Title:

Prediabetes diagnosis is associated with the progression of coronary artery calcification: the Kangbuk Samsung Health Study

Running title: Prediabetes and coronary artery calcification

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ABSTRACT

Aims: The implications of prediabetes diagnosed by isolated glucose versus glycated hemoglobin (HbA1c) on subclinical atherosclerosis are uncertain. We investigated associations between prediabetes defined by different diagnostic criteria and coronary artery calcification (CAC) and its progression over time.

Materials and methods: The cross-sectional study included 146,436 Korean adults without diabetes who underwent CAC estimation computed tomography (CT) during health examinations between 2011 and 2019. We used multinomial logistic regression models. The longitudinal study comprised 41,100 participants with at least one follow-up cardiac CT and annual CAC progression rates and ratios were estimated. Prediabetes was categorized into 3 groups: isolated glucose prediabetes (fasting blood glucose (FBG) 100–125 mg/dl, HbA1c < 5.7%); isolated HbA1c prediabetes (FBG < 100 mg/dl, HbA1c 5.7–6.4%), and prediabetes meeting both FBG and HbA1c criteria (FBG 100–125 mg/dl, HbA1c 5.7%–6.4%).

Results: After adjusting for covariates, the prevalence ratios (95% CI) for CAC score> 100 comparing isolated glucose prediabetes, isolated HbA1c prediabetes, and prediabetes fulfilling both criteria to those of normoglycemia were 1.12 (0.99–1.26), 1.24 (1.11–1.39), and 1.31 (1.18–1.45), respectively. The multivariable-adjusted ratio (CIs) of annual CAC progression rates comparing the corresponding groups to the normoglycemia group were 1.031 (1.023–1.039), 1.025 (1.019–1.032), and 1.054 (1.047–1.062), respectively.

Conclusions: CAC risk and CAC progression were consistently highest in individuals meeting both glucose and HbA1c criteria, while all three prediabetes types showed significantly increased risk of CAC progression. Atherosclerosis risk reduction management is necessary for prediabetes, especially in patients meeting both criteria.

Keywords: prediabetes; hemoglobin A1c; fasting plasma glucose; coronary artery

calcification; subclinical atherosclerosis

People with prediabetes, the intermediate stage between normoglycemia and diabetes, are at a high risk of developing diabetes, and more than 470 million people are projected to have prediabetes by 2030.[1] Prediabetes is also associated with an increased risk of diverse clinical outcomes, including cardiovascular disease (CVD) and all-cause mortality.[2,3] A diagnosis of prediabetes is based on composite criteria of fasting plasma glucose, glycated hemoglobin (HbA1c), and a 2-h glucose tolerance test.[4] However, due to the practical difficulty of an oral glucose tolerance test (OGTT), screening for prediabetes often focuses on HbA1c and fasting blood glucose (FBG) levels, as recommended screening tools by the United Kingdom National Institute for Health and Care Excellence.[5] Furthermore, given that some heterogeneity exists across prediabetes diagnostic criteria, the implications for isolated glucose versus HbA1c hyperglycemia on clinical outcomes are not well established.

Several studies have investigated the associations of different prediabetes definitions based on FBG, HbA1c, and 2-h glucose concentrations with clinical complications, including cardiovascular events and all-cause mortality [3,6]; however, these studies did not focus on whether isolated glucose versus HbA1c prediabetes infers different clinical complications. The pathophysiologic mechanisms and clinical diagnoses of prediabetes or diabetes may differ in individuals diagnosed using HbA1c or fasting glucose measures. Coronary artery calcium scoring estimated by computed tomography (CT) is a reliable predictor of early coronary atherosclerosis,[7,8] as well as future CVD events,[7,9] and is considered a proxy measure of subclinical atherosclerotic burden. To date, there have been no studies on the impact of isolated glucose versus HbA1c hyperglycemia on subclinical atherosclerosis and its progression.

This study aimed to investigate whether subsets of prediabetes, including a) isolated glucose-defined prediabetes, b) isolated HbA1c-defined prediabetes, and c) combined glucose and HbA1c-defined prediabetes, are differently associated with the prevalence of

coronary artery calcification (CAC) and its progression among Korean adults without diabetes who participated in a health screening program.

RESEARCH DESIGN AND METHODS

Study population

The Kangbuk Samsung Health Study (KSHS) is a cohort study of Korean men and women who underwent comprehensive annual or biennial health examinations at the Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea.[10] The study population consisted of a subset of KSHS participants who underwent cardiac CT to measure CAC scores as part of a comprehensive health examination between March 2011 and December 2019 (n = 163,946) (Figure 1). First, for the analysis of the cross-sectional associations between subsets of prediabetes and the prevalence of CAC, we excluded participants who met the following criteria: missing information on glucose and HbA1c levels (n = 21), a history of CVD (n = 2,213), estimated glomerular filtration rate <60 ml/min/1.73 m^2 (n = 730), anemia (defined as hemoglobin <13 g/dl in men and <12 g/dl in women; n = 5,403), or a diagnosis of diabetes (defined as fasting serum glucose ≥126 mg/dl, HbA1c ≥6.5%, a self-report of a previous diagnosis, or use of blood glucose-lowering agents; n = 10,243). Accordingly, the final sample size included 146,436 participants for the cross-sectional study. For the analysis of prospective CAC progression, we excluded 41,100 participants without follow-up visits with cardiac CT.

This study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital (IRB No. 2021-09-046) and was exempted from the requirement for informed consent as we used de-identified data routinely collected as part of health screening examinations for the analyses.

Measurements

Data on demographic characteristics, lifestyle factors, medical history, and family history of CVD were collected using standardized, self-administered questionnaires during the health screening visits.[10] The questionnaire asked about the frequency of alcohol drinking and the amount of alcohol consumed per drinking day, recorded in standard units.[11] Smoking status was categorized as never, former, or current smoker. Physical activity level was measured using the short form of the validated Korean version of the International Physical Activity Questionnaire [12] and classified as inactive, minimally active, or engaging in health-enhancing physical activity (HEPA). HEPA was defined as physical activity meeting either of two criteria: (i) vigorous-intensity activity on three or more days per week accumulating ≥ 1,500 metabolic equivalent (MET) min/week or (ii) seven days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving at least 3,000 MET min/week.[12] Usual dietary intake was assessed using a 106-item self-administered food frequency questionnaire designed and validated for use in Korea.[13]

Blood pressure (BP), height, and weight were measured by trained nurses. Obesity was defined as a BMI of ≥25 kg/m^2 according to the Asian-specific criteria.[14] Hypertension was defined as a systolic BP (SBP) ≥140 mmHg, a diastolic BP ≥90 mmHg, or the use of antihypertensive medications.

Blood tests were performed after at least 10 hours of fasting and included lipid profiles (total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels); alanine aminotransferase, gamma-glutamyl transferase, and high-sensitivity C-reactive protein (hsCRP) levels; and markers of glucose metabolism, including FBG, HbA1c, and serum insulin levels, which we used to calculate the homeostasis model assessment of insulin resistance (HOMA-IR).[15] Serum LDL-C levels were measured directly using a homogenous enzymatic colorimetric assay on a Cobas 8000 c702 (Roche Diagnostics, Tokyo, Japan). The

blood specimen was centrifuged within 30 minutes after blood sampling to determine serum FBG levels. We determined HbA1c levels using the Cobas Integra 800 analyzer (Roche Diagnostics, Basel, Switzerland) based on turbidimetric inhibition immunoassays for hemolyzed whole blood. HbA1c measurements were standardized to the reference method of the Diabetes Control and Complications Trial and the National Glycohemoglobin Standardization Program standards. The intraassay coefficient of variation was 2.3%, and the interassay coefficient of variation was 2.4%, both of which were within the acceptable range of the aforementioned standardization programs.[16] Serum insulin levels were measured on the day of blood collection using an electrochemiluminescence immunoassay with the Modular E170 system (Roche Diagnostics). Prediabetes was defined as an FBG level between 100 and 125 mg/dl or HbA1c between 5.7% and 6.4% [17] based on FGB and HbA1c levels at baseline; prediabetes was further subdivided into three groups: isolated-glucose prediabetes (FBG level 100–125 mg/dl, and HbA1c level < 5.7%), isolated-HbA1c prediabetes (FBG level < 100 mg/dl and HbA1c level 5.7─6.4%), and prediabetes meeting both the FBG and HbA1c criteria. The normoglycemic individuals were set as the reference group, defined as individuals meeting both criteria: FBG level < 100 mg/dl and HbA1c level < 5.7% based on baseline examination.

CAC estimation by multidetector CT

CT was measured with a Lightspeed VCT XTE-64 slice MDCT scanner (GE Healthcare, Chicago, IL, USA) in both the Seoul and Suwon centers using the same standard scanning protocol of 2.5-mm thickness, 400-ms rotation time, 120-kV tube voltage, and 124-mAS (310 mA × 0.4 seconds) tube current under electrocardiogram-gated dose modulation. CAC scores were calculated as previously described by Agatston et al.[18] The interobserver and intraobserver reliabilities for CAC scores were both excellent (intraclass correlation

coefficient of 0.99).[19] CAC scores >300 were considered clinically relevant; however, the number of those with high scores was too small to be examined as a separate category. Thus, CAC scores were categorized as 0, 1–100, and >100 for the analysis.[20]

Statistical analyses

The characteristics of the study participants were summarized according to prediabetes status based on FBG and HbA1c levels at baseline as follows: 1) normoglycemic (reference group, glucose level < 100 mg/dl and HbA1c level < 5.7%), 2) isolated glucose prediabetes (prediabetes meeting only the glucose criteria but not the HbA1c criteria, defined as a glucose level of 100–125 mg/dl and HbA1c level < 5.7%), 3) isolated HbA1c prediabetes (prediabetes meeting only the HbA1c criteria but not the glucose criteria, defined as HbA1c ≥ 5.7% and glucose level < 100 mg/dl), and 4) prediabetes meeting both the glucose and HbA1c criteria (combined prediabetes, defined as glucose of 100–125 mg/dl and HbA1c of 5.7–6.4 %).[4]

For the cross-sectional analysis of the associations between prediabetes subtypes and CAC, we used multinomial logistic regression models to estimate prevalence ratios and 95% CIs for the CAC score groups of 1–100 and >100 points among prediabetes subtypes compared with the normoglycemia group using participants with a CAC score of 0 points as the reference group. The model was first adjusted for age and sex; Model 2 was further adjusted for the center; year of the screening exam; smoking status; alcohol intake; physical activity level; education level; total energy intake; family history of CVD; dyslipidemia medication; BMI; LDL-C, HDL-C, and triglyceride levels; and SBP. To evaluate the association between prediabetes subtypes and CAC as a continuous variable, we also used a Tobit regression model for natural log(CAC score + 1) with Huber–White estimation of standard errors [21,22]. For example, a CAC ratio of 1.50 was interpreted as a 50% increase in

the CAC score for a specific category compared to the reference category. In another sensitivity analysis, we used a logistic regression model to estimate the odds ratios (OR) with 95% CIs for the prevalence of CAC in comparisons between the prediabetes subtypes and the normoglycemic group.

For the longitudinal cohort analysis to estimate the progression of CAC scores over time in the exposure subgroup, we used linear mixed models with random intercepts and slopes with adjustment for potential confounders. Analyses were performed after the transformation of CAC scores to $\log_e(CAC+1)$ because the CAC score was right-skewed. Then, we estimated the ratio of the annual progression rates of CAC scores (with 95% CIs), comparing each prediabetes subgroup category with the reference group (normal group). These analyses of CAC progression were performed in all participants and then separately in those with CAC scores of zero and CAC>0 at baseline. Since participants in the longitudinal analyses had to have at least two visits, we used inverse probability weights to correct for potential selection bias between participants with a single CAC measurement and those with two or more CAC measurements. Inverse probability weights were obtained from a logistic regression model that included all participants with at least one CAC measurement. Multivariable models were adjusted for smoking status, alcohol intake, physical activity, total energy intake, lipid-lowering medications, BMI, LDL-C, HDL-C, triglyceride levels, and SBP as time-dependent variables and age at baseline, sex, study center, year of screening examination, education level, and family history of CVD as time-fixed variables.

As a sensitivity analysis, we also conducted additional analyses regarding the absolute mean of CAC scores and their progression based on the absolute difference. We estimated the marginally adjusted geometric means at baseline, at 5 years, and the 5-year change in geometric means of CAC scores for each prediabetes subgroup category and compared these estimates to the reference group (normal group). Geometric means were calculated by

averaging the predicted log-transformed (CAC +1) scores across participants and then exponentiating the predicted results

Statistical analyses were performed using STATA version 17.0 (StataCorp LP, College Station, TX, USA). All reported P-values were two-tailed, and comparisons were considered statistically significant at $P < 0.05$.

RESULTS

The mean (standard deviation) age of the study participants was 41.2 (8.5) years, and 75.4% of the participants were men. The numbers (percentages) of the normoglycemia group (glucose level < 100 mg/dl and HbA1c level < 5.7%), isolated glucose prediabetes (glucose level of 100–125 mg/dl and HbA1c level < 5.7%), isolated HbA1c prediabetes (HbA1c level of 5.7–6.4 % and glucose level < 100 mg/dl), and prediabetes meeting both criteria (glucose level of 100–125 mg/dl and HbA1c level of 5.7–6.4 %) were 81,102 (55.4%), 21,239 (14.5%), 24,050 (16.4%), and 20,045 (13.7%), respectively. Compared with the normoglycemia group (Table 1), participants in the prediabetes groups were more likely to be older, men, current smokers, obese, and to use dyslipidemia medication, with higher BP, total cholesterol, LDL-C, triglyceride, hsCRP, and HOMA-IR levels, as well as higher CAC scores. The prediabetes group meeting both glucose and HbA1c criteria was the oldest and showed the highest prevalence of current smokers, obesity, and CAC.

In the age- and sex-adjusted multinomial logistic regression models using CAC scores as outcomes categorized as 0, 1–100, and >100 (Table 2), all prediabetes subtypes were significantly associated with both CAC scores 1–100 and >100, with the highest prevalence ratio in the prediabetes group meeting both the glucose and HbA1c criteria. The age- and sex-adjusted prevalence ratios (PRs) (95% CIs) for CAC scores >100 in participants with isolated glucose prediabetes, isolated HbA1c prediabetes, and combined prediabetes compared to

those of normoglycemia were 1.38 (1.23–1.55), 1.47 (1.32–1.63), and 1.90 (1.72–2.09), respectively. Conversely, after further adjustments for potential confounders (multivariable-adjusted model), the association of isolated glucose diabetes with CAC scores was attenuated and no longer significant, while the other prediabetes subtypes showed a significant association with CAC in a dose-response manner. The multivariable-adjusted PR (95% CI) for CAC scores 1–100 in participants with isolated glucose prediabetes, isolated HbA1c prediabetes, and combined prediabetes compared to normoglycemia were 0.98 (0.93–1.03), 1.06 (1.01–1.12), and 1.07 (1.02–1.13), while corresponding PRs for CAC scores > 100 were 1.12 (0.99–1.26), 1.24 (1.11–1.39), and 1.31 (1.18–1.45), respectively. In the sensitivity analysis, binomial logistic regression models and robust Tobit regression models showed similar results (Supplemental Tables S1 and S2).

Table 3 presents the longitudinal cohort analysis of the associations between prediabetes subtypes and CAC progression. The median follow-up duration was 4.0 years (interquartile range, 2.6–5.7 years). All four groups showed increased CAC progression over time and the annual progression rates of CAC for the normal and prediabetes subgroups relative to their baseline scores were 6.1% (normal group), 9.2% (isolated glucose prediabetes), 8.4% (isolated HbA1c prediabetes), and 11.4% (prediabetes meeting both glucose and HbA1c criteria). The ratio of annual CAC progression rates compared with the normal group was 3.1% higher for isolated-glucose prediabetes, 2.5% higher for isolated-HbA1c prediabetes, and 5.4% higher for prediabetes meeting both glucose and HbA1c criteria (Table 3). Since newly developing coronary calcium and CAC score progression over time may represent different biological phenomena, we stratified the analysis for participants with CAC ≥ 0 at baseline. In patients with CAC scores = 0 at baseline, the absolute annual rates were lower than those with CAC scores > 0 at baseline, and although the relative trends of CAC progression were similar, this pattern was evident in those with CAC scores = 0 at baseline. Similarly, the

adjusted 5-year increases in geometric mean CAC for the prediabetes subgroups compared with those of the normal group were 1.1% higher for isolated-glucose prediabetes, 0.8% higher for isolated-HbA1c prediabetes, and 2.2% higher for prediabetes meeting both glucose and HbA1c criteria (Table 4). We also performed analyses regarding the absolute mean CAC scores and their progression according to the baseline CAC category, including zero-CAC, CAC 1–100, 100–300, and >300 to show the absolute change in CAC (Supplementary table S3). For the presentation of the absolute value of CAC by each CAC category, we present a geometric CAC score at the first follow-up visit since the majority of participants had one additional follow-up CAC. Among participants with at least one follow-up CAC visit, the median frequency of CAC measurements was 2 times (interquartile range: 2–3 times) and the median interval between baseline and the first follow-up CAC measurement was 3.1 years (interquartile range, 2.0–4.6 years). In all CAC strata, prediabetes meeting both glucose and HbA1c criteria showed the highest levels of CAC score at baseline and subsequent visits. The highest increase in absolute CAC score was observed in the strata with a CAC score >300. During the follow-up, overall 29.4 % of prediabetic participants became normoglycemic: 37.4% for participants with isolated glucose prediabetes, 38.2% for participants with isolated HbA1c prediabetes, and 12.5% for participants meeting both glucose and HbA1c prediabetes criteria (Supplementary Table S4). At the first follow-up visit, 13% of participants with concordant prediabetes meeting both glucose and HbA1c criteria became diabetic while 2.6% and 2.8% of those with isolated glucose prediabetes and isolated HbA1c prediabetes became diabetic (Supplementary Table 5). In the sensitivity analysis, after excluding participants who developed incident diabetes during follow-up, the results were similar (Supplemental Table S6).

In analyses by stratifying the group by sex and age (<40, 40-49, and 50 years or older), overall patterns showing the highest CAC score at baseline and subsequent visits were similar

to the main findings (Supplementary Table S7).

DISCUSSION

Our major and novel findings are as follows: 1) the cross-sectional analysis demonstrated an increased risk of subclinical atherosclerosis measured by CAC scores >100 in prediabetes meeting both the combined glucose and HbA1c and isolated HbA1c prediabetes criteria, (but not the isolated glucose prediabetes criteria) and 2) the prospective longitudinal analysis showed that all three prediabetes groups had increased ratios of annual CAC progression rates.

CAC is a well-established indicator of atherosclerosis, incident coronary heart disease, and all-cause mortality in patients with and without diabetes.[23,24] Although not all studies have reported a significant association between prediabetes and CAC scores,[25] most studies have demonstrated an independent association between them,[26-28] consistent with our study results. However, none of these studies have focused on the differences in CAC scores between prediabetes defined by HbA1c and FBG levels.

Although a few studies have investigated CVD risk according to the diagnostic heterogeneity of prediabetes, many studies have concentrated on CVD risk differences between patients with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Both IGT and IFG were strongly associated with CVD and all-cause mortality.[29] Many studies have reported that both IGT and IFG are risk factors for developing clinically significant atherosclerotic CVD and that IGT is a better predictor of macrovascular complications than IFG.[30,31] Although IGT, by definition, can be diagnosed using only an OGTT, some studies have concluded that evaluating only FBG or HbA1c level is not suitable for IGT screening, but that a combination of the two parameters (FBG and HbA1c) improves the sensitivity and specificity and can be used for case finding in clinical research.[32,33] In our study, subjects with prediabetes meeting both the glucose and HbA1c criteria, who may have

both IFG and IGT, consistently had the highest levels of increased subclinical atherosclerosis risk and progression.

While FBG level, which reflects basal dysglycemia, is used to measure IFG, HbA1c level reflects chronic states of basal and postprandial hyperglycemia, some of the earliest presentations of diabetes.[34,35] Thus, there may be differences in CVD risk according to the glycemic measures used to diagnose prediabetes. Indeed, in some previous studies that analyzed the occurrence of CVD following the diagnosis of various types of prediabetes, prediabetes defined by HbA1c level showed a higher correlation with CVD outcomes and mortality than prediabetes defined by glucose levels.[3,6] However, some studies did not prove the differences in CVD risks, according to the glycemic measures used to diagnose prediabetes.[31,36,37] In our cross-sectional study, prediabetes meeting both the glucose and HbA1c criteria along with isolated-HbA1c prediabetes criteria showed statistical significance. However, in the longitudinal study, participants with prediabetes meeting both the glucose and HbA1c criteria, isolated-HbA1c prediabetes criteria, and isolated-glucose prediabetes criteria had significantly increased CAC progression. Although the onset of insulin resistance in skeletal muscle or liver can differ in the early stages of glucose dysregulation, insulin resistance in skeletal muscle and liver together with β-cell failure, referred to as “the triumvirate,” develops over time as glucose dysregulation progresses.[38] Therefore, our results may be explained, at least in part, by the initial differences in postprandial glucose and FBG level regulation and the subsequent deterioration in both postprandial and fasting glucose regulation levels over time, contributing to increased CVD risk.[30]

This study had some limitations. First, because the 2-h glucose concentration was not routinely tested at the Kangbuk Samsung Hospital Health Screening Center, which was used as the data source in this study, this aspect of glucose intolerance among the two characteristics of prediabetes was not included in the analysis. Second, lifestyle factors such

as smoking status and alcohol use were assessed via self-administered structured questionnaires used in health check-up programs in Korea, as part of the National Health Insurance plan. Measurement errors in these variables might introduce some degree of residual confounding, similar to that in most epidemiological studies. Finally, our results were derived from a sample of relatively healthy, young, middle-aged, and educated Koreans who participated in health check-up programs with high health accessibility; therefore, these observations might not be generalizable to other ages and ethnic populations.

In conclusion, our large cross-sectional and longitudinal studies demonstrated that the presence and progression of subclinical atherosclerosis measured by CAC scores increased in the prediabetes stage, and the risk differed according to the diagnostic heterogeneity of prediabetes. The risk of CAC and its progression was consistently highest in individuals who met both the glucose and HbA1c criteria, whereas all three types of prediabetes showed a significantly increased risk of CAC progression. The results suggest that preventing asymptomatic atherosclerosis is necessary for patients with prediabetes defined only by glucose levels as well as for patients with prediabetes defined only by isolated HbA1c levels.

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Author contributions

In Young Choi designed the research concept, conducted and analyzed the data and wrote the manuscript.

Yoosoo Chang designed the research concept, conducted and analyzed the data and revised the manuscript.

Yoosun Cho revised the manuscript.

Jeonggyu Kang revised the manuscript.

Hyun-Suk Jung revised the manuscript.

Sarah H. Wild conducted data interpretation and revised the manuscript.

Christopher D Byrne conducted data interpretation and revised the manuscript.

Seungho Ryu designed the research concept, conducted and analyzed the data and revised the manuscript.

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Table 1. General characteristics of study participants by ADA fasting glucose and HbA1c clinical categories

Characteristics	Overall	Normoglycemia	Prediabetes		
		FBG <100 mg/dl HbA1c <5.7%	Discordance FBG 100–125 mg/dl HbA1c <5.7 %	Discordance FBG <100 mg/dl HbA1c 5.7–6.4 %	Concordance FBG 100–125 mg/dl HbA1c 5.7–6.4 %
Number of participants	146,436	81,102	21,239	24,050	20,045
Age (years)*	41.2 (8.5)	39.7 (7.7)	41.6 (8.2)	43.1 (9.1)	44.8 (9.1)
Male (%)	75.4	71.9	86.2	70.9	83.2
Current smoker (%)	21.9	19.9	24.4	23.0	26.5
Alcohol intake† (%)	25.2	22.2	35.9	20.0	32.2
HEPA (%)	16.4	15.9	18.1	16.0	16.9
Education level‡ (%)	83.2	85.2	82.6	80.4	79.1
Family history of CVD (%)	12.1	11.3	11.5	13.7	13.6
Hypertension (%)	14.7	10.5	20.3	15.4	25.3
Dyslipidemia medication (%)	3.6	2.2	3.2	5.8	7.4
Obesity (%)	38.7	31.2	45.4	42.3	57.7
BMI (kg/m^2)*	24.3 (3.3)	23.7 (3.1)	24.9 (3.1)	24.6 (3.4)	25.9 (3.4)
Systolic BP (mmHg)*	112.4 (12.4)	110.4 (11.9)	116.5 (12.3)	111.7 (12.4)	116.8 (12.2)
Diastolic BP (mmHg)*	72.7 (9.7)	71.1 (9.3)	75.9 (9.8)	72.2 (9.5)	76.3 (9.6)
Glucose (mg/dl)*	95.6 (8.4)	91.1 (5.4)	104.6 (4.5)	92.8 (4.9)	107.3 (6.1)
HbA1c (mg/dl)*	5.5 (0.3)	5.4 (0.2)	5.4 (0.2)	5.8 (0.1)	5.9 (0.2)
eGFR	99.9 (13.2)	101.5 (13.0)	98.9 (13.1)	98.3 (13.3)	96.4 (13.1)
Total cholesterol (mg/dl)*	198.3 (34.1)	194.3 (32.9)	199.1 (33.0)	203.5 (35.2)	207.2 (36.0)
LDL-C (mg/dl)*	130.1 (32.1)	126.5 (31.2)	131.1 (31.1)	134.3 (33.1)	138.2 (33.0)
HDL-C (mg/dl)*	56.0 (14.8)	57.8 (15.1)	55.0 (14.3)	54.3 (14.2)	51.6 (12.9)
Triglycerides (mg/dl)§	109 (76–158)	97 (69–140)	123 (89–177)	113 (79–164)	141 (100–200)
ALT (U/L) §	21 (15–31)	19 (14–28)	23 (17–33)	22 (15–34)	27 (19–40)
hsCRP (mg/L) §	0.5 (0.3–1.0)	0.4 (0.3–0.9)	0.5 (0.3–1.0)	0.6 (0.3–1.2)	0.7 (0.4–1.3)
HOMA-IR §	1.45 (0.97–2.15)	1.25 (0.85–1.79)	1.93 (1.38–2.69)	1.37 (0.91–2.03)	2.15 (1.48–3.11)

CAC score >0 (%)	12.3	8.9	13.9	14.8	21.4
CAC score if > 0	19 (5–62)	16 (4–48)	19 (5–62)	21 (6–70)	25 (6–82)
CAC score category (%)					
Zero	87.7	91.1	86.1	85.2	78.6
1–100	10.2	7.7	11.5	12.1	16.9
101–300	1.4	0.9	1.6	1.9	3.0
>300	0.6	0.3	0.8	0.8	1.5
Total energy intake (kcal/d) [§,‖]	1,429 (1,068–1,825)	1,403 (1,040–1,800)	1,392 (1,038–1,796)	1,511 (1,156–1,902)	1,476 (1,127–1,871)

Data are presented as [*]means (standard deviations), [§]medians (interquartile ranges), or percentages; [†]≥ 20 g of ethanol per day; [‡]≥ college graduate. [‖]among 60,856 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake).

Abbreviations: ADA, American Diabetes Association, ALT, alanine aminotransferase; BP, blood pressure; CAC, coronary artery calcium; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1C, glycated hemoglobin; HEPA, health-enhancing physically active; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein.

Table 2. Prevalence ratios* (95% CI) of coronary artery calcification by ADA fasting glucose and HbA1c clinical categories at baseline (n = 146,436)

Coronary artery calcium score ratios	Normoglycemia FBG <100 mg/dl HbA1c <5.7 %	Prediabetes		
		Discordance FBG 100–125 mg/dl HbA1c <5.7 %	Discordance FBG <100 mg/dl HbA1c 5.7–6.4 %	Concordance FBG 100–125 mg/dl HbA1c 5.7–6.4 %
Total number	81,102	21,239	24,050	20,045
CAC score 1–100				
%	7.7	11.5	12.1	16.9
Age- and sex-adjusted model	1.00 (reference)	1.13 (1.08–1.20)	1.22 (1.16–1.29)	1.42 (1.36–1.49)
Multivariable-adjusted model	1.00 (reference)	0.98 (0.93–1.03)	1.06 (1.01–1.12)	1.07 (1.02–1.13)
CAC score > 100				
%	1.2	2.4	2.7	4.5
Age- and sex-adjusted model	1.00 (reference)	1.38 (1.23–1.55)	1.47 (1.32–1.63)	1.90 (1.72–2.09)
Multivariable-adjusted model	1.00 (reference)	1.12 (0.99–1.26)	1.24 (1.11–1.39)	1.31 (1.18–1.45)

*Estimated from multinomial logistic regression models using CAC scores as outcomes categorized as 0, 1–100, and > 100

The multivariable model was adjusted for age and sex. Model 2: Model 1 plus adjustments for the center; year of screening examination; smoking status; alcohol intake; physical activity level; education level; total energy intake; family history of CVD; dyslipidemia medication; BMI; LDL-C, HDL-C, and triglyceride levels; and SBP at baseline.

Abbreviations: ADA, American Diabetes Association, CAC, coronary artery calcification; CVD, cardiovascular disease; FG, fasting glucose; HbA1C, glycated hemoglobin, SBP, systolic blood pressure

Table 3. Ratios* (95% CI) of annual progress rates of coronary artery calcification by ADA fasting glucose and HbA1c clinical categories at baseline (n = 41,100)

Coronary artery calcification progression	Normoglycemia	Prediabetes		
	FBG <100 mg/dl HbA1c <5.7 %	Discordance FBG 100–125 mg/dl HbA1c <5.7 %	Discordance FBG <100 mg/dl HbA1c 5.7–6.4 %	Concordance FBG 100–125 mg/dl HbA1c 5.7–6.4 %
Overall				
Number	20,355	5,517	8,320	6,908
Annual rates of coronary artery calcification progression	1.061 (1.059–1.064)	1.092 (1.085–1.099)	1.084 (1.078–1.089)	1.114 (1.108–1.121)
Ratio of annual progression rate				
Model 1	1.000 (reference)	1.029 (1.022–1.036)	1.021 (1.015–1.027)	1.050 (1.043–1.057)
Model 2	1.000 (reference)	1.031 (1.023–1.039)	1.025 (1.019–1.032)	1.054 (1.047–1.062)
CAC score = 0 at baseline				
Number	17,523	4,446	6,854	5,309
Annual rates of CAC progression	1.043 (1.040–1.045)	1.066 (1.059–1.073)	1.059 (1.054–1.064)	1.085 (1.078–1.092)
Ratio of annual progression rate				
Model 1	1.000 (reference)	1.022 (1.015–1.030)	1.016 (1.010–1.021)	1.040 (1.033–1.048)
Model 2	1.000 (reference)	1.024 (1.016–1.032)	1.017 (1.011–1.024)	1.042 (1.034–1.050)
CAC score> 0 at baseline				
Number	2,832	1,071	1,466	1,599
Annual rates of coronary artery calcification progression	1.210 (1.198–1.222)	1.230 (1.211–1.249)	1.219 (1.202–1.236)	1.228 (1.214–1.243)
Ratio of annual progression rate				
Model 1	1.000 (reference)	1.017 (0.998–1.036)	1.008 (0.991–1.025)	1.016 (0.999–1.031)
Model 2	1.000 (reference)	1.020 (0.999–1.040)	1.013 (0.996–1.031)	1.022 (1.005–1.039)

*Annual coronary artery calcification progression rates and ratios were estimated from a mixed model with random intercepts and slopes with natural log(CAC + 1) as the outcome and inverse probability weighting

Multivariable Model 1 was adjusted for age at baseline and sex. Model 2 was adjusted for smoking status; alcohol intake; physical activity level; total energy intake; dyslipidemia medication; BMI; LDL-C, HDL-C, and triglyceride levels; and SBP as time-dependent variables and age at baseline, sex, center, year of screening examination, education level, and family history of CVD as time-fixed variables.

ADA, American Diabetes Association, CAC, coronary artery calcium; CVD, cardiovascular disease; FG, fasting glucose; HbA1C, glycated hemoglobin, SBP, systolic blood pressure

Table 4. 5-Year Progression of coronary artery calcification by ADA fasting glucose and HbA1c clinical categories at baseline (n = 41,100)

Estimated CAC score at baseline & 5th year	Normoglycemia	Prediabetes		
		Discordance	Discordance	Concordance
	FBG <100 mg/dl	FBG 100–125 mg/dl	FBG <100 mg/dl	FBG 100–125 mg/dl
	HbA1c <5.7 %	HbA1c <5.7 %	HbA1c 5.7–6.4 %	HbA1c 5.7–6.4 %
Number	20,355	5,517	8,320	6,908
Geometric mean CAC score (95% CI)				
Baseline	0.050 (0.040, 0.059)	0.052 (0.042, 0.062)	0.053 (0.042, 0.063)	0.056 (0.045, 0.068)
Year 5	0.081 (0.065, 0.097)	0.081 (0.065, 0.097)	0.079 (0.064, 0.095)	0.097 (0.077, 0.117)
5-year difference (year 5 – baseline)	0.018 (0.015, 0.022)	0.029 (0.023, 0.036)	0.027 (0.021, 0.032)	0.040 (0.032, 0.049)
Difference in geometric mean CAC scores (95% CI)				
Baseline	0 (reference)	0.002 (0.000, 0.004)	0.003 (0.001, 0.005)	0.007 (0.004, 0.009)
Year 5	0 (reference)	0.013 (0.008, 0.018)	0.011 (0.007, 0.015)	0.029 (0.021, 0.037)
Difference in differences (year 5 – baseline)	0 (reference)	0.011 (0.007, 0.015)	0.008 (0.006, 0.011)	0.022 (0.017, 0.028)

Values in the Table were estimated from a random intercept and random slope mixed model for $\log_e$(CAC +1) with inverse probability weights (see text for details) and adjusted for smoking status; alcohol intake; physical activity level; total energy intake; dyslipidemia medication; BMI; LDL-C, HDL-C, and triglyceride levels; and SBP as time-dependent variables and age at baseline, sex, center, year of screening examination, education level, and family history of CVD as time-fixed variables.

ADA, American Diabetes Association, CAC, coronary artery calcium; CVD, cardiovascular disease; FG, fasting glucose; HbA1C, glycated hemoglobin, SBP, systolic blood pressure

FIGURE LEGEND

Figure 1. Flow chart of study participants

*Some individuals met more than one criterion for exclusion