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Observational Study

Cardiometabolic risk factors in young Indian men and their association with parameters of insulin resistance and beta-cell function

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Abstract

BACKGROUND

There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

AIM

To evaluate young North Indian men (aged 20-50 years) for burden of cardiometabolic risk factors, in relation to parameters of homeostatic model assessment for insulin resistance (HOMA-IR) and beta-cell function (oral disposition index [oDI]).

METHODS

Study participants were invited in a fasting state. Sociodemographic, anthropometric, and medical data were collected, and 75 g oral glucose tolerance test was performed with serum insulin and plasma glucose estimation at 0, 30, and 120 min. Participants were divided into quartiles for HOMA-IR and oDI (category 1: Best HOMA-IR/oDI quartile; category 3: Worst HOMA-IR/oDI quartile) and composite HOMA-IR/oDI phenotypes (phenotype 1: Best quartile for both HOMA-IR and oDI; phenotype 4: Worst quartile for both HOMA-IR and oDI) were derived.

RESULTS

We evaluated a total of 635 men at a mean ($\pm$ SD) age of 33.9 ± 5.1 years and body mass index of 26.0 ± 3.9 kg/m². Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Overweight/obesity, metabolic syndrome, and hypertension were present in 388 (61.1%), 258 (40.6%), and 123

(19.4%) participants, respectively. The prevalence of dysglycaemia, metabolic syndrome, and hypertension was significantly higher in participants belonging to the worst HOMA-IR and oDI quartiles, either alone (category 3 *vs* 1) or in combination (phenotype 4 *vs* 1). The adjusted odds ratios for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI (category 3), compared to those in the best quartile (category 1). The adjusted odds ratios further increased to 21.1, 5.6, and 13.7, respectively, in individuals with the worst, compared to the best composite HOMA-IR/oDI phenotypes (phenotype 4 *vs* 1).

CONCLUSION

The burden of cardiometabolic risk factors is high among young Asian Indian men. Our findings highlight the importance of using parameters of insulin resistance and beta-cell function in phenotyping individuals for cardiometabolic risk.

Key Words: Cardiometabolic; Insulin resistance; Asian; Disposition index; Men; Young

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Core Tip: There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia. Against this backdrop, this study aimed to evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

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INTRODUCTION

There is a huge burden of type 2 diabetes in South Asia. According to the latest International Diabetes Federation (IDF) estimates, 90 million adults suffer from diabetes in the South-East Asia region. These numbers are projected to increase to 113 million by 2030 and 152 million by 2045[1]. Several factors contribute to the diabetes epidemic in this region, with the prominent ones being increasing urbanisation and unhealthy changes in diet and lifestyle, reduced physical activity, unfavourable changes in leisure time activities, and decreasing sleeping quality and quantity[2]. Some predisposing factors integral to a “South Asian phenotype” also contribute. For instance, it has been found that despite a lower body mass index (BMI), Asian Indians develop diabetes at least a decade earlier, and are at a higher cardiovascular risk, compared to their Caucasian counterparts[3]. Existing data suggest significant beta cell dysfunction and insulin resistance (IR) in Asian Indians, even in the absence of diabetes[4]. This dual pathophysiological defect, manifested at a lower BMI and younger age, explains the huge burden of dysglycaemia in South Asians. Importantly, most studies on this subject were performed in a relatively older population (mean age in 40s or 50s), in those at high risk for diabetes, screened and selected for clinical trials, or in individuals of this ethnicity residing outside South Asia[5-8]. Thus, there is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia. Against this backdrop, this study aimed to evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

MATERIALS AND METHODS

Settings and study design

This cross-sectional evaluation was performed from January 2016 to February 2020 at a tertiary care centre in North India (All India Institute of Medical Sciences, New Delhi). This is a post-hoc analysis of the data collected in two previously published studies that primarily evaluated the concordance of cardiometabolic risk factors among spouses of women with hyperglycaemia in pregnancy[9-10]. Both studies were approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Inclusion and exclusion criteria

We included all men aged 20-50 years who participated in the aforementioned studies. For the purpose of this study, we excluded 20 participants who were diagnosed with diabetes requiring pharmacotherapy. Participants with missing blood insulin values (required to calculate IR and composite beta-cell function) were also excluded. The details of participant identification and recruitment have been provided earlier[9-10]. Briefly, participants were identified through their spouses and invited to visit the hospital, where study-related procedures (detailed below) were performed.

Procedure on the day of testing

Participants were invited to attend the hospital in a fasting state (minimum fast of 10 h) at 08:30 h. A detailed questionnaire was completed for each participant at the scheduled visit, documenting demographic details, education and employment status, and family history of diabetes mellitus.

Measurements

Weight, height, and waist circumference were recorded using standard methods (see supplementary material). A mean of three blood pressure readings was recorded. A 75 g oral glucose tolerance test with measurement of plasma glucose and serum insulin at 0, 30, and 120 min was performed using 83.3 g of glucose monohydrate (equivalent to 75 g anhydrous glucose) dissolved in 300 mL water and consumed over 5-10 min. Blood was also collected for a lipid profile and glycated hemoglobin (HbA_{1c}) measurement in the fasting state. The details of biochemical and hormonal measurements are provided in supplementary material.

Insulin index calculations

IR was measured by parameters of homeostatic model assessment for IR (HOMA-IR) using the standard formula [fasting plasma glucose (mmol/L) × fasting insulin (μIU/mL)/22.5]. Insulin secretion was measured by the insulinogenic index using the formula $\Delta I_{0-30} / \Delta G_{0-30}$ and composite beta-cell function was measured by the oral disposition index using the formula: $\Delta I_{0-30} / \Delta G_{0-30} \times 1/\text{fasting insulin}$ (where ΔI_{0-30} is the change in serum insulin over 30 min [pmol/L] and ΔG_{0-30} is the change in plasma glucose over 30 min [mmol/L]). Negative insulinogenic and disposition index results because of a negative insulin or glucose response, and positive results from combined negative insulin and glucose responses were excluded[11].

Definitions of exposure variables

Participants were divided into quartiles for IR (HOMA-IR) and beta-cell function (oDI), based on which categories were defined[12]. Participants with values in the lowest (best) quartile (Q1 for HOMA-IR) and in the highest (best) (Q4 for oDI) were classified as the reference category (category 1). Participants in the worst or most affected quartile (Q4 for HOMA-IR and Q1 for oDI) were labelled as category 3. Participants with intermediate values (Q2/Q3 of HOMA-IR and oDI) were classified as category 2. Based on categories of HOMA-IR and oDI, composite IR/beta-cell function phenotypes were derived. Phenotype 1 was used as a reference category and included participants classified in category 1 (best quartile) for both HOMA-IR and oDI. Phenotype 4 was most severe, and included participants classified in category 3 (worst quartile) for both HOMA-IR and oDI. Phenotype 3 included participants who had either HOMA-IR or oDI (not both) in category 3 (worst). All remaining participants were categorized as phenotype 2. These phenotypes and the categories based on HOMA-IR and oDI were used as exposure variables for the principal analysis, and cardiometabolic parameters were used as outcome variables.

Definitions of outcome variables

Individuals were classified as having normoglycaemia (fasting plasma glucose < 5.6 mmol/L, 2 h plasma glucose < 7.8 mmol/L, and HbA_{1c} < 39 mmol/mol [5.7%]), prediabetes (fasting plasma glucose 5.6-6.9 mmol/L and/or 2 h plasma glucose 7.8-11.0 mmol/L and/or HbA_{1c} 39-46 mmol/mol [5.7-6.4%]), or diabetes mellitus (fasting plasma glucose ≥ 7.0 mmol/L and/or 2 h plasma glucose ≥ 11.1 mmol/L and/or HbA_{1c} ≥ 48 mmol/mol [6.5%]) as per ADA criteria. Participants with prediabetes or diabetes were labelled as having dysglycaemia[13]. Metabolic syndrome was defined as per the IDF criteria: Waist circumference ≥ 90 cm, plus two of the following: Serum triglycerides ≥ 1.7 mmol/L, fasting plasma glucose ≥ 5.6 mmol/L, HDL-cholesterol < 1.03 mmol/L, and BP ≥ 130/85 mmHg[14]. Overweight and obesity were defined as BMI 25-29.9 and ≥ 30 kg/m², respectively (WHO international classification)[15]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or treatment with antihypertensive medications[16].

Statistical analysis

Statistical analyses were carried out using Stata 15.0 (Stata Corp, College Station, TX, United States). Data are presented as *n* (%), the mean ± SD, or median (q25-q75), as appropriate. Qualitative variables were compared between groups using the Pearson χ^2 test or Fisher's exact test. Quantitative variables were assessed for normality using the Shapiro-Wilk test. Variables with a normal distribution were

compared using Student's *t*-test for independent samples, and those that did not follow a normal distribution (*i.e.*, HOMA-IR, insulinogenic index, disposition index) were compared using the Wilcoxon rank-sum test. Logistic regression analysis was also used to evaluate the association of HOMA-IR, oDI, and mixed HOMA-IR/oDI categories with dysglycaemia, hypertension, and metabolic syndrome. The results are expressed as unadjusted and adjusted odds ratios (95% confidence interval [CI]). For adjusted analysis, the following covariates that are known to have a bearing on the outcome were accounted: Age and family history of diabetes (for dysglycaemia and metabolic syndrome), and age alone (for hypertension). The association of age and BMI with HOMA-IR and oDI was assessed using linear regression analysis. A *P* value of < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

We evaluated 635 men at a mean ($\pm$ SD) age of 33.9 ± 5.1 years (range 21–49 years), and a mean ($\pm$ SD) BMI of 26.0 ± 3.9 kg/m². Of the study participants, 312 (49.1%) and 76 (12.0%) were overweight and obese, respectively, and 245 (38.6%) had a family history of diabetes. Hypertension was present in 123 (19.4%) participants, and 19 (3.1%) were on pharmacotherapy. Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Metabolic syndrome was present in 258 (40.6%) participants. There were only 132 (20.8%) participants who did not have any adverse cardiometabolic risk factor, *i.e.*, dysglycaemia, hypertension, metabolic syndrome, and overweight/obesity. The results of various clinical, anthropometric, and biochemical variables are summarised in Table 1.

Burden of cardiometabolic risk factors in relation to age and body mass index

The prevalence of dysglycaemia increased with age, from 39.2% (in third decade) to 52.3% (in fourth decade) and to 68.0% (in fifth decade) ($P < 0.001$). The corresponding figures for hypertension and metabolic syndrome were 12.0%, 18.7%, and 32.0%, respectively ($P = 0.001$), and 30.4%, 41.4% and 50.5%, respectively ($P = 0.009$). There was no significant HOMA-IR increment [beta coefficient 0.15 ($P = 0.553$) for 4th decade and 0.50 ($P = 0.147$) for 5th decade, compared to 3rd decade] and oDI decrement [beta coefficient: -0.59 ($P = 0.137$) for 4th decade and -1.00 ($P = 0.057$) for 5th decade, compared to 3rd decade] with age.

Similarly, the prevalence of dysglycaemia (34.8%, 60.3%, and 75.0%, respectively), hypertension (12.2%, 22.5%, and 30.3%, respectively), and metabolic syndrome (15.4%, 52.6%, and 73.7% respectively) increased across the three BMI categories, namely, normal weight, overweight, and obese ($P < 0.001$). HOMA-IR showed a significant increment across BMI categories [beta coefficient, adjusted for age: 1.34 ($P < 0.001$) for overweight and 3.37 ($P < 0.001$) for obese, compared to normal weight participants]. On the other hand, oDI showed a significant decrement across BMI categories [beta coefficient, adjusted for age: -1.38 ($P < 0.001$) for overweight and -1.58 ($P = 0.002$) for obese, compared to normal weight participants]

Cardiometabolic risk factors in relation to different IR (HOMA-IR) categories

We found a significantly higher burden of dysglycaemia (78.5% *vs* 34.8%, $P < 0.001$), hypertension (32.5% *vs* 12.0%, $P < 0.001$) and metabolic syndrome (66.5% *vs* 13.9%, $P < 0.001$) in participants belonging to the worst, compared to the best HOMA-IR quartile. The burden of adverse lipid parameters, *i.e.*, high total cholesterol (≥ 5.2 mmol/L; 39.5% *vs* 14.6%, $P < 0.001$), high LDL-cholesterol (≥ 2.6 mmol/L; 70.7% *vs* 38.0%, $P < 0.001$), high triacylglycerol (≥ 1.7 mmol/L; 58.0% *vs* 25.3%, $P < 0.001$), and low HDL-cholesterol (< 1.29 mmol/L; 61.8% *vs* 44.3%; $P = 0.008$), was also significantly higher in these participants (Table 2). The adjusted odds ratios (ORs) for dysglycaemia (OR = 7.04, 95%CI: 4.20–11.79; $P < 0.001$), hypertension (OR = 3.56, 95%CI: 1.97–6.43; $P < 0.001$), and metabolic syndrome (OR = 12.20, 95%CI: 6.91–21.54; $P < 0.001$) were significantly higher in participants belonging to quartile 4, compared to quartile 1 (Supplementary Table 1).

Cardiometabolic risk factors in relation to different composite beta-cell function (oral disposition index) categories

We found a significantly higher burden of dysglycaemia (80.4% *vs* 36.1%, $P < 0.001$), hypertension (30.6% *vs* 12.0%, $P < 0.001$), and metabolic syndrome (62.0% *vs* 26.6%, $P < 0.001$) in participants belonging to the worst, compared to the best oDI quartile. The burden of adverse lipid parameters, *i.e.*, high total cholesterol (≥ 5.2 mmol/L; 34.8% *vs* 20.3%, $P = 0.005$), high LDL-cholesterol (≥ 2.6 mmol/L; 65.2% *vs* 50.0%, $P = 0.023$), and high triacylglycerol (≥ 1.7 mmol/L; 57.6% *vs* 32.3%, $P < 0.001$), was also significantly higher in these participants (Table 3). The adjusted ORs for dysglycaemia (OR = 6.54, 95%CI: 3.90–10.97; $P < 0.001$), hypertension (OR = 2.89, 95%CI: 1.60–5.24; $P < 0.001$), and metabolic syndrome (OR = 4.02, 95%CI: 2.48–6.53; $P < 0.001$) were significantly higher in participants belonging to the worst, compared to the best quartile (Supplementary Table 2).

Table 1 Baseline characteristics of the study cohort

Variable	Total (n = 635)
Age (yr)	33.9 ± 5.1
Education (graduation or beyond)	373 (58.7)
Family H/O Diabetes	245(38.6)
BMI (kg/m ²)	26.0 ± 3.9
BMI ≥ 25 kg/m ²	388 (61.1)
BMI ≥ 30 kg/m ²	76 (12.0)
Waist circumference (cm) (n = 633)	94.1 ± 9.6
Waist circumference ≥ 90 cm	448 (70.8)
Systolic BP (mmHg) (n = 634)	122.2 ± 12.4
Systolic BP ≥ 140 mmHg	46 (7.3)
Diastolic BP (mmHg) (n = 634)	81.5 ± 9.6
Diastolic BP ≥ 90 mmHg	111 (17.5)
Hypertension	123(19.4)
Hypertension medications (n = 606)	19(3.1)
Total cholesterol (mmol/L) (n = 634)	4.7 ± 1.0
Total cholesterol ≥ 5.2 mmol/L	193 (30.4)
LDL-C (mmol/L) (n = 634)	2.9 ± 0.9
LDL-C ≥ 2.6 mmol/L	378 (59.6)
HDL-C (mmol/L) (n = 634)	1.0 ± 0.3
HDL-C < 1.03 mmol/L	336 (53.0)
Triacylglycerol (mmol/L) (n = 634)	1.6 (1.2-2.2)
Triacylglycerol ≥ 1.7 mmol/L	281 (44.3)
The metabolic syndrome	258 (40.6)
HOMA-IR (mmol/L × μIU/mL)	2.7 (1.9-4.0)
Matsuda index (n = 633)	2.8 (1.9-4.5)
Insulinogenic index (pmol _{ins} /mmol _{glu})	203.2 (109.9-348.2)
Disposition index (l/mmol _{glu})	2.6 (1.5-4.3)
Dysglycaemia	331 (52.1)
Prediabetes	297(46.8)
Diabetes	34(5.4)
Glucose at 0 min [mmol/L]	5.3 ± 1.2
Glucose at 30 min [mmol/L]	8.8 ± 2.3
Glucose at 120 min [mmol/L]	6.7 ± 2.8
HbA1c%	5.6 ± 0.8
HbA1c mmol/mol	38.1 ± 8.5
Insulin at 0 min [pmol/L]	84.5 (58.3-117.0)
Insulin at 30 min [pmol/L]	719.5 (438.1-1134.8)
Insulin at 120 min (n = 633) [pmol/L]	495.0 (257.2-861.9)
No risk factor	132 (20.8)

Data are the mean ± SD, median (q25-q75), or n (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-

cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Table 2 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories of insulin resistance

Variable	Quartile 1 HOMA-IR < 25 th percentile of total cohort <i>n</i> = 158	Quartile 2-3 HOMA-IR 25 th to 75 th percentile of total cohort <i>n</i> = 319	Quartile 4 HOMA-IR > 75 th percentile of total cohort <i>n</i> = 158	<i>P</i> value ^a
Age (yr)	33.9 ± 5.0	33.8 ± 5.0	34.1 ± 5.2	0.775
Family H/O diabetes	45 (28.5)	124 (38.9)	76 (48.1)	0.002
BMI (kg/m ²)	23.3 ± 3.4	26.1 ± 3.2	28.5 ± 4.0	< 0.001
BMI ≥ 25 kg/m ²	53 (33.5)	204 (64.0)	131 (82.9)	< 0.001
Waist circumference (cm)	87.2 ± 8.9	94.4 ± 7.9	100.6 ± 9.0	< 0.001
Waist circumference ≥ 90 cm	66 (41.8)	239 (74.9)	143 (91.7)	< 0.001
Systolic BP ≥ 140 mmHg	7 (4.4)	18 (5.6)	21 (13.4)	0.003
Diastolic BP ≥ 90 mmHg	17 (10.8)	49 (15.4)	45 (28.7)	< 0.001
Hypertension	19 (12.0)	53 (16.6)	51 (32.5)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	23 (14.6)	108 (33.9)	62 (39.5)	< 0.001
LDL-C ≥ 2.6 mmol/L	60 (38.0)	207 (64.9)	111 (70.7)	< 0.001
HDL-C < 1.03 mmol/L	70 (44.3)	169 (53.0)	97 (61.8)	0.008
Triacylglycerol ≥ 1.7 mmol/L	40 (25.3)	150 (47.0)	91 (58.0)	< 0.001
The metabolic syndrome	22 (13.9)	131 (41.1)	105 (66.5)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	1.3 (1.0-1.6)	2.7 (2.3-3.2)	5.6 (4.6-7.3)	< 0.001
Insulinogenic index (pmol _{ins} /mmol _{glu})	139.3 (85.0-218.0)	233.0 (136.4-362.0)	225.2 (99.8-425.7)	< 0.001
Disposition index (l/mmol _{glu})	3.5 (2.2-5.8)	2.7 (1.6-4.1)	1.5 (0.7-2.6)	< 0.001
Dysglycaemia	55 (34.8)	152 (47.7)	124 (78.5)	< 0.001

^aData are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Cardiometabolic risk factors in relation to phenotypes based on different combinations of HOMA-IR and oral disposition index

As mentioned in the methodology section, we evaluated the prevalence of cardiometabolic variables under four phenotypes based on different combinations of IR and beta-cell function (phenotype 4: Most affected; phenotype 1: Least affected). The burden of dysglycaemia (90.0% *vs* 28.4%; *P* < 0.001), hypertension (38.0% *vs* 9.0%; *P* < 0.001), and metabolic syndrome (70.0% *vs* 13.4%; *P* < 0.001) was significantly higher in phenotype 4 (oDI < 25th centile and HOMA-IR > 75th centile), compared to phenotype 1 (oDI > 75th centile and HOMA-IR < 25th centile). The burden of adverse lipid parameters, *i.e.*, high total cholesterol (≥ 5.2 mmol/L; 40.0% *vs* 14.9%, *P* = 0.007), high LDL-cholesterol (≥ 2.6 mmol/L; 73.8% *vs* 38.8%, *P* < 0.001), high triacylglycerol (≥ 1.7 mmol/L; 60.0% *vs* 19.4%, *P* < 0.001), and low HDL-cholesterol (< 1.03 mmol/L; 57.5% *vs* 49.3%; *P* = 0.012), was also significantly higher in these participants. These participants were also more likely to be overweight/obese (83.8% *vs* 29.9%; *P* < 0.001) and have central obesity (92.3% *vs* 35.8%; *P* < 0.001) (Table 4). The adjusted ORs for dysglycaemia (OR = 21.09, 95%CI: 8.47-52.53; *P* < 0.001), hypertension (OR = 5.60, 95%CI: 2.14-14.64; *P* < 0.001), and metabolic syndrome (OR = 13.65, 95%CI: 5.80-32.13; *P* < 0.001) were significantly higher in the participants belonging to phenotype 4, compared to phenotype 1 (Supplementary Table 3).

Table 3 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories of beta-cell function (oral disposition index)

Variable	Quartile 4 oDI > 75 th percentile of total cohort <i>n</i> = 158	Quartile 2-3 oDI 25 th to 75 th percentile of total cohort <i>n</i> = 319	Quartile 1 oDI < 25 th percentile of total cohort <i>n</i> = 158	<i>P</i> value ^a
Age (yr)	33.1 ± 5.1	33.8 ± 4.9	35.0 ± 5.3	0.003
Family H/O diabetes	48 (30.4)	124 (38.9)	73 (46.2)	0.015
BMI (kg/m ²)	25.0 ± 3.9	25.9 ± 3.8	27.2 ± 3.7	< 0.001
BMI ≥ 25 kg/m ²	75 (47.5)	195 (61.1)	118 (74.7)	< 0.001
Waist circumference (cm)	91.8 ± 9.5	93.6 ± 9.5	97.6 ± 9.1	< 0.001
Waist circumference ≥ 90 cm	93 (58.9)	224 (70.2)	131 (84.0)	< 0.001
Systolic BP ≥ 140 mmHg	9 (5.7)	20 (6.3)	17 (10.8)	0.135
Diastolic BP ≥ 90 mmHg	15 (9.5)	53 (16.6)	43 (27.4)	< 0.001
Hypertension	19 (12.0)	56 (17.6)	48 (30.6)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	32 (20.3)	106 (33.3)	55 (34.8)	0.005
LDL-C ≥ 2.6 mmol/L	79 (50.0)	196 (61.6)	103 (65.2)	0.013
HDL-C < 1.03 mmol/L	80 (50.6)	163 (51.3)	93 (58.9)	0.232
Triacylglycerol ≥ 1.7 mmol/L	51 (32.3)	139 (43.7)	91 (57.6)	< 0.001
The metabolic syndrome	42 (26.6)	118 (37.0)	98 (62.0)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	2.1 (1.2-3.0)	2.6 (1.9-3.7)	4.0 (2.7-6.0)	< 0.001
Insulinogenic index (pmol _{ins} /mmol _{glu})	410.5 (257.1-651.6)	215.6 (146.6-299.4)	85.6 (51.2-127.7)	< 0.001
Disposition index (l/mmol _{glu})	6.1 (4.9-9.1)	2.6 (2.0-3.3)	0.8 (0.5-1.2)	< 0.001
Dysglycaemia	57 (36.1)	147 (46.1)	127 (80.4)	< 0.001

^aData are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

Odds ratio of dysglycaemia per SD change in HOMA-IR and oDI

On logistic regression analysis, the OR for dysglycaemia per SD increase in HOMA-IR was 3.22 (95% CI: 2.30-4.52; *P* < 0.001). After adjustment for age and family history of diabetes, the OR was 3.16 (95% CI: 2.24-4.47; *P* < 0.001). Similarly, the unadjusted and adjusted OR for dysglycaemia per SD decrease in oDI were 2.03 (95% CI: 1.60-2.59; *P* < 0.001) and 1.92 (95% CI: 1.51-2.44; *P* < 0.001), respectively.

DISCUSSION

We evaluated a large cohort of young Asian India men for the burden of cardiometabolic risk factors in relation to parameters of IR and beta-cell function. Apart from the traditional risk factors such as age and BMI, across which abnormal cardiometabolic traits increased, we found that individuals in the most severely affected quartiles of IR (HOMA-IR), beta-cell function (oDI), and a combination of both had a significantly higher burden of dysglycaemia, hypertension, metabolic syndrome, and adverse lipid parameters. These findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

Our study cohort comprised of relatively young participants, with a mean age of ~34 years. Nearly one in two study participants had dysglycaemia, metabolic syndrome, or overweight/obesity, and every one in five participants had hypertension at such a young age. Previously, Staimetz *et al*[5] reported a high dysglycaemia rate of 73% in 1264 individuals enrolled as a part of Diabetes Community Lifestyle Improvement Program in Chennai, India. The mean age and BMI were 44.2 years and 27.3 kg/m², respectively, compared to 33.9 years and 26.0 kg/m², in the current study; these differences

Table 4 Comparison of cardiometabolic and glycaemic variables for men depending upon different categories based on beta-cell function (oral disposition index) and insulin resistance

Variable	Phenotype 1 oDI > 75 th and HOMA-IR < 25 th percentile of total cohort <i>n</i> = 67	Phenotype 2 oDI 25 th to 75 th and/or HOMA-IR 25 th to 75 th percentile of total cohort <i>n</i> = 332	Phenotype 3 oDI < 25 th or HOMA-IR > 75 th percentile of total cohort <i>n</i> = 156	Phenotype 4 oDI < 25 th and HOMA-IR > 75 th percentile of total cohort <i>n</i> = 80	<i>P</i> value ^a
Age (yr)	33.3 ± 4.5	33.7 ± 5.1	34.0 ± 5.2	35.1 ± 5.3	0.096
Family H/O diabetes	18 (26.9)	113 (34.0)	79 (50.6)	35 (43.8)	0.001
BMI (kg/m ²)	23.2 ± 3.3	25.4 ± 3.5	27.1 ± 3.6	28.5 ± 4.0	< 0.001
BMI ≥ 25 kg/m ²	20 (29.9)	186 (56.0)	115 (73.7)	67 (83.8)	< 0.001
Waist circumference (cm)	86.9 ± 8.4	92.5 ± 8.9	97.2 ± 8.7	101.0 ± 9.1	< 0.001
Waist circumference ≥ 90 cm	24 (35.8)	222 (66.9)	130 (83.3)	72 (92.3)	< 0.001
Systolic BP ≥ 140 mmHg	3 (4.5)	18 (5.4)	12 (7.7)	13 (16.5)	0.014
Diastolic BP ≥ 90 mmHg	4 (6.0)	45 (13.6)	36 (23.1)	26 (32.9)	< 0.001
Hypertension	6 (9.0)	48 (14.5)	39 (25.0)	30 (38.0)	< 0.001
Total cholesterol ≥ 5.2 mmol/L	10 (14.9)	98 (29.5)	53 (34.2)	32 (40.0)	0.007
LDL-C ≥ 2.6 mmol/L	26 (38.8)	197 (59.3)	96 (61.9)	59 (73.8)	< 0.001
HDL-C < 1.29 mmol/L	33 (49.3)	159 (47.9)	98 (63.2)	46 (57.5)	0.012
Triacylglycerol ≥ 1.7 mmol/L	13 (19.4)	134 (40.4)	86 (55.5)	48 (60.0)	< 0.001
The metabolic syndrome	9 (13.4)	102 (30.7)	91 (58.3)	56 (70.0)	< 0.001
HOMA-IR (mmol/L × μIU/mL)	1.1 (0.7-1.5)	2.4 (1.9-3.0)	4.0 (2.7-5.0)	5.9 (4.7-8.8)	< 0.001
Insulinogenic index (pmol _{ins} /mmol _{glu})	237.4 (156.4-377.1)	228.6 (147.9-348.5)	159.0 (72.8-418.7)	99.9 (57.3-166.1)	< 0.001
Disposition index (l/mmol _{glu})	6.5 (5.1-9.4)	3.0 (2.3-4.1)	1.5 (1.0-2.6)	0.7 (0.3-1.1)	< 0.001
Dysglycaemia	19 (28.4)	133 (40.1)	107 (68.6)	72 (90.0)	< 0.001

^aData are the mean ± SD, median (q25-q75), or *n* (%). H/O: History of; BMI: Body mass index; BP: Blood pressure; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance.

explain the higher burden of dysglycaemia in the former study, compared to ours. In a similar vein, we also found that the burden of various risk factors increased across age and BMI, being higher in individuals in the fourth and fifth decades of life, and in those with overweight/obesity. The mean HOMA-IR (mmol/L × μIU/mL) in the former study was 2.9, compared to 2.7 in the current study. Notably, we found that mean HOMA-IR in participants in the fifth decade of life (who also had a comparable BMI of 26.9 kg/m²) was strikingly similar at 2.9. This highlights the convergence of phenotype in terms of obesity and IR, in two studies performed in geographically diverse regions of the country, and lends credibility to generalisation of our study findings to a wider population base.

Both IR and beta cell dysfunction contribute to the pathophysiology of diabetes, and the relative contribution of the latter is proposed to be higher in South Asians[4-6]. In fact, early beta cell dysfunction has been reported not only in Native Asian Indians, but also in migrant populations. The MASALA study found that after adjusting for visceral adiposity and other risk factors, oDI, not Matsuda index, was associated significantly with prediabetes and diabetes among migrant Asian Indians in the United States[6]. Previously, an Iranian study found that HOMA-IR is significantly associated with hypertension in subjects with and without diabetes[17]. We investigated whether and to

what extent the burden of cardiometabolic risk factors varies across severity of HOMA-IR (a parameter of IR) and oDI (a parameter of composite beta-cell function), individually and in combination. The prevalence of dysglycaemia was especially high in participants belonging to the worst HOMA-IR (78.5%) and oDI (80.4%) quartile. Further, the prevalence was 90.0% in participants who had both HOMA-IR and oDI in the worst quartile, compared to 28.4% in those with both indices in the best quartile. We also found that the adjusted ORs for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI, compared to those in the best quartile. When accounting for individuals with the worst, compared to those with the best HOMA-IR and oDI combined, the corresponding adjusted ORs further increased to 21.1, 5.6, and 13.7, respectively. Our study findings are in line with those reported in a recent cross-sectional study by Wang *et al*, where authors found that the prevalence of various cardiometabolic risk factors increased across quintiles of HOMA-IR and HOMA-B in Chinese adults ($n = 93690$)[18]. Compared to this study, we used oDI as a marker of composite beta-cell function, since it corresponds to biological definition of beta-cell function, in the sense that insulin secretion ($\Delta I_{0-30} / \Delta G_{0-30}$) is measured in relation to existing insulin sensitivity ($1/\text{fasting insulin}$), and is also known to predict the development of future diabetes[19].

The strengths of our study are a comprehensive evaluation of cardiometabolic risk in a cohort of young Indian men, and reporting of data in relation to parameters of IR and beta-cell function, both relevant to the pathophysiology of diabetes. We used oDI to measure beta-cell function, compared to other more extensive studies that used HOMA-B[12]. Our study findings add to the limited and evolving understanding of diabetes pathophysiology in South Asians. We acknowledge certain limitations of this work. Our study provides a cross-sectional association between cardiometabolic risk factors and parameters of insulin action/beta-cell function; however, causality cannot be ascertained. We did not evaluate the study participants for cardiovascular complications such as coronary artery disease and peripheral vascular disease. However, it may be too early for these complications to manifest in this young cohort. In this regard, it would be of interest to follow this cohort longitudinally and evaluate incident glycemic and cardiometabolic deterioration, and development of cardiovascular complications, based on baseline quartiles of oDI and HOMA-IR.

CONCLUSION

To conclude, the burden of cardiometabolic risk factors is high among young Asian Indian men, and both IR and beta cell dysfunction contribute to the pathophysiology of dysglycaemia in this population. Future longitudinal studies should evaluate incident cardiometabolic risk among individuals profiled at baseline for these insulin parameters, and suggest strategies to mitigate the increased risk.

ARTICLE HIGHLIGHTS

Research background

Existing data suggest significant beta cell dysfunction and insulin resistance (IR) in Asian Indians, even in the absence of diabetes. This dual pathophysiological defect, manifested at a lower body mass index (BMI) and younger age, explains the huge burden of dysglycaemia in South Asians. Importantly, most studies on this subject were performed in a relatively older population (mean age in 40s or 50s), in those at high risk for diabetes, screened and selected for clinical trials, or in individuals of this ethnicity residing outside South Asia. Thus, there is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

Research motivation

There is an unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults, who are not preselected for glycaemia.

Research objectives

To evaluate young North Indian men (aged 20-50 years) for: (1) Burden of glycemic and cardiometabolic traits; and (2) Their relation to parameters of insulin action and beta-cell function.

Research methods

Study participants were invited in a fasting state. Sociodemographic, anthropometric, and medical data were collected, and 75 g oral glucose tolerance test was performed with serum insulin and plasma glucose estimation at 0, 30, and 120 min. Participants were divided into quartiles for homeostatic model assessment for IR (HOMA-IR) and oDI (category 1: Best HOMA-IR/oDI quartile; category 3: Worst HOMA-IR/oDI quartile) and composite HOMA-IR/oDI phenotypes (phenotype 1: Best quartile for

both HOMA-IR and oDI; phenotype 4: Worst quartile for both HOMA-IR and oDI) were derived.

Research results

We evaluated a total of 635 men at a mean ($\pm$ SD) age of 33.9 ± 5.1 years and BMI of 26.0 ± 3.9 kg/m². Diabetes and prediabetes were present in 34 (5.4%) and 297 (46.8%) participants, respectively. Overweight/obesity, metabolic syndrome, and hypertension were present in 388 (61.1%), 258 (40.6%), and 123 (19.4%) participants, respectively. The prevalence of dysglycaemia, metabolic syndrome, and hypertension was significantly higher in participants belonging to the worst HOMA-IR and oDI quartiles, either alone (category 3 *vs* 1) or in combination (phenotype 4 *vs* 1). The adjusted odds ratios for dysglycaemia (6.5 to 7.0-fold), hypertension (2.9 to 3.6-fold), and metabolic syndrome (4.0 to 12.2-fold) were significantly higher in individuals in the worst quartile of HOMA-IR and oDI (category 3), compared to those in the best quartile (category 1). The adjusted odds ratios further increased to 21.1, 5.6, and 13.7, respectively, in individuals with the worst, compared to the best composite HOMA-IR/oDI phenotypes (phenotype 4 *vs* 1).

Research conclusions

The burden of cardiometabolic risk factors is high among young Asian Indian men. Our findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

Research perspectives

We evaluated a large cohort of young Asian India men for the burden of cardiometabolic risk factors in relation to parameters of IR and beta-cell function. Apart from the traditional risk factors such as age and BMI, across which abnormal cardiometabolic traits increased, we found that individuals in the most severely affected quartiles of IR (HOMA-IR), beta-cell function (oDI), and a combination of both had a significantly higher burden of dysglycaemia, hypertension, metabolic syndrome, and adverse lipid parameters. These findings highlight the importance of using parameters of IR and beta-cell function in phenotyping individuals for cardiometabolic risk.

FOOTNOTES

Author contributions: Gupta Y conceived the idea and wrote the manuscript; Goyal A, Kalaivani M, and Tandon N read and edited the manuscript; Kalaivani M did the statistical analysis; all authors approved the final version of this manuscript.

Institutional review board statement: This is a post-hoc analysis of the data collected in two previously published studies that primarily evaluated the concordance of cardiometabolic risk factors among spouses of women with hyperglycaemia in pregnancy. Both studies were approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Yashdeep Gupta, Alpesh Goyal, Mani Kalaivani, and Nikhil Tandon have nothing to disclose for this article.

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