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Cardiometabolic risk factors in Thai individuals with prediabetes treated in a high-risk, prevention clinic: Unexpected relationship between high-density lipoprotein cholesterol and glycemia in men

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ABSTRACT

Aims/Introduction: Relationships between cardiometabolic risk and glycemia have rarely been studied in people under clinical evaluation and treatment for cardiometabolic risk and with prediabetes. We investigated relationships between glycemia and cardiometabolic risk factors in clinic participants with prediabetes.

Materials and Methods: This was a cross-sectional analysis of data collected at a center in Thailand. Clinic attendees were at high risk of diabetes or cardiovascular disease, with hemoglobin A1c (HbA1c) 39–<48 mmol/mol or fasting plasma glucose (FPG) 5.6–<7.0 mmol/L. The relationships between glycemia and cardiometabolic risk factors were explored.

Results: Of 357 participants, two or more insulin resistance-related metabolic disturbances were present in 84%; 61% took a statin and 75% an antihypertensive agent. Independently of age, sex, adiposity, medication use, possible non-alcoholic fatty liver disease and sex–glycemia interaction, neither FPG nor HbA1c were associated with variation in any other cardiometabolic risk factors. High-density lipoprotein cholesterol decreased with HbA1c in women (female–HbA1c interaction, $P = 0.03$) but, unexpectedly, increased with FPG in men (male–FPG interaction, $P = 0.02$).

Conclusions: Overall, in Thai people treated for high cardiometabolic risk and with prediabetes defined by FPG and/or HbA1c, neither FPG nor HbA1c were associated with other cardiometabolic risk factors. However, according to sex, high-density lipoprotein cholesterol showed the expected relationship with glycemia in women, but the reverse in men.

INTRODUCTION

Prediabetes is characterized by hyperglycemia below the threshold used to define diabetes, and is a high-risk state for diabetes or cardiovascular disease[1–4]. Based on glycemic parameters, prediabetes can be categorized into impaired fasting plasma glucose (IFG), impaired glucose tolerance (IGT) or hemoglobin A1c (HbA1c)-defined prediabetes (39–<48 mmol/mol, HbA1c 5.7–<6.5%). However, epidemiological studies have shown that these categories describe distinct populations that only partially overlap[5–7], likely reflecting differences in the contributions of β-cell

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dysfunction and insulin resistance to the pathophysiology of impaired glucose homeostasis[8–10]. These differences might affect not only variation in progression to diabetes, but also variation in cardiovascular disease risks in people with prediabetes[11–17].

A number of studies have shown that, over the full range of glycemia, fasting plasma glucose (FPG), postprandial glucose or HbA1c are positively associated with cardiovascular risk, but risk might vary according the measure of glucose homeostasis used[3,18,19]. In the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe study in Europe, postprandial glucose concentrations were more strongly correlated with cardiovascular risks than FPG[3]. In the Atherosclerosis Risk in Communities study in the USA[12], and in an extensive Asian, community-based cohort study[19], HbA1c was more strongly associated with cardiovascular risks than FPG.

In people with prediabetes, relationships between these glycemic parameters and cardiometabolic risk factors are now well established, but primarily in population-based studies[12,20,21]. However, there is little information on those who are already undergoing clinical evaluation and treatment for cardiometabolic risks. In a previous analysis, we compared, between different ethnic groups and among people with high-risk HbA1c-defined prediabetes (42–<48 mmol/mol, 6.0–<6.5%), the extent to which cardiometabolic risk factors are independently related to variation in glycemic parameters[22]. That analysis included a Thai subgroup drawn from individuals under clinical evaluation and treatment for cardiometabolic risks. Our present analysis addresses relationships in this Thai clinic-based subgroup by extending the sample to include all people from the original clinical population with either IFG or with HbA1c prediabetes. The analysis also addresses the heterogeneity inherent in our metabolically unhealthy clinical population by exploring the influence of degrees of metabolic ill health on the relationships we observe.

METHODS

Data for the present analysis were derived from records of the Continuity of Care clinic, Siriraj Hospital, Bangkok. Attendees at the clinic are generally at high risk of diabetes or cardiovascular disease, or have been diagnosed with diabetes, hypertension, obesity or multiple metabolic risk factors. Attendance at the clinic is at regular intervals, and attendees are provided with education and prevention strategies, including medications (e.g., oral hypoglycemic agent, blood pressure [BP] or cholesterol-lowering). In addition to those under the care of hospital clinicians, the clinic receives self-referrals and referrals from health checkup or primary care services.

The source dataset for the present analysis included people aged 18–74 years judged on the basis of preliminary investigations to be at risk of developing diabetes and cardiovascular diseases (n = 779). For the present analysis, participants were included if HbA1c was 39–<48 mmol/mol (5.7–<6.5%) and/or FPG was 5.6–<7.0 mmol/L. Participants were also required to have no previous diagnosis of diabetes, not be taking hypoglycemic agents, or be pregnant or breastfeeding, and to have complete data recorded at baseline for age, sex, body mass index (BMI) and waist circumference. After exclusions, 357 participants were available for analysis.

This study was approved by the Siriraj Institutional Review Board. All participants gave written informed consent.

Procedures and Measurements

All participants underwent BP and anthropometric measurements including height, weight and waist circumference. The mean of the last two measures of two or more BP measurements was taken at an office visit after 5 min of quiet rest with the patient seated; measurements were made with the use of an automated measurement system.

The midway waist circumference was measured between the lower rib margin and the iliac crest with gentle tightening of the tape measure during the end of expiration. The mean of the last two measurements of a series of two or more waist circumference measurements was taken. Central obesity was defined by ethnicity-specific waist circumference cut-offs[23]: waist circumference ≥90 cm for men and ≥80 cm for women.

Blood samples were taken in the fasted state for measurement of HbA1c, plasma glucose and serum lipids. HbA1c measurements included in the present analysis used International Federation of Clinical Chemistry and Laboratory Medicine-approved immunoassay methodology and standardization (turbidimetric inhibition immunoassay using a COBAS Integra; Roche, Mannheim, Germany). Plasma glucose concentrations and serum total, high-density lipoprotein (HDL) cholesterol and triglyceride concentrations, and aspartate aminotransferase and alanine aminotransaminase activities were measured by standard routine laboratory procedures. Low-density lipoprotein (LDL) cholesterol was calculated by using Friedwald's formula.

Cardiovascular risk factor disturbances considered included insulin resistance-related metabolic disturbances: central obesity (according to ethnicity-specific waist circumference cut-offs of men ≥90 cm, women ≥80 cm), hypertriglyceridemia (fasting triglyceride ≥1.7 mmol/L); high BP (>130/85 mmHg) and low HDL cholesterol (men <1.0 mmol/L, women <1.2 mmol/L). Disturbances also included the hypercholesterolemia indices: total cholesterol ≥5 mmol/L and LDL cholesterol ≥2.5 mmol/L, and possible non-alcoholic fatty liver disease (NAFLD) evaluated using a clinical risk score developed in Thai people with metabolic syndrome (NAFLD-MS score)[24]. This risk score sums the following criteria: alanine aminotransaminase ≥40, aspartate aminotransferase/alanine aminotransaminase ≥1, BMI ≥25, central obesity and type 2 diabetes to give an index between 1 and 5. A score of <3 is taken to signify the absence of NAFLD, and ≥3 signifies possible NAFLD.

Statistical Analysis

Baseline characteristics were compared between those with FPG in the ranges: (i) <5.6 mmol/L; (ii) 5.6 to <6.1 mmol/L; and (iii) 6.1 to <7.0 mmol/L; and HbA1c in the ranges (i)

<39 mmol/mol); (ii) 39–<42 mmol/mol; and (iii) 42–<48 mmol/mol. Continuous, normally distributed variables and continuous skewed distribution variables were summarized as the mean ± standard deviation (SD) or median and interquartile range, respectively, and categorical variables by percentage and number. Significant variation across FPG and HbA1c categories was identified for normally distributed continuous variables by ANOVA, for non-normally distributed variables by Kruskal–Wallis non-parametric ANOVA and for categorical variables by the χ^2-test. These analyses were carried out in men and women separately. In the dataset as a whole, the association with glycemia was explored by univariable and multivariable linear regression analysis, with log transformation of non-normally distributed variables. The independent contributions of variation in FPG or HbA1c to variation in cardiometabolic risk factors were explored with adjustment for age, sex, adiposity, and BP-lowering medication and statin use. In the light of sex-specific findings, interactions between sex and glycemia were explored in relation to variation in HDL cholesterol concentrations. These analyses were also explored in subgroups distinguished by degrees of metabolic ill health according to whether no BP-lowering or lipid-lowering medications, one of either medication or both medications were being taken and whether metabolic abnormalities were present.

RESULTS

Of the 357 participants, 63% were women. Overall, the mean age was 59.7 years (SD 10.3 years), the mean HbA1c was 5.9% (SD 0.3; 41.4 mmol/mol [SD 3.0 mmol/mol]) and mean FPG was 5.7 mmol/L (SD 0.3 mmol/L; 102.5 mg/dL [SD 8.6 mg/dL]). With regard to clinically managed metabolic disturbance, antihypertensive use was recorded in 75% (n = 268) and statin use in 61% (n = 216). A total of 71 of the present participants with prediabetes were not taking BP-lowering or lipid-lowering medication, but 60 of those had at least one abnormality in BP, total or LDL cholesterol, triglycerides or HDL cholesterol. A total of 68 were taking only BP-lowering medication; 16 were taking only lipid-lowering medication; 200 were taking both BP-lowering and lipid-lowering medication and 173 of these had at least one abnormality in BP, total or LDL cholesterol, triglycerides and HDL cholesterol. The prevalence of participants with two or more insulin resistance-related metabolic disturbances was 84% (n = 296), but among those not taking BP-lowering or lipid-lowering medication, this figure was reduced to 37%. Applying previously published criteria for "metabolically unhealthy"[25], 85% of our population (69, 87 and 90% in normal BMI, overweight and obese subgroup, respectively) was classified as metabolically unhealthy. In those meeting the inclusion criteria, the prevalence of IFG was 64% (n = 230; men 67%, women 63%) and the prevalence of HbA1c-defined prediabetes was 90% (n = 320; men 86%, women 92%). The prevalence of combined IFG and HbA1c prediabetes was 54% (n = 193; men 54%, women 54%).

In men, increasing FPG in the ranges <5.6, 5.6 to <6.1 and 6.1–<7.0 mmol/L was associated with higher HDL cholesterol, lower LDL cholesterol and a higher prevalence of antihypertensive drug use (Table 1). In women, increasing HbA1c in the ranges <5.7% (<39), 5.7–<6.0% (39–<42) and 6.0–<6.5% (42–<48 mmol/mol) was associated with lower HDL cholesterol, and a higher prevalence of antihypertensive drug and statin use, particularly in the range 6.0–<6.5%. We found no significant variation in possible NAFLD with increasing in glycemia in either men or women (Table 2).

In univariate linear regression analysis, neither FPG nor HbA1c were associated with HDL cholesterol. However, in sex-specific analyses, HbA1c was negatively associated with HDL cholesterol (unadjusted: beta coefficient −0.02, 95% confidence interval [CI] −0.04 to −0.005, P = 0.01) in women, whereas in men, FPG was positively associated with HDL cholesterol (0.14, 95% CI 0.03–0.25, P = 0.01). Otherwise, there were no further sex-specific univariate associations of FPG or HbA1c with cardiometabolic risk factors. These divergent relationships between HDL cholesterol concentrations and glycemia in men and women suggested an interaction with sex whereby HDL cholesterol decreased with increasing HbA1c in women and increased with increasing FPG in men. These potential interactions were tested in two models, one predicting HDL cholesterol from HbA1c, female sex and an HbA1c–female sex interaction term, and the other predicting HDL cholesterol from FPG, male sex and an FPG–male sex interaction term. In these analyses, there was no association of either HbA1c or FPG with HDL cholesterol, but there was a significant negative interaction between female sex and HbA1c with respect to HDL cholesterol (coefficient: −0.027, 95% CI −0.053 to −0.002, P = 0.03), and a significant positive interaction between male sex and FPG with respect to HDL cholesterol (coefficient: 0.184, 95% CI 0.019–0.349, P = 0.02).

In multivariable linear regression analysis (Table 3) with adjustment for the individual characteristics of age, sex, BMI, waist circumference, possible NAFLD, male–FPG interaction, female–HbA1c interaction, antihypertensive drug or statin use and FPG or HbA1c, neither HbA1c nor FPG were independently associated with any of the cardiometabolic risk factors analyzed, including HDL cholesterol (P = 0.6), but the negative interaction between female sex and HbA1c with respect to HDL cholesterol was still apparent, albeit at borderline significance (Table 3; coefficient: −0.02, 95% CI −0.05 to 0.003 mmol/L, P = 0.08), whereas the positive interaction between male sex and FPG with respect to HDL cholesterol was still fully significant (Table 3; coefficient: 0.21, 95% CI 0.05–0.37 mmol/L, P = 0.009).

The relationships between glycemia and HDL cholesterol were further explored in six subanalyses distinguishing the ranges of glycemia: HbA1c <39, 39–<42 and 42–<48 mmol/mol, and FPG <5.6 mmol/L, 5.6–<6.1 mmol/L and 6.1 to <7.0 mmol (Table S1). The positive male–FPG interaction we observed with respect to HDL cholesterol in the group as a whole was present only in the prediabetes subgroup with HbA1c range 39–<42 mmol/mol (P = 0.06). The negative

Table 1 | Prediabetes participants with prediabetes: Comparison of clinical characteristics among those in the FPG ranges

Parameters	FPG <5.6 *n* = 127	FPG 5.6–<6.1 *n* = 154	FPG 6.1–<7.0 *n* = 76	*P*†
HbA1c (mmol/mol)				
M	41.6 ± 1.9	40.6 ± 3.6	41.1 ± 3.7	0.3
F	41.6 ± 2.1	41.2 ± 3.0	42.0 ± 3.8	0.2
FPG (mmol/L)				
M	5.2 ± 0.2	5.7 ± 0.2	6.4 ± 0.2	<0.001
F	5.2 ± 0.2	5.8 ± 0.1	6.4 ± 0.2	<0.001
Age (years)				
M	58.4 ± 11.5	61.3 ± 12.1	57.2 ± 9.4	0.2
F	59.3 ± 9.8	60.2 ± 9.5	60.3 ± 9.3	0.7
BMI (kg/m^2)				
M	26.4 ± 3.5	26.7 ± 4.2	26.9 ± 3.4	0.8
F	26.6 ± 5.1	25.8 ± 4.6	27.3 ± 5.0	0.2
Waist circumference (cm)				
M	93.8 ± 7.9	94.4 ± 11.2	95.1 ± 11.9	0.8
F	86.7 ± 12.2	86.5 ± 10.4	88.8 ± 9.5	0.4
Systolic BP (mmHg)				
M	129.2 ± 13.0	132.1 ± 14.6	133.7 ± 16.3	0.4
F	130.5 ± 18.2	129.2 ± 14.6	132.9 ± 14.8	0.4
Diastolic BP (mmHg)				
M	78.3 ± 9.2	80.6 ± 9.8	82.3 ± 11.4	0.2
F	77.3 ± 13.1	76.9 ± 11.4	78.4 ± 10.8	0.7
Antihypertensive drug use				
M	74 (32)	90 (55)	93 (25)	0.04
F	70 (59)	65 (60)	77 (37)	0.3
Total cholesterol (mmol/L)				
M	4.83 ± 1.05	4.57 ± 0.86	4.52 ± 0.80	0.2
F	5.21 ± 1.06	5.19 ± 0.94	5.10 ± 0.94	0.8
Triglyceride (mmol/L)				
M	1.40, 0.96–1.83	1.28, 0.92–1.76	1.24, 0.86–1.58	0.5
F	1.19, 0.86–1.61	1.11, 0.85–1.51	1.33, 0.94–1.68	0.1
HDL-c (mmol/L)				
M	1.18 ± 0.29	1.28 ± 0.27	1.37 ± 0.32	0.02
F	1.63 ± 0.39	1.65 ± 0.38	1.55 ± 0.45	0.3
LDL-c (mmol/L)				
M	2.90 ± 0.93	2.56 ± 0.56	2.49 ± 0.66	0.02
F	2.98 ± 0.99	2.98 ± 0.81	2.87 ± 0.96	0.7
Statin use				
M	63 (27)	66 (40)	70 (19)	0.8
F	60 (50)	56 (51)	60 (29)	0.8
Possible NAFLD‡				
M	40 (17)	36 (22)	44 (12)	0.7
F	43 (82)	40 (36)	48 (22)	0.6

Prediabetes was defined by hemoglobin A1c (HbA1c) 39–47 mmol/mol and or fasting plasma glucose (FPG) 5.7–6.9 mmol/L. Categorical variable: percentage (*n*); continuous normally distributed variable: mean ± standard deviation; or continuous skewed distribution variable: median and interquartile range are shown. †Significant variation across FPG categories was identified for normally distributed continuous variables by ANOVA, for non-normally distributed variables by Kruskal-Wallis non-parametric ANOVA and for categorical variables by the χ^2-test. ‡Risk calculation from the non-alcoholic fatty liver disease (NAFLD) evaluated using a clinical risk score developed in Thai people with metabolic syndrome score. BMI, body mass index; BP, blood pressure; F, female; HDL-c, high-density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; M, male; SD, standard deviation.

female–HbA1c interaction and with respect to HDL cholesterol was present only in the prediabetes subgroup with FPG range 5.6–<6.1 mmol/L (P = 0.006).

Independent associations between individual characteristics other than glycemia and cardiometabolic risk variables were as follows: (i) increasing systolic BP, with increasing BMI; (ii)

Table 2 | Prediabetes participants with prediabetes: Comparison of clinical characteristics among those in the HbA1c ranges

Parameters	HbA1c <39 *n* = 37	HbA1c 39–<42 *n* = 146	HbA1c ≥42–<48 *n* = 174	*P*†
HbA1c (mmol/mol)				
M	35.4 ± 2.9	40.1 ± 1.0	43.5 ± 1.6	<0.001
F	35.7 ± 3.3	40.0 ± 0.9	43.8 ± 1.3	<0.001
FPG (mmol/L)				
M	5.9 ± 0.3	5.6 ± 0.5	5.7 ± 0.5	0.06
F	5.9 ± 0.3	5.6 ± 0.5	5.8 ± 0.5	0.003
Age (years)				
M	56.8 ± 12.3	59.8 ± 12.6	60.0 ± 10.2	0.5
F	59.4 ± 7.8	60.8 ± 10.3	59.2 ± 9.1	0.4
BMI (kg/m^2)				
M	27.9 ± 5.0	26.6 ± 3.9	26.3 ± 3.3	0.3
F	25.9 ± 4.9	25.6 ± 4.8	27.1 ± 4.9	0.4
Waist circumference (cm)				
M	98.3 ± 14.6	95.4 ± 10.3	92.2 ± 8.4	0.05
F	86.1 ± 10.7	85.0 ± 10.9	88.8 ± 10.8	0.04
Systolic BP (mmHg)				
M	135.2 ± 17.2	130.4 ± 13.2	131.3 ± 14.7	0.4
F	132.9 ± 15.5	129.6 ± 16.2	130.7 ± 16.1	0.7
Diastolic BP (mmHg)				
M	83.0 ± 12.1	80.3 ± 10.5	79.3 ± 8.6	0.3
F	77.6 ± 11.9	76.6 ± 12.1	78.0 ± 11.8	0.7
Antihypertensive drug use				
M	94 (17)	83 (44)	85 (51)	0.4
F	47 (9)	61 (56)	81 (91)	0.001
Total cholesterol (mmol/L)				
M	4.65 ± 0.73	4.65 ± 0.98	4.64 ± 0.91	0.9
F	5.43 ± 1.04	5.22 ± 0.96	5.09 ± 0.99	0.3
Triglyceride (mmol/L)				
M	1.36, 0.90–2.21	1.41, 0.96–1.84	1.21, 0.87–1.62	0.2
F	1.15, 0.93–1.48	1.10, 0.77–1.58	1.26, 0.90–1.62	0.1
HDL-c (mmol/L)				
M	1.26 ± 0.27	1.23 ± 0.28	1.29 ± 0.32	0.5
F	1.78 ± 0.47	1.71 ± 0.42	1.52 ± 0.35	0.001
LDL-c (mmol/L)				
M	2.62 ± 0.59	2.65 ± 0.80	2.67 ± 0.72	0.9
F	3.05 ± 0.77	2.95 ± 0.88	2.95 ± 0.96	0.9
Statin use				
M	56 (10)	64 (34)	70 (42)	0.5
F	42 (8)	46 (42)	71 (80)	0.001
Possible NAFLD‡				
M	41 (7)	41 (22)	37 (22)	0.8
F	37 (7)	41 (37)	45 (49)	0.7

Prediabetes was defined by hemoglobin A1c (HbA1c) 39–47 mmol/mol and or fasting plasma glucose (FPG) 5.7–6.9 mmol/L. Categorical variable: percentage (*n*); continuous normally distributed variable: mean ± standard deviation; or continuous skewed distribution variable: median and interquartile range. †Significant variation across FPG categories was identified for normally distributed continuous variables by ANOVA, for non-normally distributed variables by Kruskal-Wallis non-parametric ANOVA and for categorical variables by the χ^2-test. ‡Risk calculation from non-alcoholic fatty liver disease (NAFLD) evaluated using a clinical risk score developed in Thai people with metabolic syndrome score. BMI, body mass index; BP, blood pressure; F, female; HDL-c, High-density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; M, male; SD, standard deviation.

increasing diastolic BP with increasing BMI, and increasing prevalence of antihypertensive drug use and decreasing diastolic BP with increasing age; (iii) decreasing cholesterol with increasing age; (iv) increasing triglyceride with male sex, increasing BMI; (v) decreasing HDL cholesterol with male sex; and (vi) decreasing LDL cholesterol with increasing age (Table 3).

Analyses were undertaken in subgroups distinguished by degrees of metabolic ill health. However, variation in numbers

Table 3 | Independent influences of fasting plasma glucose, hemoglobin A1c, age, *sex*, body mass index, waist circumference, possible non-alcoholic fatty liver disease and sex–glycemia interaction on blood pressure and lipids: multivariable analysis

	Systolic BP	Diastolic BP	Cholesterol	Triglycerides[§]	HDL-C	LDL-C
FPG	2.39 (−1.88, 6.65)$^{0.2}$	1.25 (−1.68, 4.18)$^{0.4}$	−0.12 (−0.39, 0.15)$^{0.3}$	0.04 (−0.02, 0.09)$^{0.2}$	−0.04 (−0.14, 0.06)$^{0.4}$	−0.14 (−0.37, 0.10)$^{0.2}$
HbA1c	−0.61 (−1.45, 0.22)$^{0.1}$	−0.27 (−0.84, 0.30)$^{0.3}$	−0.02 (−0.08, 0.03)$^{0.3}$	−0.01 (−0.02, 0.001)$^{0.07}$	0.004 (−0.02, 0.02)$^{0.6}$	−0.02 (−0.06, 0.03)$^{0.5}$
Age	0.11 (−0.06, 0.28)$^{0.2}$	−0.28 (−0.40, −0.17)$^{<0.001}$	−0.01 (−0.02, −0.003)$^{0.01}$	−0.001 (−0.003, 0.001)$^{0.3}$	0.003 (−0.001, 0.007)$^{0.1}$	−0.01 (−0.02, 0.00)$^{0.04}$
Male	21.73 (−39.28, 82.74)$^{0.4}$	11.52 (−30.38, 53.43)$^{0.5}$	−0.24 (−4.01, 3.54)$^{0.9}$	0.88 (0.06, 1.71)$^{0.03}$	−2.40 (−3.81, −1.06)$^{0.001}$	1.06 (−2.25, 4.38)$^{0.5}$
BMI	0.98 (0.32, 1.63)$^{0.004}$	0.52 (0.07, 0.97)$^{0.02}$	−0.02 (−0.06, 0.03)$^{0.4}$	0.01 (0.001, 0.02)$^{0.02}$	−0.02 (−0.03, 0.002)$^{0.08}$	−0.01 (−0.05, 0.03)$^{0.5}$
Waist circumference	−0.13 (−0.39,0.14)$^{0.3}$	0.02 (−0.17, 0.20)$^{0.8}$	0.001 (−0.02, 0.02)$^{0.8}$	0.00 (−0.004, 0.003)$^{0.8}$	−0.002 (−0.008, 0.004)$^{0.4}$	0.003 (−0.01, 0.02)$^{0.6}$
Possible NAFLD[‡]	1.73 (−1.90, 5.35)$^{0.3}$	−1.23 (−3.72, 1.26)$^{0.3}$	−0.07 (−0.30, 0.16)$^{0.5}$	0.03 (−0.02, 0.08)$^{0.2}$	−0.07 (−0.15, 0.02)$^{0.1}$	−0.08 (−0.28, 0.12)$^{0.4}$
Medication[†]	3.47 (−0.60,7.55)$^{0.09}$	4.02 (1.23, 6.82)$^{0.005}$	−0.13 (−0.34, 0.09)$^{0.2}$	0.0 (−0.002, 0.09)$^{0.06}$	−0.004 (−0.08, 0.07)$^{0.9}$	−0.16 (−0.34, 0.03)$^{0.1}$
Male–FPG interaction	−0.37 (−7.42, 6.69)$^{0.9}$	0.28 (−4.57, 5.13)$^{0.9}$	0.04 (−0.41, 0.48)$^{0.8}$	−0.08 (−0.17, 0.02)$^{0.1}$	0.21 (0.05, 0.37)$^{0.009}$	−0.08 (−0.47, 0.30)$^{0.6}$
Female–HbA1c interaction	0.46 (−0.64, 1.56)$^{0.4}$	−0.28 (−0.47, 1.03)$^{0.4}$	0.01 (−0.06, 0.08)$^{0.7}$	0.01 (−0.01, 0.03)$^{0.1}$	−0.02 (−0.05, 0.003)$^{0.08}$	0.02 (−0.04, 0.08)$^{0.4}$

[†]Adjusted with antihypertensive drug use for systolic blood pressure (BP), diastolic BP and with statin use for lipids. [‡]Risk calculation from non-alcoholic fatty liver disease (NAFLD) evaluated using a clinical risk score developed in Thai people with metabolic syndrome score. The beta coefficients and their 95% confidence intervals, and the significance are shown. [§]Log-transformed. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

in each subgroup introduced uncertainties in statistically-based conclusions. The most informative of these analyses, therefore, contrasted approximately equal numbers of participants, exemplified in the contrast between the 151 participants not taking or taking only one blood pressure or lipid-lowering agent (i.e., the less metabolically unhealthy) and the 173 participants receiving drug treatment for both hypertension and hypercholesterolemia and with at least one abnormal cardiovascular risk factor (i.e., the most metabolically unhealthy). Among the 151 with less severe metabolic disturbance, the relationships we reported in the group as a whole were not apparent (Table S2). However, in the 173 with the most severe metabolic disturbance, the relationships we reported in the group as a whole were clearly apparent (Table S3). This contrast was equally apparent when smaller subgroups were analyzed (e.g., those taking no medication or those taking only a single medication – results not shown). It was also noteworthy that among the 151 with less severe metabolic disturbance, the expected significant positive relationships of total or LDL cholesterol with age and of triglycerides with adiposity were not apparent.

DISCUSSION

In accord with our group of Thai people with prediabetes being at high-risk for cardiovascular disease, there was a high prevalence of two or more insulin-related metabolic disturbances and prevalent use of a statin or of antihypertensive agents. Overall, then, in high-risk Thai people under clinical supervision and with FPG and/or HbA1c prediabetes, neither variation in FPG nor HbA1c were independently associated with variation in cardiometabolic risk factors. In this group, age, BMI and male sex were the principal variables independently associated with risk factor variation: age was positively associated with diastolic blood pressure and total and LDL cholesterol; BMI with increased blood pressure and dyslipidemia; and male sex with dyslipidemia. However, in sex-specific analyses, interactions were detected between sex and glycemia with regard to HDL cholesterol, whereby HDL cholesterol tended to fall with HbA1c in women, but, unexpectedly, rose with FPG in men. Subgroup analyses suggested that in Thai people with prediabetes under clinical supervision, these interactions are primarily a feature of the most severe degrees of metabolic disturbance and are characteristic of prediabetes either in the lower ranges of HbA1c (positive for men) or in the lower ranges of FPG (negative for women).

In our previous study in an ethnically diverse sample selected specifically for high-risk HbA1c prediabetes (42–47 mmol/mol), the Thai subgroup (n = 158) showed the highest prevalence of IFG (Thai 74%, Black 39%, South Asian 48%, other or mixed 49%, White 56%), but, like the Black and South Asian groups, had a more favorable cardiometabolic profile than White people[22]. Nevertheless, as in the present analysis, increasing FPG was not independently associated with a more adverse cardiometabolic risk profile, further confirming that in Thai people at high cardiometabolic risk, under clinical supervision and

with prediabetes, monitoring of glycemia might add little to a cardiometabolic risk evaluation that takes into account age, BMI and sex.

In contrast to our present and previous analyses, the majority of previous studies of these relationships have explored variation across the full range of glycemia[26,27]. In these studies, people with prediabetes have generally shown a higher prevalence of cardiometabolic risk factor abnormalities than normoglycemic individuals. Nevertheless, incorporating measures or categories of glycemia across the full range of glycemia into cardiovascular prediction models appeared to add little to CVD risk prediction by other characteristics, such as age, adiposity or sex[20,28,29]. This accords with our observations on glycemia and cardiometabolic risk factors specifically in people with prediabetes and suggests that measures of glycemia, such as FPG or HbA1c, might simply be signifiers for other risk factors.

Our present analysis did, however, suggest that within the prediabetes category, there might be sex-specific associations between glycemia and variation in cardiometabolic risk factors, specifically HDL cholesterol. In the present group of high cardiovascular risk Thai participants, HDL cholesterol levels in women and men showed opposite directions of association with glycemia, such that, with increasing glycemia, they converged and the well-established advantage of high HDL cholesterol levels in women[30] was eliminated. In the Thai women we studied, HDL cholesterol levels fell with increasing HbA1c, which accords with previously reported observations of the relationship between glycemia and HDL cholesterol across the full range of glycemia; and with the adverse effect of increasing glycemia on the CVD risk profiles being greater in women than in men[31,32]. In men, however, there was a rise in HDL cholesterol levels with increasing FPG, which is contrary to the expected relationship. Importantly, these relationships were still apparent when variation in other characteristics, including statin use, was taken into account. Moreover, in further analyses (not shown), there were no sex/statin use interactions detected with regard to variation in HDL cholesterol. We did, however, establish that the sex–glycemia interactions we observed in the group as a whole were primarily apparent in those with the most severe metabolic disturbance, but not in those with less severe metabolic disturbance. It is possible that the greater range of metabolic disturbance in the former group allowed for these interactions to become apparent and, in this respect, it is noteworthy that those with more severe metabolic disturbance also showed the relationships between total or LDL cholesterol and age and triglycerides and adiposity expected from broader, population-based studies. However, the sex–glycemia interaction we observed appeared to be characteristic of prediabetes either in the lower ranges of HbA1c (positive for men) or in the lower ranges of FPG (negative for women). The lower ranges of HbA1c in prediabetes could be associated with the inception of IGT and a profile more characteristic of insulin resistance and hyperinsulinemia, rather than β-cell dysfunction and insulin deficiency. Whether this could explain the subgroup difference we observed would have required accompanying plasma insulin concentration measurements.

In previously published studies of relationships between HDL cholesterol and glycemia, it is noteworthy that in an analysis from the Thailand National Health Examination Survey IV (NHES IV), HDL cholesterol levels in women were lower among women with IFG relative to normoglycemic women, and this was not the case in men[21]. Furthermore, in the NHES IV survey, the HDL cholesterol level in women with IFG was comparable with that in men with IFG, and this parallels the convergence we observed within the IFG range. Also, in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe/Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia study, as expected, HDL cholesterol levels were consistently lower among women with IFG compared with normoglycemic women[33], but in accord with our unexpected observation of a rise in HDL cholesterol with increasing glycemia in men, there was no difference or slightly higher HDL cholesterol concentrations in Asian-origin or European men with IFG compared with their normoglycemic equivalents.

The present analysis had strengths and limitations. To the best of our knowledge, this is the first study to explore the extent to which variation in glycemic parameters is related to cardiometabolic risk factors in an exclusively high-risk clinic sample of Thai people, and therefore of concern for practicing clinicians. The aforementioned Thailand NHES IV population-based study provided important information regarding relationships between IFG and cardiometabolic risk factors at the population level. Among its limitations, our analysis necessarily drew on a heterogeneous recruitment base that included variously: people attending for a hospital health check; people self-referred after a private clinic health check or self-monitoring (e.g., of blood pressure); or second opinion referrals or referrals from primary care services where BP and capillary blood glucose had been checked. This might have led to disruption in the expected relationships between glycemia and individual characteristics; for example, the lack of a relationship between BMI and the unexpected reduction in waist circumference with increasing HbA1c in men. In this high-risk clinic population, it is possible that there was some degree of lipodystrophy, with redistribution of fat to ectopic areas and an accompanying increase in insulin resistance[34]. However, in the absence of regional body fat measurements, we were unable to fully explore this possibility. It should be noted that the present study population was selected to be dysglycemic, and associations between adiposity and glycemia established in population studies with a broad range of glucose homeostasis might be weaker when the range of glycemia is restricted. Furthermore, some degree of relative insulin deficiency might have disrupted established associations. The present study sample was weighted in favor of identification of prediabetes by HbA1c, with HbA1c prediabetes apparent in 90% of participants and IFG in just 64%; this might have biased the study towards identifying significant relationships with HbA1c rather than FPG. It should

also be noted that the hemoglobin E variant, which can interfere in some HbA1c measurement methods, is relatively common in the Thai population[35]. However, the antibody used for HbA1c measurement in the present study responds primarily to an epitope on the hemoglobin molecule that is remote from the majority of hemoglobin E mutation sites[36].

In summary, we have shown that overall variation in glycemia, as assessed by FPG or HbA1c in Thai clinic attendees with prediabetes and with a high prevalence of cardiometabolic risk factors, was not independently associated with variation in the cardiometabolic risk profile. Potential increased risks of diabetes in those with higher glycemia in the prediabetic range justify attention to glucose lowering, but with regard to cardiovascular risk, attention to BMI, age and sex might be more warranted. Sex differences in relationships between glycemia and lipid profiles in the Thai population, in particular the possibility of an increase in HDL cholesterol levels with increasing glycemia in Thai men, should be confirmed in larger, population-based studies.

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DISCLOSURE

Nick S Oliver reports personal fees from Medtronic diabetes; grants, personal fees and non-financial support from Dexcom; and personal fees from Roche Diabetes, outside the submitted work. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Glycemia subgroup: independent influences of fasting plasma glucose, hemoglobin A1c, age, sex, body mass index, waist circumference, non-alcoholic fatty liver disease and sex–glycemia interaction on high-density lipoprotein cholesterol: multivariable analysis.

Table S2 | Less metabolically unhealthy prediabetes subgroup: not taking or taking only one blood pressure or lipid-lowering agent. Independent influences of fasting plasma glucose, hemoglobin A1c, age, sex, body mass index, waist circumference, non-alcoholic fatty liver disease, and sex–glycemia interaction on blood pressure and lipids: multivariable analysis.

Table S3 | Most metabolically unhealthy prediabetes subgroup: receiving drug treatment for both hypertension and hypercholesterolemia, and with at least one abnormal cardiovascular risk factor. Independent influences of fasting plasma glucose, hemoglobin A1c, age, sex, body mass index, waist circumference, non-alcoholic fatty liver disease, and sex–glycemia interaction on blood pressure and lipids: multivariable analysis.