitting position, using the mean of the second and third value of three measurements [19]. Body mass index (BMI) was calculated from standardised measurements of height and weight with participants in light underwear without shoes.

Diagnostic conventions A history of manifest coronary artery disease was assessed by self reports of previous events (myocardial infarction and/or revascularisation of coronary arteries including balloon dilatation and coronary bypass surgery). Participants were classified as having diabetes if they reported a history of diagnosis of this disease or intake of glucose-lowering drugs. Antihypertensive therapy included the following classes of drugs or any combination of them: diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, calcium channel blockers, centrally active antihypertensive drugs and hydralazine. Lipid-lowering medication included HMG CoA reductase inhibitors (statins), fibrates, bile acid sequestrants and nicotinic acid derivatives.

Statistical analyses Analyses were performed on a subgroup of the study population with NFG or IFG, excluding participants with a self-reported history of CAD ($n=327$), known and unknown diabetes mellitus ($n=581$), with a fasting state less than 8 h ($n=1,629$) or lacking data for CAC ($n=93$). The final study group consisted of 2,184 (1,200 women, 984 men) study participants. We did not find evidence for differences in the main population characteristics between those participants excluded because of non-fasting status or missing CAC data and those available for analysis. Given extreme sex differences in the distribution of the CAC score, all analyses were conducted separately for men and women.

We categorised CAC scores a priori into four risk groups: minimal (<10), mild (≥10 to <100), moderate (≥100 to <400) and extensive (≥400) atherosclerotic plaque burden [20]. Overweight (BMI ≥25 to <30 kg/m^2) and obesity (BMI ≥30 kg/m^2) were defined according to the WHO conventions [21]. To control for socioeconomic status, education was classified as total years of formal education, classified into ≤10 and >10 years of education.

The crude association between IFG and CAC was visualised by plotting the log$_e$-transformed mean CAC score +1 against the fasting plasma glucose (see Electronic supplementary material [ESM] Fig. 1). Because of the high sample size, we categorised plasma glucose into sex-specific deciles of glucose. We used multiple logistic regression to analyse the association between IFG and CAC. The CAC score as outcome was divided into two groups on the basis of (1) the presence or absence of any CAC (CAC >0) and (2) the age- and sex-specific 75th percentiles, determined by the CAC distribution of all study participants of the Heinz Nixdorf Recall Study not taking any cardiovascular medication [22]. Finally, ordinal logistic regression models were fitted to evaluate the association between an increase in level of CAC score, in order to study associations regardless of where the cut-off point was set for the ordinal outcome [23]. We used the proportional odds model (POM), which can be interpreted as an intermediate approach between a binary cut-off point and a continuous distribution model. The ordinal outcome has four levels according to the CAC risk groups (see above). The special feature of a POM is that the OR of a predictor can be interpreted as a summary of the ORs obtained from separate binary logistic regression models using all possible cut-off points of the ordinary outcome [24]. Whereas a binary logistic regression models a single logit, the POM models several logits. Therefore, since the outcome CAC has four levels (cut-off points), three logits were will be modelled. For a POM to be valid, the assumption that the ORs can be interpreted as a constant across all possible cut-off points of the outcome must be tested (in SAS 9.1 this is called the score test for the proportional odds assumption). Here the proportional odds assumption held true (χ^2 score tests >0.05), so the association between glucose status and CAC could be expressed as a single summary estimate (OR) across all the CAC risk categories. For all regression models, we initially fit a crude model (model 1), expanding the model by adjusting for age (model 2), age and BMI (model 3) and a final model with additional adjustment for smoking, HDL-cholesterol, total cholesterol and blood pressure (model 4). In addition we performed age-stratified analyses using model 4 for each age-group (45–54, 55–64 and 65–75 years). Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Of 2,184 participants 29% ($n=633$) had IFG. Among men a higher prevalence than in women was observed (37% vs 22%). Characteristics of the study population according to the glucose status are shown in Table 1. Participants with IFG were particularly characterised by a higher mean BMI

and waist circumference than those with NFG. Accordingly, more participants with IFG were classified as being obese (BMI ≥30 kg/m^2). In addition the participants with IFG were more likely to be older and hypertensive. Dyslipidaemia, smoking status and use of medications differed between sexes with regard to glucose status.

For both sexes a positive association between fasting plasma glucose levels and CAC can be shown (ESM Fig. 1). The prevalence of NFG and IFG by CAC risk group and age group is presented in Table 2. A higher proportion of men and women with NFG had no or only small amounts of CAC (<10) compared with those with IFG. On the other hand, participants with IFG were more likely to exhibit high amounts of CAC (≥400). However, in the age group 55–64 years as well as in the CAC risk-groups with values

of CAC ≥10 to <100 and ≥10 to <400, this tendency is less pronounced, especially in men.

Results of the logistic regression analyses showed an association between the presence of CAC (>0) in participants with IFG compared with those with NFG (Fig. 1). In men, the crude OR was 1.90 (95% CI 1.33–2.70), in women 1.63 (1.23–2.15). Controlling for CVD risk factors weakened this association among men (1.63, 1.12–2.36) and women (1.26, 0.93–1.70). Stratification by age showed an association between IFG and CAC only in men in the youngest age group (OR 2.76, 1.51–5.04). A similar tendency, with the highest OR in the youngest age group, could be observed in women, but at a lower level (OR 1.36, 0.78–2.39).

Using a cut-off point for CAC above the 75th age- and sex-specific percentile revealed a stronger association

Table 1 Characteristics of the study population according to NFG and IFG

	Women (n=1,200)		Men (n=984)	
	NFG (n=933)	IFG (n=267)	NFG (n=618)	IFG (n=366)
Age (years)	58.9 (7.9)	60.4 (7.7)	58.1 (7.7)	59.6 (7.4)
BMI (kg/m^2)	26.7 (4.4)	29.1 (5.3)	27.5 (3.6)	28.3 (3.5)
BMI classes (kg/m^2), % (n)				
<25	38.7 (359)	22.6 (60)	23.5 (145)	14.5 (53)
25–30	40.3 (374)	38.7 (103)	55.7 (344)	60.9 (223)
≥30	21.0 (1950)	38.7 (103)	20.9 (129)	24.6 (90)
Waist (cm)	85.9 (11.4)	92.5 (12.1)	98.0 (10.1)	100.3 (9.4)
Plasma glucose (mmol/l)	5.46 (0.38)	6.40 (0.24)	5.60 (0.34)	6.43 (0.25)
HbA$_{1c}$ (%)	5.26 (0.50)	5.47 (0.48)	5.32 (0.54)	5.43 (0.53)
Total cholesterol (mmol/l)	5.99 (1.0)	6.12 (1.06)	5.87 (0.98)	6.07 (0.93)
HDL-cholesterol (mmol/l)	1.72 (0.43)	1.62 (0.40)	1.35 (0.34)	1.34 (0.37)
LDL-cholesterol (mmol/l)	3.75 (0.95)	3.91 (0.95)	3.84 (0.93)	3.98 (0.89)
Triacylglycerol (mmol/l), median (Q1;Q3)[b]	1.16 (0.88; 1.60)	1.38 (1.02; 2.01)	1.36 (1.99; 1.94)	1.53 (1.12; 2.14)
Lipid-lowering medication, % (n)	6.7 (61)	11.3 (29)	7.1 (42)	8.3 (29)
Systolic pressure (mmHg)	123.9 (19.4)	131.2 (22.0)	133.9 (18.2)	138.0 (17.9)
Diastolic pressure (mmHg)	77.1 (10.2)	80.5 (10.3)	83.2 (10.3)	84.5 (9.8)
Blood pressure [a], % (n)				
Normal (<120/<80 mmHg)	43.6 (406)	31.1 (83)	18.3 (113)	12.4 (45)
Prehypertension (120–139/80–89 mmHg)	32.9 (307)	31.8 (85)	43.7 (270)	36.8 (134)
Stage 1 (140–159/90–99 mmHg)	18.2 (170)	27.0 (72)	28.3 (175)	39.8 (145)
Stage 2 (≥160/≥100 mmHg)	5.3 (49)	10.1 (27)	9.7 (60)	11.0 (40)
Antihypertensive medication, % (n)	26.6 (241)	39.7 (102)	25.3 (150)	27.9 (98)
Smoking status, % (n)				
Never smoker	55.5 (518)	55.8 (149)	31.0 (204)	29.1 (106)
Ex-smoker	22.1 (206)	23.2 (62)	40.3 (249)	47.1 (172)
Current smoker	22.4 (209)	21.0 (56)	26.7 (165)	23.8 (87)
School years, % (n)				
≤10	62.1 (579)	66.3 (177)	55.3 (341)	58.9 (215)
>10	37.9 (354)	33.7 (90)	44.7 (276)	41.1 (150)
CAC score, median (Q1;Q3)	0 (0; 22.7)	3.1 (0; 46.9)	43.6 (1.5; 178.2)	51.1 (6.4; 234.9)
CAC=0, % (n)	51.3 (479)	39.3 (105)	22.7 (140)	13.4 (49)
CAC>0, % (n)	48.7 (454)	60.7 (162)	77.3 (478)	86.6 (317)

Values are means with standard deviation unless otherwise stated
[a] According to JNC-7 guidelines [46]; given as systolic/diastolic
[b] Q1 and Q3 indicate the first and third quartiles, respectively

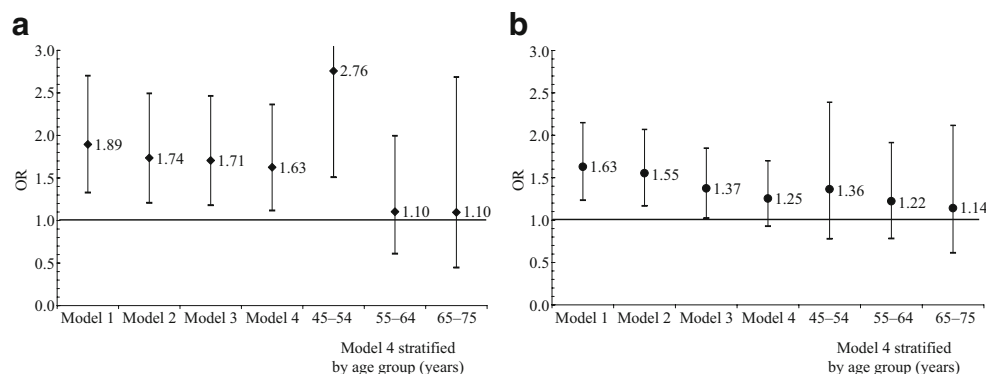**Table 2** Prevalence of NFG and IFG by CAC risk groups, stratified by sex and age-group

Age group (years)		CAC risk groups							
		0 to <10		≥10 to <100		≥100 to <400		≥400	
		n	Percentage	n	Percentage	n	Percentage	n	Percentage
Men									
45–54	NFG	132	54.8	66	27.4	36	14.9	7	2.9
	IFG	49	46.2	37	34.9	13	12.3	7	6.6
55–64	NFG	68	30.2	66	29.3	55	24.4	36	16.0
	IFG	42	27.5	52	34.0	38	24.8	21	14.0
65–75	NFG	29	19.3	45	30.0	43	28.7	33	22.0
	IFG	16	15.0	29	27.1	29	27.1	33	31.0
Women									
45–54	NFG	283	85.2	36	10.8	13	3.9	0	0
	IFG	54	75.0	17	23.6	1	1.4	0	0
55–64	NFG	233	67.5	76	22.0	31	9.1	5	1.4
	IFG	69	59.0	31	26.5	10	8.5	7	6.0
65–75	NFG	129	50.8	58	22.8	39	15.4	28	11.0
	IFG	32	41.1	19	24.4	16	20.5	11	14.0
All									
45–54	NFG	415	72.4	102	17.8	49	8.6	7	1.2
	IFG	103	57.9	54	30.3	14	7.9	7	3.9
55–64	NFG	301	52.8	142	24.9	86	15.1	41	7.2
	IFG	111	41.1	83	30.7	48	17.8	28	10.0
65–75	NFG	158	39.1	103	25.5	82	20.3	61	15.0
	IFG	48	25.9	48	25.9	45	24.3	44	24.0

between CAC and IFG in women than in men (Fig. 2). In men the association attenuated, whereas in women the OR remained elevated even in the fully adjusted model (OR 1.41, 1.02–1.94).

Similar observations were found using a cut-off point independent model (Fig. 3). The POM generated elevated crude proportional odds in men (OR 1.34, 1.06–1.69) and women (OR 1.59, 1.21–2.09). In other words, men with IFG were approximately 30% (women 60%) more likely to be in the higher coronary calcification groups than those participants with NFG. Since the proportional odds assumption is

met, this interpretation holds across the entire range to the CAC risk score groups. However, in the full model the observed associations became weaker among both men and women, with barely any association among men (OR 1.13, 0.89–1.44; women: 1.34, 1.01–1.78).

Adjustments for further potential confounders (i.e. socioeconomic status) did not substantially change these associations. Since we did not perform an OGTT, we were not able to exclude all participants with undiagnosed diabetes mellitus. We performed a sensitivity analysis to estimate the possible influence of these undetected cases. We calculated
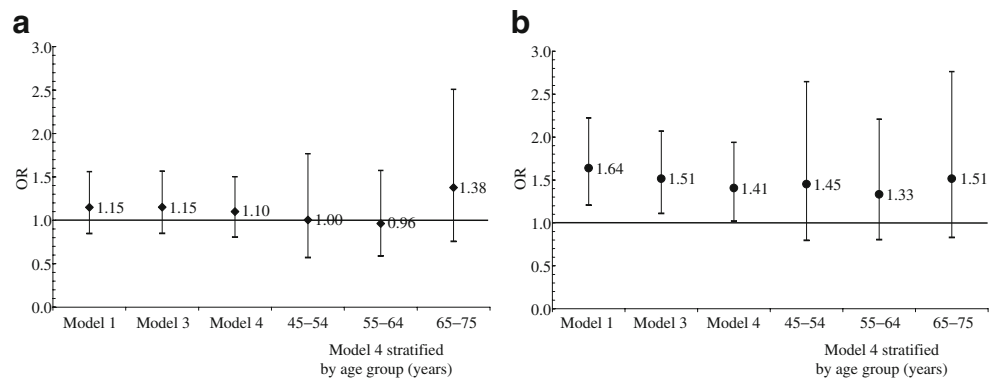

Fig. 1 Crude (model 1) and adjusted ORs for presence of any CAC (CAC >0) for men (**a**) and women (**b**). Vertical lines indicate 95% CI. Adjusted for age (model 2), model 2+BMI (model 3), and model 3+smoking, blood pressure, total cholesterol and HDL-cholesterol (model 4). Analyses were also done separately for age groups: the ORs of the fully adjusted model (model 4) are shown

Fig. 2 Crude (model 1) and adjusted ORs for a CAC score above the age- and sex-specific 75th percentile of the total sample of the Heinz Nixdorf Recall Study for men (**a**) and women (**b**). Vertical lines indicate 95% CI. Adjusted as in Fig. 1 without adjusting for age

the number of undiagnosed diabetes mellitus cases, relying on several assumptions. (1) Since many studies could show a similar diagnostic performance of HbA_{1c} to that of fasting glucose or an OGTT, we used HbA_{1c} measurements of our cohort to define undiagnosed diabetes (although this is not recommended as a test for diabetes). However, since no actual reference value exists and many individuals with IGT may have normal or near normal glycated haemoglobin levels, we additionally used an elevated CAC score as a screening tool for undiagnosed diabetes. In a first step we excluded participants with HbA_{1c} values above the sex-specific means of our subgroup with undiagnosed diabetes (detected by IFG) and recalculated our results. In a second step we excluded participants with additionally elevated CAC scores (above the sex-specific mean). The results of the two approaches did not differ and reduced only marginally our point estimates. (2) Assuming that 30% of people with diabetes are not diagnosed as such if only IFG is used, we conducted a sensitivity analysis excluding a random 30% of the study sample, repeating our analysis three times. With this approach we obtained slightly elevated but still comparable point estimates.
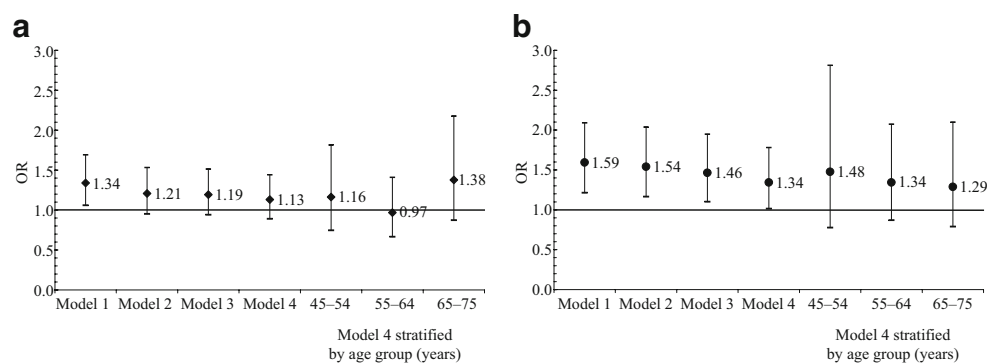
Discussion

Our study shows a positive association between impaired fasting glucose as a sign of a pre-diabetic state (borderline fasting hyperglycemia) and CAC as a marker of subclinical

atherosclerosis in a population-based cohort of middle-aged men and women without overt CVD and diabetes mellitus. Adjustment for potential confounders did not substantially change these associations.

Our study has several strengths. (1) We screened in a large population-based sample for the prevalence and extent of CAC. The CAC score has been shown to correlate with traditional cardiovascular risk factors [25–27] and is strongly related to CHD events [28, 29]. (2) We excluded participants with a history of CVD as well as known and unknown diabetes. (3) The large sample size made it possible to study the association between IFG and CAC separately for men and women, which is especially important given the sex differences in relation to the CAC burden. (4) We conducted a consistent quality assurance with a comprehensive assessment of standard cardiovascular risk factors, lifestyle behaviours and medication use under one protocol from one single assessment centre. (5) Blood samples were prepared immediately and analysed in the same laboratory with the same machine by the same trained staff using the same methodology.

The strengths are balanced by a number of limitations. Although we tried to minimise errors due to pre-analytical and analytical conditions exposure misclassification is unavoidable, bearing in mind the following factors: (1) measurement errors of glucose of at least ±2%; (2) biological variation of about ±5% [30] (these first two factors result in an optimal reference change value [RCV] of 14% [6]); (3) probably incorrect statements of the study participants of

Fig. 3 Crude (model 1) and adjusted ORs of the ordinal logistic regression analysis (POM), using as ordinal categories the CAC risk score groups: minimal (<10), mild (≥10–<100), moderate (≥100–<400) and extensive atherosclerotic calcification (≥400) for men (**a**) and women (**b**). Vertical lines indicate 95% CI. Adjusted as in Fig. 1

their fasting status; (4) the narrow interval of IFG from 6.1 to 6.9 mmol/l; and (5) that we did not measure IGT by an OGTT. This last factor means that we could not distinguish between participants with IFG or IGT, and probably misclassified some participants with unknown diabetes as having NFG or IFG. However, we performed several sensitivity analyses by estimating the number of participants with unknown diabetes (see results). We found only marginally changed point estimates and concluded that the influence of these cases on our results seems negligible.

To our knowledge there are currently only two published studies reporting on glucose metabolism and CAC. The association between high fasting blood glucose in the non-diabetic range and CAC was evaluated in a study of 458 selected non-diabetic Brazilian men without CVD who presented for an obligatory cardiac risk assessment paid for by their employers [31]. Although different glucose and CAC risk categories were used, similar results were reported, demonstrating a relationship between fasting blood glucose and CAC in the non-diabetic range.

In a subsample of the Framingham Offspring Study, the risk for CAC in 325 men and women according to insulin resistance, normal glucose tolerance, impaired glucose tolerance or type 2 diabetes was assessed [32]. The ORs for subclinical atherosclerosis (defined as the upper CAC quartile, ranging from 170 to 3,266) tended to be higher in participants with IFG and/or IGT (fully adjusted OR 1.49; 95% CI 0.65–3.38). Because of their small sample size they could not conduct sex-specific analysis and their results had constrained analytic power. However, our results are in line with their observations, confirming their results in a practical sense.

Most studies that have investigated the impact of an abnormal glucose homeostasis on the risk of subclinical atherosclerosis or CVD have aimed to identify and explain differences in IFG and IGT. Furthermore, the majority of studies investigated atherosclerosis in the peripheral arteries, in particular the carotid intima–media. The results indicate a positive association between IFG/IGT and carotid intima–media thickness [33–35], corresponding to our results. One study investigated in 232 Japanese men the association between IFG and brachial ankle pulse wave velocity, a novel indicator of early stage atherosclerosis [36]. As in our study, IFG was closely related to pulse wave velocity regardless of age, blood pressure or BMI, providing further evidence of an independent association between IFG and atherosclerosis.

It is accepted meanwhile that participants with diabetes mellitus are at high risk of developing CVD and that CVD accounts for a large proportion of the excess mortality related to diabetes mellitus [37]. Less evident is the relationship between elevated blood glucose and the development of atherosclerosis, the underlying cause of CVD. Several studies have shown that CAC is higher in participants with diabetes mellitus than without diabetes mellitus [11–14, 38], suggesting that atherosclerosis already starts in the pre-diabetic state. This is in line with a meta-analysis of 38 prospective studies in which CVD incidence or mortality was predicted by elevated blood glucose levels among participants without diabetes, independently of traditional risk factors [39]. However, other investigators could not find an independent impact of elevated blood glucose on CVD [40–42]. So far, evidence for an involvement of high blood glucose in the pathogenesis of CVD is mixed and possible pathways are still unclear.

We found that the association between IFG and CAC was explained only in part by differences in medication use and CVD risk factors, but was considerably affected by age, sex and the cut-off point of the CAC score. For men a marked elevated OR could be found only when comparing no vs any CAC. When using the age- and sex-specific 75th percentile, the risk-factor-adjusted association between IFG and CAC vanished. Furthermore, stratification by age revealed that an association could be detected only in younger men (aged 45–54 years). This might be explained by the fact that men with no CAC were scarce and most likely to be found in the youngest age-group (age 45–54: 30%, 55–64: 15%, 65–75: 9%). In any case, these data show that the probability of no CAC is higher in those men with normal fasting glucose levels.

Compared with men, a higher proportion of women in every age-group had no CAC (65%, 46%, 32%), and the association between IFG and CAC>0 was less pronounced in women. However, stronger associations could be detected using cut-off points representing higher accumulations of CAC. One explanation for these differences is that women exhibited a considerably lower burden of CAC than men. In addition, other investigators found that more men than women had IFG, whereas women more often had IGT [43–45], reflecting different physiological processes in men and women: IFG reflects the basal fasting state with an impaired insulin secretion, whereas IGT represents post-prandial abnormalities with insulin resistance. In addition there might be a different impact of glucose on atherosclerotic processes in men and women. Results of the Framingham study showed qualitatively different relationships between glucose and mortality in men and women; there was a rapidly rising risk in men through the normal range of blood glucose and a flattening curve thereafter, whereas in women no relationship between the normal glucose range and mortality could be observed but there was a steep risk increase in the impaired glucose range [42]. These results emphasise the need for sex-specific analysis, at least when determining CAC as outcome.

In conclusion, in this subsample of the population-based Heinz Nixdorf Recall Study, men and women with IFG exhibited higher amounts of CAC than those with NFG.

These data provide further evidence that CAC is already present in the pre-diabetic state and that a high normal plasma blood glucose has a modest and independent impact on the atherosclerotic process. The strength of association seems to differ between men and women, and this will be explored further in this ongoing study.

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