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Glycemic and metabolic sub-classification of prediabetes and risk factors for cardiovascular disease in the D2d cohort

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ABSTRACT

Objectives: Prediabetes represents a spectrum of metabolic abnormalities, including insulin resistance and secretory impairment, that carries increased cardiovascular disease (CVD) risk. It is unclear whether specific glycemic and metabolic sub-classifications are associated with CVD risk. This cross-sectional analysis of 3946 participants from the Vitamin D and Type 2 Diabetes (D2d) study cohort aimed to determine the associations between various baseline CVD risk factors, glycemic sub-classifications of prediabetes (FPG, 2hPG, and HbA1c), and measures of insulin sensitivity and secretion from an OGTT.

Methods: The metabolic syndrome and atherosclerotic cardiovascular disease (ASCVD) risk scores were determined for tertiles of insulin sensitivity (HOMA2S) and insulinogenic index (IGI). Unadjusted analyses showed elevated CVD risk factors in the lowest tertile for both IGI and HOMA2S.

Results: After adjustment for age, gender, race, obesity, and smoking status, the association remained between HOMA2S and ASCVD score ($r = -0.11$, $p < 0.001$) but not for IGI. Those who met at least 2 diagnosic criteria for prediabetes had the largest proportion (> 40%) of participants with high ASCVD risk score >20. A higher percentage of individuals that met all 3 criteria for prediabetes had metabolic syndrome and ASCVD risk score >20 (87.2% and 15.3%, respectively) than those who only met 1 prediabetes criterion (51.6% and 7.1%, respectively).

Conclusions: In conclusion, multiple metabolic (HOMA2S, IGI) and glycemic criteria of prediabetes (FPG, 2hPG, & HbA1c) are needed to fully recognize the elevated CVD risk profile that can manifest in prediabetes.

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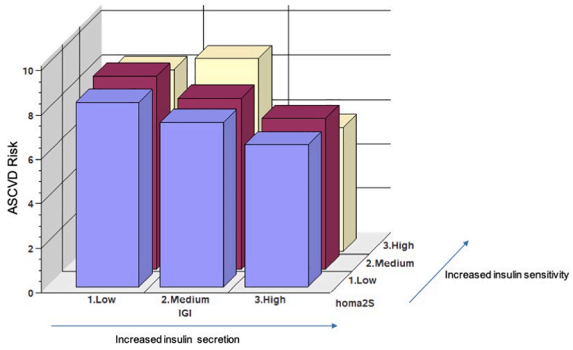
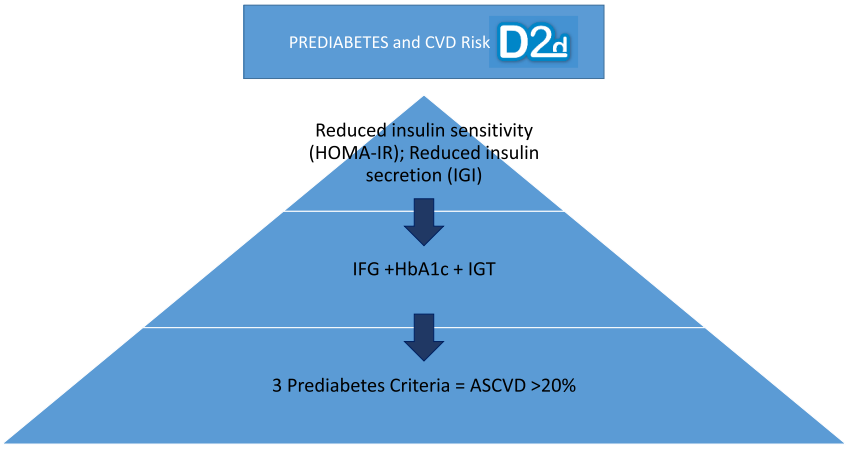


From an anlaysis of covariance model: log(ASCVD) = IGI(tertile) + HOMA2s(tertile), IGI(tertile) p<0.001, HOMA2s(tertile) p=0.64. An exploratory model was tested with the interaction term log(ASCVD) = IGI(tertile) + HOMA2s(tertile) + IGI(tertile)*HOMA2s(tertile) and this interaction was not statistically significant.

Central graph

cellular level, hyperinsulinemia stimulates mitogenic pathways that induce endothelial dysfunction and are atherogenic [16], but clinical data related to the association of hyperinsulinemia in prediabetes with hypertension, hyperlipidemia, and other CVD risk factors are lacking. Therefore, we postulate that not all individuals with prediabetes carry similar CVD risk and, accordingly, sought to define the relationship between potential metabolic subtypes of prediabetes defined by degrees of insulin sensitivity and secretory measures with specific cardiovascular risk factors (e.g. dyslipidemia, hypertension, metabolic syndrome, and obesity) and a CVD risk score.

We performed a cross-sectional analysis using data from the baseline visit of the Vitamin D and Type 2 Diabetes (D2d) study, which enrolled a modern multiethnic cohort at risk for developing T2DM [17]. We hypothesized that participants with prediabetes and insulin hypersecretion (i.e., high insulinogenic index [IGI]) would have greater CVD risk than those without hypersecretion (i.e., low IGI). Similarly, those with reduced insulin sensitivity (lower HOMA2S) would have greater CVD risk than those with greater insulin sensitivity (higher HOMA-S).



Central illustration

Prediabetes is a highly prevalent asymptomatic condition that is underdiagnosed and often overlooked. Worldwide, 472 million people are projected to have prediabetes by 2030 [1] and the prevalence of prediabetes is estimated to be 36.2% among U.S. adults [2]. Prediabetes is an intermediate state between normoglycemia and diabetes mellitus (DM) characterized by early disruption in insulin secretion and impaired insulin action [3–5]. The pathophysiological features of insulin secretion and resistance are variably expressed in adults with prediabetes and manifest clinically as elevated fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG), and/or glycated hemoglobin (HbA1c) levels.

Recent studies have highlighted the association between prediabetes and risk for adverse cardiovascular events including myocardial infarction, stroke, and death [5–10]. Observational studies, like DECODE, Hoorn, DECODA, and the Funagata Diabetes studies, reported that cardiovascular-related mortality in subjects with impaired glucose tolerance (IGT) was similar to individuals with established type 2 diabetes (T2DM) while greater than in subjects with impaired fasting glucose (IFG) [11–14]. While insulin resistance is commonly detected in IGT individuals, the relationship between insulin secretion and cardiovascular disease (CVD) risk factors in individuals with prediabetes is not clear. Indeed, IGT and IFG states do not differentiate impairments in insulin secretion vs. insulin resistance and thus, further phenotyping with specific metabolic indices that calculate these measures are required. Whereas the ACCELERATE trial showed that fasting hyperinsulinemia in T2DM is an independent risk factor for CVD and CVD-related mortality [15], the clinical impact of the degree of impairment in insulin secretion and insulin resistance in prediabetic individuals on various CVD risk factors is not well described. On a

Consequently, we defined metabolic subtypes and diagnostic criteria for prediabetes and identified the cardiovascular disease risk profile (C-reactive protein [CRP] levels, LDL/HDL ratio, systolic blood pressure to diastolic blood pressure ratio [SBP/DBP], albuminuria, metabolic syndrome, and Atherosclerotic Cardiovascular Disease [ASCVD] score) for each subtype and determined the strength of the associations through adjusted multivariate analyses.

1. Methods

1.1. Overview of the D2d study (ClinicalTrials.gov: NCT01942694)

The D2d study is a U.S.-based multicenter, randomized, placebo-controlled, primary prevention clinical trial with 2 groups (oral 4000 IU/day of vitamin D_3 versus placebo) in participants at risk for developing diabetes. Participants were recruited from 22 academic medical centers in the United States (https://d2dstudy.org/sites). The design of and results on the primary outcome of diabetes of D2d has been published previously [17]. The study was approved and monitored by an independent Data and Safety Monitoring Board and the Institutional Review Board of each collaborating clinical site, and all participants provided informed consent.

1.2. Study population

To be eligible for randomization in D2d, participants met 2 out of 3 glycemic criteria for prediabetes established by the American Diabetes Association in 2010[18]. The criteria include: FPG, 100–125 mg/dL

(5.5–6.9 mmol/L); 2hPG after 75-gram glucose load, 140–199 mg/dL (7.7–11.0 mmol/L); HbA1c, 5.7–6.4% (39–46 mmol/mol). In-person screening was performed in 2 steps. At the first screening visit, non-glycemic eligibility criteria (e.g., medical history, laboratory tests for safety) were confirmed and glycemic criteria for prediabetes were preliminarily evaluated by measuring FPG and HbA1c at either the local laboratory or the central laboratory at the University of Vermont. At the second screening visit, a 75-gram oral glucose tolerance test (OGTT) was performed, and FPG, 2hPG, and HbA1c were analyzed by the D2d central laboratory to determine final eligibility. All participants who completed the second screening visit, regardless of study eligibility, were included in this analysis. During the OGTT, fasting, 30-minute, and 120-minute plasma glucose and insulin concentrations were determined [17].

1.3. Calculations

The IGI, derived from an OGTT, has been found to correlate with corresponding indices of the early insulin response to changes in glucose derived from IVGTT [5]. It has been utilized as a measure of β-cell function and is associated with higher degrees of glycemia in different populations and instituted in large multicenter epidemiological and clinical trials [7,8]. Analysis for insulin sensitivity and insulin secretion was performed on data obtained from the screening 2-hour OGTT. Early-phase insulin secretory responses to the glucose challenge were calculated using the insulinogenic index (IGI), which is the ratio between the 0 to 30-min insulin increment and the corresponding glucose increment:

$$IGI = \frac{(Insulin_{30} - Insulin_0)}{(Glucose_{30} - Glucose_0)}$$

Insulin sensitivity (HOMA2S) was calculated using the HOMA2 Calculator version 2.2.3 (Diabetes Trials Unit, University of Oxford, Oxford, U.K.) [19]. The HOMA2 calculator estimates insulin sensitivity from simultaneously measured FPG and fasting plasma insulin values. HOMA2S assesses insulin sensitivity with higher levels conferring greater insulin sensitivity across the diabetes spectrum and is used in epidemiological studies to guage risk for and response to various anti-diabetic interventions. A cardiovascular risk score was determined using the ASCVD risk calculator, which incorporates participant parameters such as age, sex, race, smoking status, cholesterol, and blood pressure into a pooled population risk [20]. Patients were divided into low (< 7.5%), intermediate (7.5–20%), and high (>20%) [21] ASCVD risk groups as these are commonly used clinical thresholds for initiating medication. Metabolic syndrome defined by NCEP ATP III criteria is present if 3 or more of the following 5 criteria are met: waist circumference over 40 inches (men) or 35 inches (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar over 100 mg/dl. The prevalence of metabolic syndrome for diagnostic categories of prediabetes was determined.

1.4. Statistical analysis

The approach in this analysis is based on simple indices of insulin sensitivity and insulin secretion used in epidemiological studies designed to predict diabetes incidence. This included the Pima Indian population and Diabetes Prevention Program Outcomes Study (DPPOS) cohort in which individuals were either normal glucose-tolerant or with prediabetes at baseline [22–24]. In these analyses, the lowest tertile of insulin sensitivity and lowest tertile of insulin secretory capacity had the highest incidence of diabetes, dyslipidemia, and other cardiovascular risk factors. The tertiles are defined using the 33rd and 66th percentiles of the IGI (80 and 136 arbitrary units [au], respectively) and HOMA-2S levels (0.123 and 0.205 au, respectively). The median level of insulin sensitivity was defined by distribution analysis, and tertiles of insulin sensitivity were defined into low, intermediate, and high based on 33rd and 66th percentiles. Each insulin dynamic group was tested for associations with baseline physical, medical, and demographic characteristics (i.e. age, gender, ethnicity, obesity, blood pressure) by Chi-squared test for categorical variables and Student's *t*-test for continuous variables. We used Spearman's rank correlation and partial rank correlation for unadjusted and adjusted measures of associations, respectively. Age, gender, body mass index (BMI), and smoking status were adjusted for as they differed in the tertile analysis. We used F-tests from an analysis of covariance model to assess the statistical signifance of the relationship between natural log transformed ASCVD risk score and IGI and HOMA2S tertile groups respectively. Two-sided *P*-values less than 0.05 were considered statistically significant. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC). No adjustments were made for multiple comparisons.

1.5. Data and resource availability

Datasets generated and analyzed during the current study and the associated data dictionary are not publicly available. Requests for datasets analyzed in the current study can be made after acceptance for publication by bona fide researchers by submitting a research proposal to the D2d Publications Committee for review. Individual participant data will be shared in a de-identified/anonymized format using a specialized SAS data platform. Protocol synopsis, contact details, publications, and the process for collaboration and data requests can be found on the website (d2dstudy.org).

2. Results

In total, 3946 participants were included in the analyses with samples sizes varying for each analysis based on available laboratory data as shown in each table. Table 1 shows the clinical characteristics of participants in the low, intermediate, or high tertile insulinogenic (IGI) status. The lowest IGI tertile was older, with less female predominance, and had a greater proportion of white participants and lower proportions of participants of Black/African-American race and/or Hispanic/Latino ethnicity than the highest IGI tertile. The lowest IGI tertile also had higher FPG, 2hPG, and HbA1c levels and lower BMI and waist circumference compared to the highest IGI tertile, but physical activity was not different. One-third of the lowest IGI group met all 3 criteria for prediabetes as compared to only 16% of the highest IGI tertile. The lowest IGI group had a greater prevalence of arrhythmias and a lower frequency of coronary artery bypass graft/percutaneous coronary intervention and myocardial infarction as compared to the middle and high IGI tertiles, although the prevalence of these conditions was very low. A greater number of participants in the lowest IGI tertile used statins and anti-platelet agents. Liver transaminase levels were highest in the highest IGI tertile but no differences in eGFR were noted across tertile groups. The cholesterol profile of the highest IGI tertile was more atherogenic with greater triglyceride (TG), CRP, and TG/HDL and LDL/HDL ratios versus the lowest IGI group. In contrast, the ASCVD risk score was significantly lower in the highest IGI tertile.

Table 2 shows the clinical characteristics of participants in the low, middle, and high tertile for insulin sensitivity (HOMA2S). The low insulin sensitivity tertile was younger and had a higher proportion of Hispanic/Latino individuals than the high sensitivity group. As expected, waist circumference and BMI were higher and physical activity was lower in the low versus the high insulin sensitivity tertile. CVD and hypertension were notably more common in the lowest insulin sensitivity tertile. Some cardiovascular agents including statins and anti-platelet agents were more commonly used in the high insulin sensitivity group than the low insulin sensitivity group. Fasting insulin, FPG, and 2hPG levels were markedly higher in the lowest insulin sensitivity tertile, as were liver transaminase levels and GFR. As expected, the low

Table 1
Baseline Clinical and Demographic Characteristics by IGI tertile groups.

Clinical Characteristic	N	Lowest IGI tertile group (n = 1047)	Middle IGI tertile group (n = 1048)	Highest IGI tertile group (n = 1047)	Middle vs Low SMD	High vs Low SMD
Age, years	3142	61.2 ± 9.9	59.9 ± 10.0	57.3 ± 10.2	0.12	0.39
Women, no (%)	3142	448 (42.8)	446 (42.6)	518 (49.5)	0	0.13
Primary race*, no (%)	3142					
Black or African-American		155 (14.8)	205 (19.6)	374 (35.7)	0.13	0.5
White		820 (78.3)	739 (70.5)	609 (58.2)	0.18	0.44
Asian		53 (5.1)	69 (6.6)	38 (3.6)	0.07	0.07
Other		19 (1.8)	35 (3.3)	26 (2.5)	0.1	0.05
Hispanic or Latino ethnicity*, no (%)	3142	79 (7.5)	99 (9.4)	123 (11.7)	0.07	0.14
Body mass index, kg/m^2	3142	30.7 ± 4.2	31.8 ± 4.5	33.1 ± 4.5	0.24	0.53
Smoking history, no (%)	3142					
Never		597 (57.0)	601 (57.3)	648 (61.9)	0.01	0.1
Current		73 (7.0)	72 (6.9)	61 (5.8)	0	0.05
Waist circumference, cm	3126	102.9 ± 11.3	104.9 ± 12.0	106.3 ± 12.0	0.17	0.29
Physical activity, total MET hour/week, median (Q1-Q3)	3065	57.7 (27.4–135.5)	59.8 (26.3–123.3)	57.9 (25.7–132.8)	0.03	0
Medical history†, no (%)						
Hypercholesterolemia	3142	555 (53.0)	558 (53.2)	515 (49.2)	0	0.08
Cardiovascular disease	3142	549 (52.4)	561 (53.5)	585 (55.9)	0.02	0.07
Cardiovascular disease excluding self-reported hypertension	3142	125 (11.9)	147 (14.0)	104 (9.9)	0.06	0.06
Hypertension	3142	769 (73.4)	794 (75.8)	812 (77.6)	0.05	0.1
Medication use†, no (%)						
Statin use	3142	328 (31.3)	328 (31.3)	244 (23.3)	0	0.18
Antihypertensive use	3142	369 (35.2)	377 (36.0)	347 (33.1)	0.02	0.04
Laboratory value						
Fasting plasma glucose, mg/dL	3142	110.2 ± 10.8	106.9 ± 9.3	103.8 ± 9.5	0.33	0.62
2-hour post-load plasma glucose, mg/dL	3135	149.8 ± 47.0	137.6 ± 42.5	125.7 ± 38.7	0.27	0.56
Hemoglobin A1c,%	3139	5.9 ± 0.3	5.9 ± 0.3	5.9 ± 0.3	0.11	0.19
Fasting insulin, uU/mL	3142	11.8 ± 8.4	15.6 ± 10.5	20.2 ± 12.5	0.41	0.8
Glycemia categories†, no (%)	3138					
All glycemia values in normal range		57 (5.4)	123 (11.7)	261 (25.0)	0.23	0.57
Met all 3 prediabetes criteria (iA1c + IFG + IGT)		317 (30.3)	265 (25.3)	170 (16.3)	0.11	0.34
iA1c + IFG only		324 (30.9)	361 (34.4)	360 (34.5)	0.07	0.08
At least 1 value in diabetes range		168 (16.0)	97 (9.3)	56 (5.4)	0.21	0.35
HOMA2S						
Mean	3142	88.0 ± 55.4	65.1 ± 41.8	50.7 ± 30.6	0.47	0.83
Median (Q1-Q3)	3142	75.5 (52.1–108.8)	57 (40.6–78.7)	43.2 (31.3–62.3)	0.48	0.86
Insulinogenic index (IGI)§						
Mean	3142	0.4 ± 1.3	1.0 ± 0.2	2.7 ± 2.3	0.69	1.25
Median (Q1-Q3)	3142	0.5 (0.3–0.6)	1 (0.9–1.2)	2.1 (1.7–2.9)	45.76	NA
Cardiometabolic disease risk factors						
ALT	3140	28.5 ± 15.2	30.1 ± 15.1	31.6 ± 17.3	0.11	0.2
AST	3138	25.7 ± 10.3	26.7 ± 10.9	26.8 ± 11.2	0.1	0.11
eGFR	3141	86.9 ± 15.2	86.6 ± 15.1	88.4 ± 16.2	0.02	0.1
Total cholesterol, mg/dL	3140	194.3 ± 42.0	191.3 ± 40.8	195.5 ± 41.5	0.07	0.03
HDL cholesterol, md/dL	3140	50.0 ± 12.3	47.0 ± 11.0	47.5 ± 11.4	0.25	0.21
LDL cholesterol, mg/dL	3140	119.3 ± 34.7	116.6 ± 33.8	121.0 ± 34.9	0.08	0.05
Triglycerides, mg/dL	3140	127.1 ± 76.2	140.9 ± 100.3	136.3 ± 80.4	0.16	0.12
C-reactive protein, mg/L	3140	4.0 ± 5.7	4.2 ± 6.2	5.0 ± 5.9	0.03	0.17
Total/HDL ratio	3140	4.0 ± 1.1	4.2 ± 1.0	4.3 ± 1.2	0.15	0.22
LDL/HDL ratio	3140	2.5 ± 0.9	2.6 ± 0.8	2.7 ± 1.0	0.08	0.19
TG/HDL ratio	3140	2.8 ± 2.2	3.3 ± 3.4	3.2 ± 2.5	0.18	0.15
UACR	3136	10.9 ± 52.2	8.9 ± 32.6	11.7 ± 46.1	0.05	0.02
Systolic blood pressure, mmHg	3141	128.3 ± 14.2	127.4 ± 13.6	127.3 ± 13.4	0.07	0.07
Diastolic blood pressure, mmHg	3141	76.2 ± 9.2	76.7 ± 9.3	77.5 ± 9.5	0.05	0.13
ASCVD score, median (Q1-Q3)	3133	8.4 (4–15.8)	7.9 (3.5–14.4)	6.4 (2.9–11.9)	0.05	0.24

Plus-minus values are means±SD. Percentages may not add up to 100 because of rounding. IFG, impaired fasting glucose defined as fasting plasma glucose 100–125 mg per deciliter (5.6–6.9 mmol per liter); IGT, impaired glucose tolerance defined as 2-hour post-load plasma glucose after a 75-gram glucose load 140–199 mg per deciliter (7.8–11.0 mmol per liter); iA1c, impaired A1c defined as HbA1c 5.7–6.4% (39–47 mmol per mol).

* Race and ethnicity were reported by the participant. The category "other" includes Asian, American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; or other race. Ethnicity includes any race.

† Self-reported.

‡ IFG, impaired fasting glucose defined as fasting plasma glucose 100–125 mg/dL (5.6–6.9 mmol/L); IGT, impaired glucose tolerance defined as 2-hour post-load plasma glucose after a 75-gram glucose load 140–199 mg/dL (7.8–11.0 mmol/L) or); iA1c, impaired A1c defined as HbA1c 5.7–6.4% (39–47 mmol/mol).

§ Insulinogenic index: IGI= (Ins30-Ins0)/(Glu30-Glu0).

insulin sensitivity tertile had the lowest HDL and highest triglyceride levels and elevated CRP as compared to the high insulin sensitivity tertile. No differences in urine albumin-to-creatinine ratio (UACR) were noted across tertile groups.

Table 3 shows the results of the adjusted multivariate correlations between insulin secretion (IGI) and sensitivity (HOMA2S) and individual CVD risk factors and the overall ASCVD risk score. Insulin sensitivity was positively correlated with HDL and negatively correlated with CRP,

Table 2
Baseline Clinical and Demographic Characteristics by HOMA2S tertile groups.

Clinical characteristics	N	Lowest HOMA2S tertile group ($n = 1151$)	Middle HOMA2S tertile group ($n = 1144$)	Highest HOMA2S tertile group ($n = 1150$)	Middle vs Low SMD	High vs Low SMD
Age, years	3445	57.6 ± 10.5	59.8 ± 10.0	61.3 ± 9.8	0.22	0.36
Women, no (%)	3445	498 (43.3)	525 (45.9)	516 (44.9)	0.05	0.03
Primary race*, no (%)	3445					
Black or African-American		299 (26.0)	280 (24.5)	245 (21.3)	0.03	0.11
White		771 (67.0)	782 (68.4)	809 (70.3)	0.03	0.07
Asian		46 (4.0)	51 (4.5)	71 (6.2)	0.02	0.1
Other		35 (3.0)	31 (2.7)	25 (2.2)	0.02	0.05
Hispanic or Latino ethnicity*, no (%)	3445	147 (12.8)	108 (9.4)	77 (6.7)	0.11	0.21
Body mass index, kg/m^2	3445	34.2 ± 4.3	31.8 ± 4.1	29.6 ± 3.8	0.56	1.13
Smoking history, no (%)	3445					
Never		669 (58.1)	691 (60.4)	656 (57.0)	0.05	0.02
Current		84 (7.3)	71 (6.2)	76 (6.6)	0.04	0.03
Waist circumference, cm	3422	110.0 ± 11.6	104.3 ± 10.8	99.7 ± 10.8	0.5	0.92
Physical activity, total MET hour/week, median (IQR)	3356	47.7 (21.1–117.2)	60.5 (27.3–131.1)	64.6 (31.3–146.8)	0.16	0.21
Medical history†, no (%)						
Hypercholesterolemia	3445	582 (50.6)	582 (50.9)	614 (53.4)	0.01	0.06
Cardiovascular disease	3445	694 (60.3)	623 (54.5)	563 (49.0)	0.12	0.23
Cardiovascular disease excluding self-reported hypertension	3445	130 (11.3)	124 (10.8)	164 (14.3)	0.01	0.09
Hypertension	3445	935 (81.2)	879 (76.8)	798 (69.4)	0.11	0.28
Medication use†, no (%)						
Statin use	3445	279 (24.2)	315 (27.5)	339 (29.5)	0.08	0.12
Hypertension medication use	3445	377 (32.8)	378 (33.0)	378 (32.9)	0.01	0
Laboratory						
Fasting plasma glucose, mg/dL	3445	109.3 ± 11.6	106.7 ± 10.0	104.7 ± 9.6	0.25	0.43
2-hour post-load plasma glucose, mg/dL	3438	149.9 ± 47.6	136.9 ± 43.6	127.6 ± 39.6	0.29	0.51
Hemoglobin A1c,%	3442	5.9 ± 0.3	5.9 ± 0.3	5.8 ± 0.2	0.21	0.28
Fasting insulin, uU/mL	3445	27.6 ± 12.8	13.3 ± 1.9	7.3 ± 2.0	1.56	2.22
Glycemia categories‡, no. (%)	3441					
All glycemia values in normal range		152 (13.2)	183 (16.0)	202 (17.6)	0.08	0.12
Met all 3 prediabetes criteria (iA1c + IFG + IGT)		309 (26.9)	265 (23.2)	214 (18.6)	0.09	0.2
iA1c + IFG only		287 (25.0)	345 (30.2)	442 (38.4)	0.12	0.29
At least 1 value in diabetes range		233 (20.3)	112 (9.8)	56 (4.9)	0.3	0.48
HOMA2S						
Mean	3445	31.1 ± 8.6	57.2 ± 7.9	114.0 ± 50.4	3.16	2.29
Median (IQR)	3445	32 (25–38.4)	56.8 (50.3–63.5)	99.1 (83.5–126.8)	27.66	NA
Insulinogenic index (IGI)‡						
Mean	3142	1.8 ± 1.5	1.4 ± 2.3	0.9 ± 1.4	0.2	0.65
Median [IQR]	3142	1.4 (0.9–2.3)	1 (0.6–1.6)	0.7 (0.4–1.1)	0.42	0.9
ALT	3443	35.1 ± 19.0	29.1 ± 15.0	26.0 ± 11.9		
AST	3441	28.1 ± 12.2	25.9 ± 11.0	25.4 ± 9.5	0.35	0.57
eGFR	3444	88.3 ± 16.4	86.7 ± 15.7	86.7 ± 14.4	0.19	0.25
Cardiometabolic disease risk factors					0.1	0.1
Total cholesterol, mg/dL	3443	190.7 ± 40.4	194.1 ± 42.9	196.6 ± 40.3	0.08	0.15
HDL cholesterol, md/dL	3443	44.0 ± 9.9	47.9 ± 10.5	52.9 ± 12.7	0.38	0.77
LDL cholesterol, mg/dL	3443	115.8 ± 33.7	120.0 ± 35.8	121.5 ± 33.2	0.12	0.17
Triglycerides, mg/dL	3443	159.1 ± 111.5	131.6 ± 67.9	111.9 ± 62.1	0.3	0.52
C-reactive protein, mg/L	3442	5.2 ± 5.6	4.4 ± 5.7	3.5 ± 6.1	0.14	0.29
Total/HDL ratio	3443	4.5 ± 1.1	4.2 ± 1.1	3.9 ± 1.0	0.27	0.58
LDL/HDL ratio	3443	2.7 ± 0.9	2.6 ± 0.9	2.4 ± 0.8	0.14	0.37
TG/HDL ratio	3443	4.0 ± 3.7	2.9 ± 1.9	2.3 ± 1.7	0.35	0.57
UACR	3437	11.2 ± 39.1	10.4 ± 53.3	9.6 ± 35.9	0.02	0.04
Systolic blood pressure, mmHg	3444	128.2 ± 13.2	128.2 ± 13.8	127.0 ± 14.0	0	0.09
Diastolic blood pressure, mmHg	3444	77.9 ± 9.2	77.2 ± 9.7	75.6 ± 9.1	0.07	0.26
ASCVD score	3434	6.9 (3–13.2)	7.6 (3.4–14.2)	7.9 (3.9–14.8)	0.08	0.11

Plus-minus values are means±SD. Percentages may not add up to 100 because of rounding. IFG, impaired fasting glucose defined as fasting plasma glucose 100–125 mg per deciliter (5.6–6.9 mmol per liter); IGT, impaired glucose tolerance defined as 2-hour post-load plasma glucose after a 75-gram glucose load 140–199 mg per deciliter (7.8–11.0 mmol per liter); iA1c, impaired A1c defined as HbA1c 5.7–6.4% (39–47 mmol per mol).

* Race and ethnicity were reported by the participant. The category "other" includes Asian, American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; or other race. Ethnicity includes any race.

† Self-reported.

‡ IFG, impaired fasting glucose defined as fasting plasma glucose 100–125 mg/dL (5.6–6.9 mmol/L); IGT, impaired glucose tolerance defined as 2-hour post-load plasma glucose after a 75-gram glucose load 140–199 mg/dL (7.8–11.0 mmol/L) or); iA1c, impaired A1c defined as HbA1c 5.7–6.4% (39–47 mmol/mol).

‡ Insulinogenic index: IGI= (Ins30-Ins0)/(Glu30-Glu0).

Table 3
Correlational analysis of Insulinogenic index and Insulin sensitivity index (HOMA2S) to CVD risk variables.

	Log Insulinogenic index (n = 3128)*				Log Insulin sensitivity index (HOMA2S) (n = 3445) †			
	Spearman correlation	P-value	Partial Spearman correlation[1]	P-value	Spearman correlation	P-value	Partial Spearman correlation[2]	P-value
Total cholesterol, mg/dL	0.013	0.472	−0.010	0.575	0.071	<0.001	0.082	<0.001
HDL cholesterol, md/dL	−0.090	<0.001	−0.079	<0.001	0.328	<0.001	0.282	<0.001
LDL cholesterol, mg/dL	0.019	0.288	−0.022	0.214	0.083	<0.001	0.107	<0.001
Log Triglycerides, mg/dL	0.064	<0.001	0.087	<0.001	−0.294	<0.001	−0.273	<0.001
Log C-reactive protein, mg/L	0.114	<0.001	0.002	0.894	−0.230	<0.001	−0.064	<0.001
Log Total/HDL ratio	0.102	<0.001	0.066	<0.001	−0.263	<0.001	−0.206	<0.001
Log LDL/HDL ratio	0.090	<0.001	0.040	0.025	−0.170	<0.001	−0.112	<0.001
Log TG/HDL ratio	0.084	<0.001	0.097	<0.001	−0.363	<0.001	−0.330	<0.001
Log ALT/AST ratio	0.067	<0.001	0.038	0.034	−0.263	<0.001	−0.237	<0.001
Log UACR	−0.045	0.012	−0.040	0.025	−0.032	0.057	−0.024	0.157
SBP	−0.039	0.03	−0.024	0.177	−0.037	0.029	−0.042	0.013
DBP	0.063	<0.001	0.016	0.361	−0.108	<0.001	−0.064	<0.001
ASCVD score‡	−0.130	<0.001	−0.008	0.659	0.057	<0.001	−0.110	<0.001

* Adjusted for age, gender, BMI, and race. Excludes 830 people without fasting or 30-minute post 75 g glucose or insulin measures and 14 participants with a negative IGI value.
† Adjusted for age, race, BMI, and smoking status. Excludes 527 people without fasting insulin or fasting glucose measures.
‡ 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.
[1] 2013 participants have baseline low ASCVD score, but 7 participants are not categorized into glycemic criteria categories as glycemia measures are incomplete.
[2] 1482 participants have baseline low ASCVD score, but 1 participant is not categorized into a glycemic criteria category as glycemia measures are incomplete.

Table 4
Proportion of Prediabetic Individuals who meet Various Prediabetes Glycemic Definition Groups in Low (<7.5), Intermediate (7.5–20), and High (>20) ASCVD scores.

Glycemic criteria met	Low ASCVD Risk Score <7.5 (total n = 2013)* no, (%)	Intermediate ASCVD Risk Score 7.5–20 (total n = 1482) † no, (%)	High ASCVD Risk Score >20 (total n = 451) no, (%)
All 3 criteria in normal range (n = 662)	432 (21.5)	194 (13.1)	36 (8)
Met-only 1 criteria in prediabetes range (n = 351)	212 (10.6)	114 (7.7)	25 (5.5)
Met 2 prediabetes criteria only (n = 1591)	761 (37.8)	642 (43.3)	188 (41.7)
Met-all 3 prediabetes criteria (iA1c + IFG + IGT) ‡ (n = 867)	380 (18.9)	354 (23.9)	133 (29.5)
At least 1 criteria in diabetes range (n = 467)	221 (11)	177 (12)	69 (15.3)

Each column shown have percentage values that add up to 100%.
IFG, impaired fasting glucose defined as fasting plasma glucose 100–125 mg per deciliter (5.6–6.9 mmol per liter); IGT, impaired glucose tolerance defined as 2-hour post-load plasma glucose after a 75-gram glucose load 140–199 mg per deciliter (7.8–11.0 mmol per liter); iA1c, impaired A1c defined as HbA1c 5.7–6.4% (39–47 mmol per mol).
* 2013 participants have baseline low ASCVD score, but 7 participants are not categorized into glycemic criteria categories as glycemia measures are incomplete.
† 1482 participants have baseline low ASCVD score, but 1 participant is not categorized into a glycemic criteria category as glycemia measures are incomplete.
‡ IFG, impaired fasting glucose defined as fasting plasma glucose 100–125 mg/dL (5.6–6.9 mmol/L); IGT, impaired glucose tolerance defined as 2-hour post-load plasma glucose after a 75-gram glucose load 140–199 mg/dL (7.8–11.0 mmol/L) or); iA1c, impaired A1c defined as HbA1c 5.7–6.4% (39–47 mmol/mol).

Table 5
P-value is from rank-based ANOVA test (i.e. Kruskal-Wallis test).

	ASCVD <5	ASCVD 5.0-<7.5	ASCVD ≥7.5	p-value
N	**1431**	**582**	**1933**	
IGI, n	**1127**	**458**	**1548**	
Mean ± SD	**1.5 ± 2.5**	**1.4 ± 1.4**	**1.2 ± 1.2**	**<0.001**
HOMA, n	**1228**	**499**	**1707**	
Mean ± SD	**65.6 ± 43.7**	**67.2 ± 47.8**	**68.9 ± 46.6**	**0.024**

UACR, and TG/HDL. After adjusting for covariates, insulin sensitivity remained correlated with ASCVD risk ($P < 0.05$). Meanwhile, insulin secretion was linearly correlated with HDL and TG; however, after adjusting for covariates, there was no association between insulin secretion and ASCVD risk.

Table 4 reports the proportion of individuals with prediabetes based on the 3 diagnostic criteria (i.e. IFG, IGT, and HbA1c [18]) stratified by low, intermediate, and high ASCVD risk score (<7.5%, 7.5–20%, and >20%, respectively). Over 40% of subjects with intermediate and high ASCVD score met at least 2 prediabetes criteria. Among those who met all 3 glycemic criteria for prediabetes, there was a trend towards increasing ASCVD risk scores in a graded, stepwise fashion. Notably, 18.9% of patients in the low ASCVD range met all 3 prediabetes criteria, compared to 23.9% of intermediate ASCVD and 29.5% of high ASCVD groups.

Table 5 categorizes IGI and HOMA2S in those with low and intermediate ASCVD risk scores. The intermediate risk score cohort has lower insulin secretion index which is associated with greater glycemic levels and is seen with advancing age.

Fig. 1 categorizes the high ASCVD risk score group into the percentage of subjects who met no, 1, 2 or 3 criteria for prediabetes as well as 1 criteria for diabetes. A higher percent of subjects who met 3 glycemic criteria for prediabetes, as compared to those who met none or only 1, had ASCVD risk score > 20 (p<0.0001 and $p = 0.0004$ respectively, Fig. 1A) and metabolic syndrome (p<0.0001, Fig. 1B).

Fig. 2 depicts the ASCVD score by tertile groups of insulin secretion (IGI) and insulin sensitivity (HOMA2S). Lower insulin secretion was

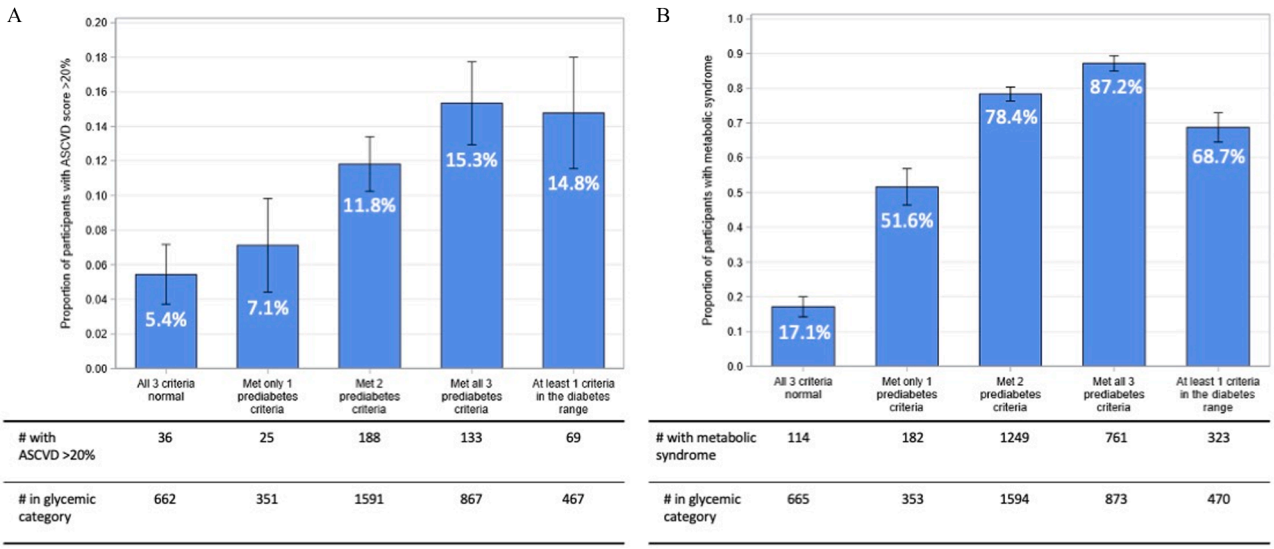


Fig. 1. 1A Percent of individuals within each glycemic category with ASCVD risk score >20. 1B Percent of individuals within each glycemic risk category with metabolic syndrome.

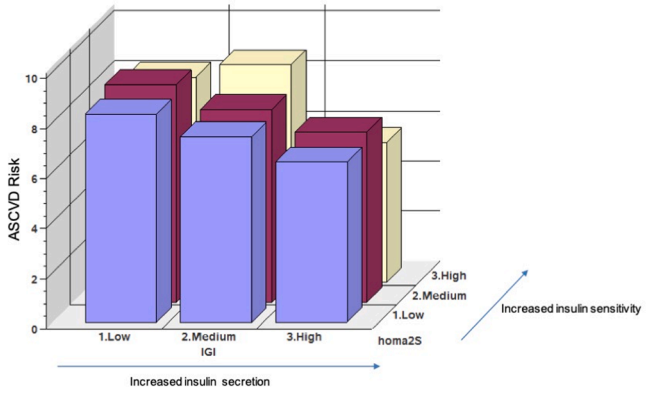


Fig. 2. ASCVD Risk Scores Across Tertile Groups of IGI and HOMA2S.
From an anlaysis of covariance model: log(ASCVD) = IGI(tertile) + HOMA2s (tertile), IGI(tertile) $p<0.001$, HOMA2s(tertile) $p = 0.64$. An exploratory model was tested with the interaction term log(ASCVD) = IGI(tertile) + HOMA2s (tertile) + IGI(tertile)*HOMA2s(tertile) and this interaction was not statistically significant.

significantly associated with a higher ASCVD risk score ($p<0.001$) while adjusting for insulin sensitivity. In contrast, insulin sensitivity, while adjusting for insulin secretion, was not significantly associated with ASCVD risk when grouped into tertiles ($p = 0.64$). An exploratory model demonstrated that the interaction between insulin sensitivity and insulin secretion was non-significant.

3. Discussion

As a borderline state between normoglycemia and diabetes, prediabetes does not universally warrant initiation of new medication according to clinical guidelines, yet insulin dynamics already insinuate abnormal homeostasis. The broad association of prediabetes with elevated cardiovascular risk warrants further investigation into potential metabolic subtypes to more precisely define populations at risk and tailor prophylactic treatments. Thus, we performed an ancillary analysis in over 3000 patients to investigate the association between diagnostic criteria for prediabetes and CVD risk while delineating tertiles for insulin sensitivity (measured by HOMA2S) and insulin secretion (measured by IGI) in a large modern multiethnic cohort. The novel results herein demonstrate that altered insulin dynamics designate discrete metabolic subtypes within the broader clinical diagnosis of prediabetes that confer divergent CVD risk). Our results also demonstrate that metabolic indices of insulin secretion and resistance are associated with certain CV risk factors (such as HDL and TG). Furthermore, we show that CVD risk increases as more prediabetes glycemic criteria are met, suggesting a need for deeper phenotyping of patients with prediabetes to better recognize their CVD risk.

Insulin resistant participants with prediabetes, categorized in the lowest tertile of HOMA2S, were younger and had higher BMI than the insulin-sensitive participants. They also had poorer CVD risk factors including elevated triglycerides, CRP, blood pressure, UACR, and liver transaminases. Insulin resistance plays an etiologic role in the pathogenesis of CVD and is independently related to several CVD risk factors, including hyperglycemia, dyslipidemia, hypertension, and thrombophilia [25,26]. Insulin resistance itself has been shown to predict subsequent CVD [27] and studies suggest insulin resistance underlies non-alcoholic fatty liver disease (NAFLD) [28] and hypertriglyceridemia [29]. Our findings suggest that the link between insulin resistance and CVD risk may be underscored by HOMA2S reflecting overall poor metabolic health (e.g. metabolic syndrome and obesity) [30,31].

Participants with low insulin secretory capacity, categorized in the lowest tertile of IGI, tended to be older, predominantly White, with a lower BMI and higher ASCVD scores. Insulin insufficiency is likely driven by older age as beta-cells are depleted. Similarly, ASCVD score is also largely driven by older age [20], which characterizes lower IGI individuals but is not associated with metabolic sub- phenotypes defined by insulin sensitivity or insulin secretion. Individuals with high IGI may develop hyperinsulinemia, and, on a molecular level, chronic excess circulating insulin can induce cellular signals in endothelial cells that predispose patients to vascular disease [32]. However, unlike HOMA2S, IGI had a weak correlation with ASCVD score that was no longer significant after adjusting for covariates, indicating that insulin secretion unlikely plays a direct causal role in CVD risk. Rather, it may simply be a marker of insulin resistance that is associated with various phenotypic characteristics of individuals at high risk for CVD.

A higher proportion of individuals who met more glycemic definitions of prediabetes (elevated FPG, 2hPG, and HbA1c) had higher ASCVD risk and metabolic syndrome than those meeting only 1 or none. According to the British Whitehall II study, 2hPG and HOMA2S were early laboratory signs of impending T2DM, whereas FPG and beta-cell

dysfunction were later signs of impending diabetes [33]. The EPIC—Norfolk study showed that every 1 percentage point increase in HbA1c within the normal range was associated with increased 10-year cardiovascular mortality [34]. Meanwhile, the Paris Prospective Study showed that patients with IGT had a 2-fold increase in CVD mortality compared to patients with normal glucose tolerance [35]. Since the transition from prediabetes to T2DM is not only driven by loss of beta-cell volume and disrupted insulin secretion, but also characterized by endothelial dysfunction, arterial stiffness, and cytokine dysregulation [36–38], each additional glycemic criteria met indicates worsening glucose regulation. Consequently, our findings suggest that meeting more prediabetes criteria not only indicates a more advanced metabolic disorder, but also a greater risk of impending heart attack or stroke. Furthermore, patients meeting different criteria for impaired glucose control (via OGTT or HbA1c) have differential prediabetic pathophysiology and therefore convey divergent CV risk profiles. Accordingly, the current diagnostic criteria for prediabetes are perhaps insufficient. Our results highlight the comprehensive value of the full OGTT as well as fasting glucose and HbA1c levels in evaluating patients with prediabetes. But, currently, less than 1% of patients whose HbA1c tests showed prediabetes were documented in the clinical records [39], and OGTTs are also infrequently ordered [40]. Therefore, a prediabetes definition that includes metabolic classifications will broaden our understanding of CV risk and may improve patients' prognosis.

The increasing CVD risk score seen in those with a higher number of glycemic criteria met may motivate intensive lifestyle and pharmacologic interventions in specific subgroups of patients with prediabetes, particularly those of older age or higher BMI. While many studies have demonstrated positive effects of lifestyle intervention and pharmacotherapy in people with prediabetes, it remains unclear which populations to definitively intervene on during this early stage. Physical activity improves insulin sensitivity and beta-cell function and has been shown to reduce the incidence of diabetes in patients with IGT [23]. Moreover, physical activity and improved insulin sensitivity prevent CVD in individuals with T2DM [41]. Pharmacological interventions may also be considered. Since metformin reduces hepatic glucose output and lowers FPG and because it has a more profound effect in prediabetic people with higher BMI and FPG levels, people with prediabetes who have those characteristics may benefit from metformin treatment [23]. Furthermore, the ACT NOW study showed that pioglitazone decreased the risk of diabetes by 70% in subjects with obesity and prediabetes [42] while the impact of thiazolidinediones, α-glucosidase inhibitors, and GLP-1 analogs on CVD risk is being studied. The use of such antidiabetic agents in patients with moderate-to-severe prediabetes should be explored [43–46].

3.1. Limitations

Due to the cross-sectional nature of this analysis, we are unable to determine incidence of cardiovascular events. However, the ASCVD risk score has well-established clinical prognostic value [47] and future statistical analysis of the D2d cohort aims to determine whether the prediabetes sub-phenotypes predict incidence of diabetes and CVD events. Worsening insulin resistance occurs with aging, thus a younger population with prediabetes may have different metabolic profile than the cohort depicted in the trial. A further limitation is that insulin secretory capacity was measured by OGTT rather than the gold-standard glucose-clamp technique [48]. However, OGTT was appropriate given the large sample size, and the OGTT-based IGI is a valid biomarker of insulin secretory function [49]. Additionally, the HOMA-S model closely correlates with glucose-clamp technique [50]. Both metabolic indices are often used for research studies and less often in the clinical setting, although HOMA2S has been measured in response to various anti-diabetic interventions in clinical trials.

4. Conclusion

We demonstrate that impaired insulin secretion and poor insulin sensitivity in patients who meet 1, 2, or 3 criteria for prediabetes are associated with increased ASCVD risk score and metabolic syndrome. Metabolic sub-phenotypes within participants with prediabetes confer differing CVD risk profile. ASCVD risk increases as more prediabetes criteria are met, suggesting that multiple clinical parameters assessing prediabetes (FPG, 2hGT, and A1c) are needed to fully understand CVD endpoints. A deeper understanding of which patient populations with prediabetes are at higher cardiovascular risk may provide greater precision to guide lifestyle and pharmacologic interventions in this population.

Registration

ClinicalTrials.gov Identifier NCT01942694, prospectively registered September 16, 2013.

Authors' contributions

SRK, RP, CD contributed to the study design. SRK, CD, VAR, SHK, LMN, SSW, PR, RP contributed to the data analysis. SRK and SSW drafted the initial manuscript. All authors reviewed, edited and approved the final manuscript.

Role of the funding source

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sun Kim reports a relationship with Aligos Therapeutics that includes: consulting or advisory. Sun Kim reports a relationship with GI Dynamics that includes: consulting or advisory. Lisa Neff reports a relationship with Eli Lilly and Company that includes: employment and equity or stocks. Lisa Neff reports a relationship with Amryt Pharmaceuticals DAC that includes: funding grants. Lisa Neff reports a relationship with Novo Nordisk Inc that includes: funding grants. Vanita Aroda reports a relationship with Applied Therapeutics Inc that includes: consulting or advisory. Vanita Aroda reports a relationship with Duke University that includes: consulting or advisory. Vanita Aroda reports a relationship with Novo Nordisk Inc that includes: consulting or advisory. Vanita Aroda reports a relationship with Pfizer that includes: consulting or advisory. Vanita Aroda reports a relationship with Sanofi that includes: consulting or advisory. Vanita Aorda reports a relationship with Applied Therapeutics Inc that includes: funding grants. Vanita Aroda reports a relationship with Eli Lilly and Company that includes: funding grants. Vanita Arodaa reports a relationship with Premier Inc that includes: funding grants. Vanita Aroda reports a relationship with Novo Nordisk Inc that includes: funding grants. Vanita Aroda reports a relationship with Sanofi that includes: funding grants. Sangeeta Kashyap reports a relationship with GI Dynamics that includes: consulting or advisory. Sangeeta Kashyap reports a relationship with Gila Therapeutics that includes: consulting or advisory. Sangeeta Kashyap reports a

relationship with Fractyl Laboratories that includes: consulting or advisory. Consultant/Educational Activities: American College of Cardiology (institution), American Diabetes Association, Cardiometabolic Health Congress, IMNE (personal), Liberum (personal), Medscape/WebMD (personal and institution), PeerView (personal and institution) - VA.

Committees: I serve on the ADA Professional Practice Committee which reviews and updates the American Diabetes Association's annual Standards of Medical Care in Diabetes (2020–2022). I serve on the ADA-EASD working group on treatment of hyperglycemia (2021-present) - VA

Associate Editor of the Journal of Clinical Endocrinology and Metabolism - SK

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