BMJ Open Diabetes Research & Care

Differences in type 2 diabetes risk between East, South, and Southeast Asians living in Singapore: the multi-ethnic cohort

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To cite: Seah JYH, Sim X, Khoo CM, *et al*. Differences in type 2 diabetes risk between East, South, and Southeast Asians living in Singapore: the multi-ethnic cohort. *BMJ Open Diab Res Care* 2023;**11**:e003385. doi:10.1136/bmjdrc-2023-003385

Received 1 March 2023
Accepted 14 July 2023

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ABSTRACT

Introduction Prospective data on differences in type two diabetes (T2D) risk between Asian ethnic groups are sparse. We, therefore, compared T2D risk for East (Chinese), South (Indian), and Southeast (Malay) Asians and examined biological factors that may contribute to ethnic differences.

Research design and methods We included 7427 adults of Chinese, Malay, and Indian origin participating in the Singapore multi-ethnic cohort. Information on sociodemographic, lifestyle, and biological risk factors (body mass index (BMI), waist circumference, blood lipids, blood pressure, C reactive protein, adiponectin, and homeostasis model assessment for insulin resistance and beta-cell function) were collected using standardized interviews and physical examinations. T2D cases were based on physician diagnoses, a national medical registry, fasting plasma glucose, or glycated hemoglobin A1c. We used multivariable logistic association and mediation analyses.

Results During an average follow-up of 7.2 years (SD 2.2 years), we documented 595 cases of incident diabetes. Ethnic Malays (OR 2.08, 95% CI 1.69 to 2.56) and Indians (OR 2.22, 95% CI 1.80 to 2.74) had an approximately twofold higher risk of T2D compared with ethnic Chinese. Higher BMI explained the higher risk for Malay compared with Chinese ethnicity. Higher BMI, waist circumference, inflammation, and insulin resistance, and lower beta-cell function and high-density lipoprotein-cholesterol significantly contributed to the higher T2D risk for Indian compared with Chinese ethnicity. However, part of the higher T2D risk associated with Indian ethnicity remained unexplained. Despite their lower diabetes risk, Chinese participants had the lowest adiponectin levels.

Conclusions Different Asian ethnic groups have unique biological risk factor profiles related to T2D development that may warrant targeted approaches for prevention and treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In cross-sectional studies, the prevalence of type 2 diabetes (T2D) and related metabolic risk factors differed substantially between South, East, and Southeast Asians residing in the same country.

WHAT THIS STUDY ADDS

⇒ The incidence of T2D was substantially higher in South (Indians) and Southeast (Malay) Asians than in East Asians (Chinese) residing in Singapore.
⇒ Greater adiposity explained the higher risk for Malays compared with Chinese ethnicity.
⇒ Unfavorable adiposity, abdominal fat distribution, systemic inflammation, high-density lipoprotein-cholesterol, insulin resistance, and beta-cell function contributed to the higher T2D risk for Indian compared with Chinese ethnicity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Different Asian ethnic groups have unique biological risk factor profiles related to T2D development that may warrant targeted approaches for prevention and treatment.

INTRODUCTION

Asia carries >60% of the global burden of diabetes mellitus, with China (89 million) and India (66 million) being the countries with the largest number of people with diabetes in the world.[1 2] It is widely recognized that Asians are more susceptible to developing type 2 diabetes (T2D) than people of European descent, which may be attributed to genetic, epigenetic, and other environmental differences.[3] Chinese (East Asians), Malays (Southeast Asians), and Indians (South Asians) are genetically distinct and represent major Asian ethnic groups.[4] The prevalence of T2D has been reported to be higher in South and Southeast Asians compared with East Asians in the USA[5] and Singapore.[6] Several reasons may explain the differences in susceptibility to T2D between these Asian ethnic groups. Results from previous studies indicate that ethnic Indians are more abdominally obese and insulin resistant than ethnic Chinese individuals.[7–11] Differences in adiponectin

levels[8 12 13] and inflammation[12 13] between Asian ethnic groups have also been reported.

There have been no prospective studies on differences in T2D risk and possible explanations for differences in T2D risk between Asian ethnic groups. In the Singapore multi-ethnic cohort (MEC), we assessed differences in T2D risk between ethnic Chinese, Malays, and Indians, considering socioeconomic status (SES), lifestyle factors, and body mass index (BMI). We also estimated the contributions of adiposity, dyslipidemia, hypertension, inflammation, insulin resistance, and beta-cell function to ethnic differences in T2D risk using mediation analyses.

RESEARCH DESIGN AND METHODS

Study population

Our study participants were from the Singapore MEC, a population-based cohort with baseline assessments conducted from 2004 to 2010. A detailed description of the methodology of this cohort has been published.[14] Briefly, the MEC was formed by inviting participants from several previous population-based studies conducted in Singapore, with oversampling of ethnic minority groups. The data collection at baseline and follow-up consisted of home interviews and physical examinations at a study site. At baseline, we interviewed 14 465 male and female participants aged 21 years and above, and 11 085 participated in the health examination.

Using standardized questionnaires, trained interviewers collected information on sociodemographic characteristics, lifestyle, and medical history. Information on ethnicity was based on the participant's National Registration Identity Card, the identity document used in Singapore. We assessed education level based on participants' highest education attained using six answer categories aligned with the local education system. Based on this information, we created a variable for education level with the categories 'primary or less' ('no formal qualifications/lower primary' and 'primary'), 'lower secondary' ('O'/'N' level), 'higher secondary' ('Institute of Technical Education/Nitec (NTC)' and 'A' level/Polytechnic/Diploma'), and 'college' ('University'). We assessed monthly household income using five response categories from <$2000 to >$10 000 (Singapore dollar). We assessed cigarette smoking using standardized questions about current and past smoking and physical activity using a locally validated questionnaire on the type, frequency, and duration of activities.[15] We expressed leisure time physical activity in metabolic equivalent of task hours per week (MET-hrs/wk) and divided the participants into three groups: 'low' (0 MET-hrs/wk), 'intermediate' (>0 to <12 MET-hrs/wk), and 'high' (≥12 MET-hrs/wk) leisure time physical activity. These cutoffs were chosen to divide the participants into approximate thirds.

We subsequently invited participants to a physical examination consisting of anthropometric measurements and collecting 8–12 hours fasting blood samples. We measured participants' height without shoes on a portable stadiometer (SECA 200 series, Germany) in the Frankfurt Plane position. Weight was measured using SECA digital scales (SECA digital scales (SECA 700 series, Germany). BMI was computed by taking the weight (kg) divided by the square of a participant's height (m^2). Using a stretch-resistant tape, we measured waist circumference at the midpoint between the last rib and iliac crest. We took two readings of systolic and diastolic blood pressure measurements using an automated digital monitor (Dinamap Carescape V100, General Electric) after the participants rested for 5 min. A third reading was taken if the difference between the first two readings was >10 mm Hg (for systolic blood pressure) or 5 mm Hg (for diastolic blood pressure). Average values of blood pressure readings were used in subsequent analyses.

Plasma glucose, insulin, adiponectin, C reactive protein (CRP), triglycerides, HDL-cholesterol, and glycated hemoglobin A1c (HbA1c) were measured using enzymatic, immunoassays, or spectrophotometric methods on the same day as the blood collection.[14] The intra-assay coefficient of variation (CV) ranged from 0.6% to 4.0%, and the inter-assay CV ranged from 2.3% to 4.5%.[14] We calculated the homeostasis model assessment of insulin resistance (HOMA-IR) by multiplying fasting insulin (mIU/L) with fasting glucose (mmol/L) and dividing by 22.5, and the homeostasis model assessment of beta-cell function (HOMA-B) by the formula (20×insulin in mIU/mL)/(glucose in mmol/L–3.5).[16]

After an average of 7.2 years (SD 2.2 years), follow-up interviews and fasting blood samples were collected. At baseline and follow-up, participants were considered to have diabetes if they had a self-reported physician diagnosis ("Has a physician ever told you that you have diabetes?"), had diabetes according to a linked national medical registry, or had fasting plasma glucose (≥7.0 mmol/L) or HbA1c (≥6.5 %) levels above American Diabetes Association cutoffs.[17]

At follow-up, 4022 participants were uncontactable, 374 participants were ineligible, and 4011 participants declined. Through linkage to a national medical registry, 9380 participants were followed up for incident T2D. We excluded participants with heart disease (n=302), stroke (n=102), cancer (n=89), or diabetes (n=1642) at baseline. In addition, participants who were not of Chinese, Malay, or Indian ethnicity (n=50) or had missing baseline data on age or sex (n=121) were excluded. Participants may have been excluded for one or more reasons. Finally, data from 7426 participants were available for our analysis.

Statistical analysis

We examined differences in characteristics according to ethnicity using analysis of variance (for continuous variables) and χ^2 tests (for categorical variables). We also assessed differences in means for biological risk factors adjusted for age, sex, education level, monthly household income, cigarette smoking, physical activity, and BMI

using analysis of covariance. BMI-adjusted waist circumference was calculated by regressing waist circumference on BMI and using the residuals in subsequent analyses. In this residual method, BMI-adjusted waist is uncorrelated with BMI and therefore reflects an abdominal body fat distribution independent of overall body fatness.[18]

In logistic regression models, we assessed associations between ethnicity and sociodemographic, anthropometric, lifestyle, and biological factors and T2D risk. The baseline model included age and sex as covariates, and an adjusted model additionally included SES (education and income level), lifestyle (smoking and physical activity), and BMI (kg/m^2). The likelihood ratio test was used to assess the goodness-of-fit of the logistic regression models and the significance of associations for risk factors. In mediation analyses, we calculated direct and indirect effects using the Stata command *medeff*.[19] The indirect effects, direct effects, proportion mediated, and 95% CIs were generated from 1000 Monte Carlo draws for quasi-Bayesian approximation.[19] For all analyses in which HOMA-B was the exposure of interest, we further adjusted for HOMA-IR as beta-cell function should be interpreted in the context of insulin sensitivity.[20]

All statistical analyses were conducted using Stata Software V.14 (StataCorp, College Station, Texas, USA), and all two-sided p values <0.05 were considered statistically significant.

RESULTS

The mean age of the study population was 43.6 (SD 12.5) years. Participants were of Chinese (n=3662, 49.3%), Malay (n=1945; 26.2%), and Indian (n=1819; 24.5%) ethnicity. The baseline characteristics of the participants by ethnicity are shown in table 1. Chinese tended to have higher education and income levels, be more physically active, have a lower BMI, and were less likely to be current smokers than Malays or Indians. Fasting plasma glucose and HbA1c were highest in Indians, intermediate in Malays, and lowest in Chinese.

We examined ethnic differences in biological T2D risk factors in basic (age-adjusted and sex-adjusted) and multivariable (age, sex, SES, lifestyle, and BMI-adjusted) models (table 2). Of the three ethnic groups, Indians had the highest insulin resistance, waist circumference, and systemic inflammation (CRP) and the lowest HDL-cholesterol levels. However, they also had the lowest blood

Table 1 Baseline characteristics of the study population by ethnicity

	Chinese	Malay	Indian	P value*
Number	3662	1945	1819	–
Age (years)	45.1±12.6†	42.4±12.4	41.8±12.2	<0.001
Male, n (%)	1653 (45.1)	796 (40.9)	758 (41.7)	0.003
Low education level,‡ n (%)	743 (20.3)	551 (28.4)	481 (26.5)	<0.001
Low household income,§ n (%)	517 (19.4)	585 (34.8)	487 (29.8)	<0.001
Current cigarette smoking, n (%)	407 (11.6)	478 (25.9)	344 (19.9)	<0.001
Low physical activity,¶ n (%)	1030 (28.1)	688 (35.4)	685 (37.7)	<0.001
BMI (kg/m^2)	22.9±3.7	26.2±5.1	25.8±4.9	<0.001
Waist (cm)	80.0±11.1	84.8±11.7	86.5±12.2	<0.001
Systolic blood pressure (mm Hg)	124.7±19.9	124.9±19.5	119.7±20.2	<0.001
HOMA-IR	1.36±1.29	1.63±1.98	1.96±1.67	<0.001
HOMA-B	115.3±101.0	123.3±129.2	132.7±109.5	<0.001
Adiponectin (µg/mL)	5.48±3.60	7.00±3.83	6.62±3.55	<0.001
C reactive protein (mg/L)	1.77±3.54	2.95±4.73	3.83±4.96	<0.001
Triglycerides (mmol/L)	1.21±0.79	1.33±0.86	1.33±0.83	<0.001
HDL-cholesterol (mmol/L)	1.44±0.36	1.25±0.33	1.11±0.32	<0.001
Fasting glucose (mmol/L)	4.74±0.49	4.89±0.64	4.93±0.57	<0.001
HbA1c (%)	5.52±0.39	5.58±0.37	5.66±0.35	<0.001
Insulin (mIU/mL)	6.42±5.18	7.42±7.54	8.85±6.68	<0.001

*P values are based on F-tests from analysis of variance for continuous variables and χ^2 tests for categorical variables.
†Mean±SD (all such values).
‡Primary school or less.
§Lower than 2000 Singapore dollars per month.
¶No leisure time for moderate-to-vigorous physical activity.
BMI, body mass index; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; HOMA-B and HOMA-IR, homeostasis model assessment of beta-cell function and insulin resistance, respectively.

Table 2 Ethnic differences in biological risk factors for diabetes after age and sex or multivariable (age, sex, socioeconomic status, lifestyle factors and BMI)* adjustment

	Chinese			Malay			Indian			
	Adjusted mean	95% CI		Adjusted mean	95% CI		Adjusted mean	95% CI		P value†
Waist circumference (cm)										
Age-adjusted and sex-adjusted	79.6	79.2	79.9	85.2	84.7	85.6	87.0	86.5	87.4	<0.001
Multivariable-adjusted	82.6	82.4	82.9	82.0	81.6	82.3	84.4	84.1	84.7	<0.001
Systolic blood pressure (mm Hg)										
Age-adjusted and sex-adjusted	123.4	122.8	123.9	126.0	125.3	126.8	121.2	120.4	122.0	<0.001
Multivariable-adjusted	123.9	123.2	124.5	123.0	122.1	123.8	118.9	118.1	119.7	<0.001
HOMA-IR										
Age-adjusted and sex-adjusted	1.34	1.29	1.40	1.63	1.55	1.71	1.97	1.88	2.05	<0.001
Multivariable-adjusted	1.58	1.52	1.65	1.40	1.32	1.49	1.78	1.70	1.87	<0.001
HOMA-B‡										
Age-adjusted and sex-adjusted	116.2	112.5	120.0	123.1	117.3	128.8	132.4	126.5	138.3	<0.001
Multivariable-adjusted	127.9	123.8	132.0	115.0	109.2	120.8	111.4	105.7	117.0	<0.001
Adiponectin (µg/mL)										
Age-adjusted and sex-adjusted	5.56	5.44	5.67	6.92	6.77	7.08	6.54	6.37	6.70	<0.001
Multivariable-adjusted	5.55	5.40	5.70	7.35	7.17	7.54	6.88	6.70	7.06	<0.001
C reactive protein (mg/L)										
Age-adjusted and sex-adjusted	1.75	1.61	1.89	2.96	2.77	3.15	3.86	3.66	4.05	<0.001
Multivariable-adjusted	2.22	2.06	2.39	2.46	2.25	2.66	3.46	3.26	3.66	<0.001
Triglycerides (mmol/L)										
Age-adjusted and sex-adjusted	1.18	1.16	1.21	1.35	1.32	1.39	1.35	1.32	1.39	<0.001
Multivariable-adjusted	1.28	1.25	1.31	1.24	1.20	1.28	1.28	1.24	1.32	0.27
HDL-cholesterol (mmol/L)										
Age-adjusted and sex-adjusted	1.44	1.43	1.45	1.25	1.23	1.26	1.12	1.10	1.13	<0.001
Multivariable-adjusted	1.39	1.38	1.40	1.27	1.26	1.29	1.14	1.12	1.15	<0.001

Values are adjusted means (95% CIs).
*Adjusted for age, sex, education level, household income, cigarette smoking, physical activity, and BMI.
†P values are based on F-tests from analysis of covariance.
‡HOMA-B analyses were additionally adjusted for HOMA-IR.
BMI, body mass index; HDL, high-density lipoprotein; HOMA-B and HOMA-IR, homeostasis model assessment of beta-cell function and insulin resistance, respectively.

Table 3 ORs* of type 2 diabetes for ethnicity, socioeconomic, and biological risk factors

	Age, ethnicity, and sex-adjusted				Multivariable-adjusted†			
	OR	95% CI		P value	OR	95% CI		P value
Ethnicity								
Chinese	Ref.	Ref.	Ref.	<0.001	Ref.	Ref.	Ref.	0.008
Malays	2.08	1.69	2.56		1.17	0.89	1.54	
Indians	2.22	1.80	2.74		1.51	1.16	1.96	
Education level								
Primary or less	Ref.	Ref.	Ref.	0.039	Ref.	Ref.	Ref.	0.256
Lower secondary	1.00	0.82	1.22		1.17	0.92	1.50	
Higher secondary	0.71	0.52	0.96		0.87	0.59	1.30	
College	0.74	0.52	1.06		1.16	0.74	1.82	
Household income (SGD/month)								
<$2000	Ref.	Ref.	Ref.	0.282	Ref.	Ref.	Ref.	0.645
$2000–$3999	0.91	0.72	1.16		0.88	0.68	1.14	
$4000–$5999	0.85	0.65	1.12		0.99	0.73	1.33	
>$6000	0.61	0.44	0.83		0.84	0.59	1.21	
BMI	1.83	1.69	2.00	<0.001	1.81	1.65	2.00	<0.001
BMI-adjusted waist	1.40	1.26	1.56	<0.001	1.50	1.32	1.70	<0.001
Systolic blood pressure	1.49	1.37	1.63	<0.001	1.32	1.19	1.47	<0.001
HOMA-IR	1.49	1.36	1.63	<0.001	1.22	1.12	1.33	<0.001
HOMA-B	0.89	0.78	1.02	0.104	0.82	0.70	0.97	<0.001
Adiponectin	0.52	0.46	0.58	<0.001	0.53	0.46	0.61	<0.001
C reactive protein	1.25	1.18	1.33	<0.001	1.13	1.05	1.23	<0.001
Triglycerides	1.47	1.37	1.58	<0.001	1.32	1.22	1.43	<0.001
HDL-cholesterol	0.63	0.56	0.70	<0.001	0.78	0.68	0.89	<0.001

*Estimates are ORs (95% CIs) per SD increase for the continuous variables.
†Further adjusted for education level (four categories), household income (four categories), cigarette smoking, physical activity, and BMI. For HOMA-B, models 1 and 2 also included HOMA-IR.
BMI, body mass index; HDL, high-density lipoprotein; HOMA-B and HOMA-IR, homeostasis model assessment of beta-cell function and insulin resistance, respectively; Ref., reference; SGD, Singapore dollar.

pressure. Chinese had the highest HDL-cholesterol levels but the lowest adiponectin levels. These differences were observed in both the basic and the multivariable model. Malays had the highest adiponectin levels and, after multivariable adjustment, the lowest waist circumference and insulin resistance. In the basic model, HOMA-B was lowest in Chinese, but after multivariable adjustment, Indians had the lowest beta-cell function. No significant ethnic differences in fasting triglycerides remained after multivariable adjustment.

During an average follow-up of 7.2 years (SD 2.2 years), we documented 595 cases (cumulative incidence 8.0%) of incident diabetes, including 216 (5.9%) in Chinese, 193 (9.9%) in Malays, and 186 (10.2%) in Indians. In the age-adjusted and sex-adjusted logistic regression model, Malays (OR 2.08, 95% CI 1.69 to 2.56) and Indians (OR 2.22, 95% CI 1.80 to 2.74) had an approximately twofold higher risk of developing T2D than Chinese (table 3). There was no significant difference in T2D risk when we compared Indians with Malays (OR 1.06, 95% CI 0.86 to 1.32). After further adjustment for SES, lifestyle factors, and BMI in the multivariable model, Indian (OR 1.51, 95% CI 1.16 to 1.96) but not Malay (OR 1.17, 95% CI 0.89 to 1.54) ethnicity remained significantly associated with a higher T2D risk compared with Chinese ethnicity. Higher education levels were associated with a lower T2D risk in the basic model, but this association was weaker and non-significant after adjustment for lifestyle factors and BMI. Cigarette smoking (OR 1.12; 95% CI 0.85 to 1.48 for current vs never) and physical activity (OR 0.87; 95% CI 0.71 to 1.08 for high vs low) were not significantly associated with T2D risk in the basic model. In contrast, higher BMI, waist circumference, systolic blood pressure, HOMA-IR, CRP levels, and triglyceride levels, and lower adiponectin and HDL-cholesterol levels were significantly associated with a higher risk of T2D in both models. HOMA-B was only significantly associated with a lower T2D risk in the multivariable model. When we adjusted for all biological risk factors simultaneously, the risk of T2D remained higher in

Table 4 Estimates for the direct and indirect effects, and percentage mediated by different risk factors for associations between ethnicity and T2D incidence*

	Malays versus Chinese					Indians versus Chinese				
	Indirect effect	Direct effect	% Mediated (95% CI)			Indirect effect	Direct effect	% Mediated (95% CI)		
BMI	0.0331	0.0149	68.8	51.7	104.0	0.0270	0.0292	47.9	36.9	69.0
BMI-adjusted waist circumference	−0.0033	0.0557	−6.3	−9.3	−4.8	0.0061	0.0524	10.4	8.0	15.1
Systolic blood pressure	0.0042	0.0476	8.1	6.2	12.1	−0.0031	0.0608	−5.3	−7.6	−4.1
HOMA-IR	0.0055	0.0518	9.6	7.2	14.8	0.0137	0.0435	23.8	17.7	36.8
HOMA-B†	0.0001	0.0491	0.3	0.2	0.4	0.0006	0.0401	1.4	1.0	2.5
Adiponectin	−0.0202	0.0737	−37.4	−53.9	−28.9	−0.0128	0.0720	−21.3	−30.1	−16.8
C reactive protein	0.0044	0.0489	8.3	6.3	12.2	0.0078	0.0514	13.1	10.2	18.8
Triglycerides	0.0058	0.0470	11.0	8.4	16.2	0.0060	0.0547	9.9	7.7	14.1
HDL-cholesterol	0.0082	0.0359	33.6	26.0	48.2	0.0321	0.0297	51.9	40.7	72.0

*The 'indirect effect' estimates the average mediation effect of risk factors on the association between ethnicity and T2D. The 'direct effect' estimates the association between ethnicity and T2D risk unaccounted for by the risk factor; '% mediated' reflects the size of the indirect effect relative to the total effect. Lifestyle factors were not included in the mediation analyses because these were not associated with T2D risk in multivariable logistic regression models.
†For HOMA-B, we adjusted for HOMA-IR.
BMI, body mass index; HDL, high-density lipoprotein; HOMA-B and HOMA-IR, homeostasis model assessment of beta-cell function and insulin resistance, respectively; T2D, type 2 diabetes.

Indians (OR 1.52, 95% CI 1.13 to 2.04) compared with Chinese participants.

We subsequently examined factors significantly associated with T2D in the multivariable model in mediation analysis. Specifically, we estimated the proportion of the excess T2D risk in Indians and Malays compared with Chinese that these risk factors may explain. A large part of the excess T2D risk in Malays and Indians compared with Chinese appeared to be mediated by BMI (Malays: 68.8%; Indians: 47.9%) and HDL-cholesterol levels (Malays: 33.6%; Indians: 51.9%) (table 4). For Indians compared with Chinese, higher insulin resistance (23.8%), CRP (13.1%), and waist circumference (10.4%) were also estimated to mediate part of the higher T2D risk in Indians. In contrast, we observed a negative mediation effect for adiponectin for the T2D risk in Indians (−21.3%) and Malays (−37.4%) compared with Chinese participants. These negative mediation estimates suggest that higher adiponectin levels in Indians and Malays resulted in a smaller excess T2D risk compared with Chinese.

DISCUSSION

We examined ethnic differences in T2D risk and possible mediation by biological risk factors in a prospective cohort including participants of East (Chinese), South (Indian), and Southeast (Malay) ancestry. Malay and Indian ethnicity was associated with an approximately twofold higher T2D risk compared with Chinese ethnicity. The higher T2D risk in Malays than in Chinese was primarily mediated by a higher BMI. The higher T2D risk in Indians than in Chinese was partly explained by a higher BMI, waist circumference, HOMA-IR, and CRP level, and a lower index for beta-cell function and HDL-cholesterol level. Despite lower diabetes risk, ethnic Chinese had the lowest adiponectin levels among the three ethnic groups. To our knowledge, this is the first study that evaluated potential mediators of differences in T2D risk in major Asian ethnic groups using a prospective design. Previous studies have either been cross-sectional[6] or focused only on ethnic differences in T2D risk factors rather than the incidence of T2D.[7–13 21–25]

Major contributors to the higher T2D risk in Indians than Chinese appeared to be the greater general and abdominal adiposity in Indians in our study. Previous studies have demonstrated that Indians have more body fat and less lean mass than Chinese[7] and Europeans[26–28] for the same BMI. Low lean mass in Indians is already apparent at birth and persists for several generations after migration, possibly resulting from genetic or epigenetic mechanisms.[29] Indians may also have larger adipocytes than Europeans,[28] contributing to insulin resistance.[30]

Consistent with our study, other authors also reported higher insulin resistance in ethnic Indians than Chinese or Malays[8–13 21 25] and Europeans,[9 22 23 26 28 31] even after adjustments for BMI or waist circumference.[21–23] In a study conducted in Singapore where body fat and insulin sensitivity were directly measured, Indians were also more insulin resistant than Chinese, independent of adiposity.[24] However, this was not observed in two other studies conducted in Canada and Singapore when matched for body fat.[9 11] In a study that examined the skeletal muscle transcriptome in Chinese, Malays, and Indians, the expression of SNRK and AMPKα2 genes involved in glucose uptake was lowest in Indians.[25] In a

UK study, higher truncal obesity and insulin resistance accounted for the twofold higher diabetes risk in Indian women compared with Europeans, but the excess risk in men remained unexplained.[31]

In addition to higher adiposity and insulin resistance, our findings suggest that a higher degree of inflammation, lower beta-cell function, and lower HDL-cholesterol contributed to the higher T2D risk in Indians than in Chinese. Inflammation may promote diabetes development by inducing insulin resistance and pancreatic beta-cell death,[32] and higher CRP levels have been consistently associated with a higher risk of T2D.[33] In previous studies, Indians also had higher CRP levels than Chinese, Malays, and Europeans.[12 34 35] Adjustments for adiposity did not explain the association between Indian ethnicity and CRP in our study and previous studies.[12 34] For a given BMI and insulin resistance, Indians in our study also had the lowest beta-cell function.[20 21] In a previous analysis of Asian men from Singapore, the differences in beta-cell function were not statistically significant between Chinese, Malay, or Indians,[21] but the authors did not adjust for measures of adiposity. In our study, HDL-cholesterol concentrations were lower in Indians than in Chinese. Lower levels of HDL-cholesterol have been associated with higher T2D risk in epidemiological studies, although this may reflect bidirectional effects.[36] In previous studies, Indians also had lower HDL-cholesterol levels than Europeans.[26] Taken together, these findings indicate that both higher insulin resistance and lower insulin secretion capacity may underpin the higher T2D risk in Indians, with body composition, dyslipidemia, and inflammation contributing to these conditions.

In our study, a higher BMI largely explained the higher T2D risk in Malays than in Chinese. In unadjusted analyses, several diabetes risk factors were elevated in Malays compared with Chinese, but adjustment for BMI explained these ethnic differences. Furthermore, adiponectin levels and BMI-adjusted waist circumference were lower in Malays compared with Chinese, suggesting that Malays have a more favorable abdominal fat distribution and adipocyte function than Chinese for a given BMI. Indeed, results from our mediation analysis suggest that the excess T2D risk in Malays, compared with Chinese, may have been larger if they would not have more favorable adiponectin levels and fat distribution.

Higher adiponectin levels have been consistently associated with a lower T2D risk.[37] Adiponectin activates AMP kinase, promotes skeletal muscle glucose uptake and oxidation, reduces hepatic glucose production and fatty acid synthesis, and promotes fatty acid oxidation. In addition, adiponectin might protect against beta-cell death.[38] Although adiponectin is secreted primarily by white adipose tissue, adiponectin levels are paradoxically inversely correlated with obesity.[39] Although ethnic Chinese had a lower T2D risk than the other ethnic groups, they had lower adiponectin levels. This paradox may reflect more favourable levels for other risk factors in Chinese participants (eg, lower adiposity), compensating for the lower adiponectin levels. Consistently, Chinese participants also had lower adiponectin levels than Malays and Indians,[8 12] or Europeans[8 28] in previous studies, even after adjusting for waist circumference.[8] In one cohort study, Indians had lower adiponectin levels than Chinese,[13] but the authors did not adjust for adiposity. Chinese may thus have a lower capacity to store fat optimally without metabolic perturbations,[13 38] which is a concern given the rising prevalence of obesity in China.[1 2]

A strength of our study was the prospective population-based MEC of ethnic Chinese, Malays, and Indians. Because all participants resided in Singapore, which has government policies that prevent ethnic segregation, ethnic differences are unlikely to be due to differences in living environments.[40] We also acknowledge several limitations. First, we used BMI and waist circumference as measures of adiposity rather than direct measurements of different fat depots. Still, BMI and waist circumference capture most of the variance in visceral abdominal fat and subcutaneous fat.[41] Similarly, we used the HOMA method for estimating insulin sensitivity and beta-cell function instead of the 'gold standard' clamp techniques. However, HOMA-IR and HOMA-B provide a reasonably good estimate of insulin resistance and beta-cell function, respectively.[20 42 43] Given the observational nature of our study, we cannot establish causality or rule out the possibility of residual confounding arising from imperfectly or unmeasured confounders. Finally, our assessment of T2D risk factors was not complete and other factors may contribute to unexplained ethnic differences in T2D risk. Given the diversity within populations (eg, North vs South Indians and Chinese) and possible influence of living environments, caution is needed in generalizing to all ethnic Chinese, Indians, and Malays worldwide. However, our findings are consistent with Asian ethnic differences observed in cross-sectional studies in other countries such as the USA.[5]

We documented marked ethnic differences in T2D risk in Malays and Indians compared with Chinese residing in the same geographical setting independent of SES. Our results suggest that the higher T2D risk in Malays compared with Chinese can largely be explained by the greater general adiposity in Malays. In contrast, higher adiposity could not fully explain the higher T2D risk in Indians than in Chinese. The levels of several T2D risk factors were worse in Indians than in Chinese, including markers of general adiposity, abdominal fat, insulin resistance, beta-cell function, inflammation, and dyslipidemia. Furthermore, a substantial proportion of the difference in T2D risk between Indians and Chinese remained unexplained, warranting further research into underlying biological mechanisms. Our results suggest that interventions preventing excess adiposity have the potential to substantially reduce ethnic disparities in T2D risk between Chinese, Malays, and Indians. However, our results also highlight that different Asian ethnic groups have unique biological risk factor profiles related to T2D

that may warrant targeted approaches for prevention and treatment.

Acknowledgements The authors thank all investigators, staff members, and study participants for contributing to the MEC. The authors also thank Dr Paul Zimmet for his comments on the manuscript.

Contributors JYJS and RMvD conceived the study and planned the data analysis. JYJS analyzed the data and drafted the manuscript. XS, EST, and RMvD supervised the data collection. All authors contributed to the interpretation of the results and revision of the manuscript and approved the final version of the manuscript. RMvD is the guarantor.

Funding This work was supported by grants from the National Medical Research Council (MOH-000271-00, 0838/2004, 1111/2007, and MOH-000271-00), Biomedical Research Council (grant 03/1/27/18/216), and National Research Foundation (through the Biomedical Research Council, grants 05/1/21/19/425 and 11/1/21/19/678) of the Republic of Singapore.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was obtained from the National University of Singapore Institutional Review Board (NUS-IRB-20220327-N). Informed consent was obtained from all participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data can be requested following standard procedures (https://blog.nus.edu.sg/sphs/).

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