Serum C-reactive protein level and prediabetes in two Asian populations

C. Sabanayagam · A. Shankar · S. C. Lim · J. Lee ·
E. S. Tai · T. Y. Wong

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Abstract

Aims/Hypothesis Prediabetes, an early stage in the hyperglycaemic continuum, increases the future risk of developing diabetes and cardiovascular disease (CVD). C-reactive protein (CRP), a marker of inflammation, is associated with diabetes and CVD. However, studies examining the association between CRP and prediabetes among participants without diabetes are limited.

Methods We analysed data from two large population-based studies in Singapore: the Singapore Prospective Study Programme (SP2, $n=4,252$ Chinese, Malay and Indians aged ≥ 24 years) and the Singapore Malay Eye Study (SiMES, $n=$

2,337 Malays aged 40–80 years), participants of which were free of diabetes mellitus. Prediabetes was defined as glycated haemoglobin of 5.7–6.4% in SiMES ($n=1,231$); fasting plasma glucose of 5.6–6.9 mmol/l in SP2 ($n=386$).

Results Elevated high sensitivity CRP (hsCRP) levels were found to be associated with prediabetes after adjusting for age, sex, race–ethnicity, education, smoking, alcohol consumption, hypertension, BMI and total cholesterol. Comparing those with hsCRP <1 mg/l (referent), the OR (95% confidence interval) of prediabetes in persons with hsCRP 1–3 mg/l and >3 mg/l was 1.31 (0.99–1.74) and 2.17 (1.61–2.92), $p_{\text{trend}} < 0.0001$ in SP2; 1.23 (1.00–1.52) and 1.31 (1.06–1.64), $p_{\text{trend}} = 0.02$ in SiMES. In subgroup analysis, the association was stronger in women, Chinese and Malays, and participants with BMI < 25 kg/m².

Conclusions Data from two population-based Asian cohorts suggest that elevated serum hsCRP levels are associated with prediabetes.

C. Sabanayagam (✉) · A. Shankar
Department of Community Medicine,
West Virginia University School of Medicine,
PO Box 9190, Morgantown, WV 26506-9190, USA
e-mail: csabanayagam@hsc.wvu.edu

S. C. Lim
Department of Medicine, Alexandra Hospital,
Singapore, Republic of Singapore

J. Lee
Department of Epidemiology and Public Health, Yong Loo Lin
School of Medicine, National University of Singapore,
Singapore, Republic of Singapore

E. S. Tai
Department of Medicine, Yong Loo Lin School of Medicine,
National University of Singapore,
Singapore, Republic of Singapore

T. Y. Wong
Singapore Eye Research Institute,
Singapore, Republic of Singapore

T. Y. Wong
Centre for Eye Research Australia, University of Melbourne,
Melbourne, VIC, Australia

Keywords Asia · BMI · C-reactive protein · Cross-sectional · Inflammation · Multi-ethnicity · Population-based · Prediabetes · Sex · Singapore

Abbreviations

CRP C-reactive protein
CVD Cardiovascular disease
hsCRP High-sensitivity C-reactive protein
SiMES Singapore Malay Eye Study
SP2 Singapore Prospective Study Programme

Introduction

Diabetes mellitus is a growing public health problem worldwide [1] associated with substantial cardiovascular

morbidity and mortality [2, 3]. Inflammation has been suggested to play a central role in the pathogenesis of diabetes and atherosclerosis [4, 5]. Prospective and cross-sectional studies have shown that C-reactive protein (CRP), a specific marker of inflammation, is associated with increased risk of diabetes [6–8] and cardiovascular disease (CVD) [9, 10]. Recent studies have also shown that CRP is associated with fasting [11–14] or post-load glucose [12, 15] or glycated haemoglobin levels [14]. According to recent ADA guidelines [16], prediabetes is an earlier stage in the hyperglycaemic continuum that is associated with increased future risk of developing diabetes and CVD [17, 18]. However, studies examining the association between CRP and prediabetes among participants without diabetes are limited [12, 19, 20]. Few studies have shown an association between CRP and prediabetes among specific population groups, including older black and white participants in the USA [12], middle-aged Japanese [19] and clinical patients in China [20]. The prevalence of diabetes is increasing in epidemic proportions among Asians [1, 16] and it has also been shown that Asians have lower levels of CRP than Western populations [21, 22]. In this context, we examined the association between CRP and prediabetes in a multi-ethnic Asian population of Chinese, Malay and Indian participants from two population-based cohorts, the Singapore Prospective Study Programme (SP2) and Singapore Malay Eye Study (SiMES) in Singapore.

Methods

Details of the study design and methods of SP2 and SiMES have been published elsewhere [23, 24]. SP2 is a population-based cross-sectional study of participants aged 24–95 years living in Singapore. Of the 7,742 eligible participants, 5,157 attended the health examination. Of the 4,834 participants with CRP and fasting glucose measurements—after excluding those with diabetes ($n=568$), ethnic groups other than Chinese, Malay and Indians ($n=5$) and those with missing information on variables included in the multivariable model including education, smoking, drinking status, systolic and diastolic BP, and total cholesterol ($n=9$)—4,252 were included in the final analysis.

SiMES is a population-based cross-sectional study of Malay adults aged 40–80 years living in Singapore [24]. Of the 4,168 eligible participants, 3,280 participated in the study. Of the 3,136 participants with CRP and HbA_{1c} measurements, after excluding those with diabetes ($n=717$), and those with missing information on variables included in the multivariable model ($n=82$), 2,337 were included in the final analysis.

Participants from both SP2 and SiMES cohorts were examined in the same study clinic (Singapore Eye Research Institute). Questionnaire and clinic examinations were similar in both studies except that blood samples were collected in non-fasting state in SiMES and fasting state in SP2. Informed consent was obtained from all study participants, and ethics approval was obtained from the institutional review boards of National University of Singapore and Singapore General Hospital for SP2 and from the institutional review board of Singapore Eye Research Institute for SiMES.

Main outcome of interest: prediabetes In SP2, venous blood was drawn from all participants in the morning following a 10 h overnight fast. Fasting plasma glucose was measured using enzymatic methods (ADVIA 2400, Bayer Diagnostics) at the National University Hospital Reference Laboratory, which is accredited by the College of American Pathologists. In SiMES, fasting plasma glucose was not measured. All participants had venous blood drawn in the non-fasting state. Serum HbA_{1c} assay was carried out using HPLC cation exchange chromatography system implemented on a Biorad variant II analyser at the National University Hospital Reference Laboratory. The assay was accredited by the National Glycoprotein Standardisation Program with controls traceable to Diabetes Control and Complications Trial. Prediabetes was defined as fasting plasma glucose of 5.6–6.9 mmol/l (110–125 mg/dl) in SP2 and HbA_{1c} value of 5.7–6.4% in SiMES following the recommendations of the ADA to include HbA_{1c} in identifying individuals at increased risk for future diabetes [16].

Measurement of exposure variables Exposure measurements were similar in both studies. Information on participants' demographic characteristics, lifestyle factors and medical history were obtained using a standardised questionnaire. Age was defined as the age at the time of clinical examination. Education was categorised into: (1) primary or lower (≤ 6 years); (2) secondary (7–10 years); and (3) post-secondary (≥ 11 years, including university education). Cigarette smoking was categorised into current smokers and former or non-smokers, and alcohol consumption into ever drinkers and non-drinkers. BMI, calculated as weight in kilograms divided by the square of height in metres (kg/m^2), was categorised into <25 and $\geq 25 \text{ kg/m}^2$. BP was measured twice and the average of the two systolic and diastolic BP measurements were taken as the systolic and diastolic BP value. Mean arterial BP was calculated as two-thirds of the diastolic plus one-third of the systolic value. Hypertension was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or self-reported physician-diagnosed hypertension. Diabetes mel-

litus was defined as fasting plasma glucose ≥ 7 mmol/l (≥ 126 mg/dl) in SP2 and non-fasting plasma glucose ≥ 11.1 mmol/l (≥ 200 mg/dl) in SiMES, or self-reported physician-diagnosed diabetes or use of glucose-lowering medication in either SP2 or SiMES. For the current analysis we excluded those with diabetes ($n=568$ in SP2 and $n=717$ in SiMES). CVD was defined as self-reported myocardial infarction, stroke or angina. High-sensitivity CRP (hsCRP) was assayed on a Roche/Integra 400 Analyser (Roche Diagnostics, Rotkreuz, Switzerland) by a particle-enhanced immunoturbidimetric method. The intra- and inter-assay precision were 0.6–1.3% and 2.3–3.1%, respectively. Serum lipids and hsCRP were measured from fasting blood samples in SP2 and from non-fasting blood samples in SiMES. All serum biochemistry tests were carried out at the National University Hospital Reference Laboratory.

Statistical analysis As prediabetes was defined differently in the two studies owing to differences in data available, we performed all analyses separately for the two study cohorts. hsCRP levels were analysed both as categorical and continuous variables. For the categorical analysis, hsCRP levels were grouped into categories (<1 , $1\text{--}3$, and >3 mg/l) based on American Heart Association recommendations [16], and also as quartiles. For the continuous analysis hsCRP was log transformed owing to its skewed distribution. We compared selected characteristics of the study population by race–ethnicity and by prediabetes status using analysis of variance or χ^2 tests as appropriate. We then examined the association between hsCRP and prediabetes in two logistic regression models. In the first model, we adjusted for age (years) and sex (female, male). In the second multivariable model, we additionally adjusted for ethnicity (Chinese, Malay, Indian), education (primary/below, secondary/higher), current smoking (absent, present), alcohol consumption (absent, present), hypertension status (absent, present), BMI (kg/m^2) and total cholesterol (mmol/l). Tests for trend were performed modelling hsCRP categories as an ordinal variable in the corresponding multivariable logistic regression models. To examine the consistency of the association between hsCRP categories and prediabetes, we performed subgroup analysis stratified by sex, race–ethnicity and BMI (<25 , ≥ 25 kg/m^2). Statistical interaction between hsCRP categories and each of the stratifying variables was examined in the corresponding logistic regression model by including cross-product interaction terms.

To examine the dose–response relationship of the observed association between serum hsCRP level and prediabetes without linearity assumptions, we used flexible nonparametric logistic regression employing the

generalised additive modelling approach (R system for statistical computing, available from Comprehensive R Archive Network [www.CRAN.R-project.org]) to calculate odds of prediabetes, adjusting for all covariates in the multivariable model; the predicted odds of prediabetes were then plotted against increasing hsCRP levels (on the log scale).

We performed several supplementary analyses. We repeated the multivariable model in Table 2: (1) using quartiles of CRP (<0.4 , $0.4\text{--}1.0$, $1.1\text{--}2.6$, >2.6 mg/l); (2) after excluding participants with hsCRP levels suggestive of clinical inflammation (>10 mg/l); and (3) after excluding participants with history of CVD. As the prevalence of prediabetes in these populations was not low (9.1% in SP2 and 52.7% in SiMES), we repeated the analysis using log-binomial regression, an alternative model to logistic regression in cross-sectional studies [25]. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows characteristics of the study population by study cohort and ethnicity. Among the three ethnic groups, Malays in both SP2 and SiMES were more likely to be primary/below educated, current smokers, have higher systolic and diastolic BP, BMI and total cholesterol, and less likely to consume alcohol; Chinese were more likely to be females, and Indians had higher levels of CRP and lower levels of HDL cholesterol. In general, participants from the SiMES cohort were older and had a higher prevalence of all risk factors examined, compared with those from the SP2 cohort. Table 2 shows characteristics of the study cohorts by prediabetes status. The prevalence of prediabetes was 9.1% in SP2 cohort and 52.7% in SiMES cohort. In both the cohorts, compared with those without prediabetes, those with prediabetes were more likely to be older, have higher systolic BP and BMI, and were less likely to be female. Further, in the SP2 cohort, those with prediabetes had higher diastolic BP and CRP, lower levels of HDL cholesterol and were less likely to consume alcohol; in the SiMES cohort, those with prediabetes had higher levels of total cholesterol.

Table 3 presents the ORs of prediabetes by categories of hsCRP in both the study cohorts. The prevalence of prediabetes increased with increasing categories of hsCRP in a dose-dependent manner ($p_{\text{trend}} < 0.0001$ in SP2 and $p_{\text{trend}} = 0.02$ in SiMES). hsCRP was significantly associated with prediabetes in both the age, sex-adjusted and the multivariable model. This positive association between hsCRP and prediabetes persisted when CRP was analysed as a continuous variable in both the cohorts.

Table 1 Characteristics of the study participants by race/ethnicity and by study cohort

Characteristic	SP2			SiMES	<i>p</i> value ^a
	Chinese (<i>n</i> =2,900)	Malay (<i>n</i> =737)	Indian (<i>n</i> =615)	Malay (<i>n</i> =2,337)	
Age (years)	48.7 (11.7)	48.3 (11.2)	50.3 (11.1)	57.3 (11.2)	<0.0001
Sex, female (%)	56.5	50.8	52.9	51.2	0.0005
Education, primary/below (%)	23.9	29.4	23.7	71.4	<0.0001
Current smoking (%)	10.4	18.9	10.7	21.9	<0.0001
Alcohol consumption (%)	46.0	6.8	33.3	2.1	<0.0001
Systolic BP (mmHg)	129.4 (20.1)	134.7 (19.3)	131.3 (20.4)	144.7 (23.5)	<0.0001
Diastolic BP (mmHg)	76.8 (10.9)	78.9 (10.3)	78.5 (10.5)	80.0 (11.3)	<0.0001
BMI (kg/m ²)	22.7 (3.7)	26.0 (4.8)	25.7 (4.5)	26.1 (5.2)	<0.0001
Total cholesterol (mmol/l)	5.2 (0.9)	5.5 (0.9)	5.2 (0.9)	5.7 (1.1)	<0.0001
HDL-cholesterol (mmol/l)	1.4 (0.4)	1.3 (0.3)	1.2 (0.3)	1.4 (0.3)	<0.0001
Fasting plasma glucose (mmol/l)	4.8 (0.5)	4.8 (0.6)	4.9 (0.6)	–	<0.0001
HbA _{1c} (%)	–	–	–	5.9 (0.6)	–
CRP (mg/l)	2.0 (4.9)	3.1 (4.5)	4.4 (8.3)	5.9 (0.6)	<0.0001

Data are mean (SD) unless stated otherwise

^a The *p* value represents difference in characteristics by ethnicity based on analysis of variance or χ^2 test as appropriate

Table 4 shows the association between hsCRP and prediabetes in subgroups of sex, race–ethnicity and BMI categories in both the study cohorts. In the SP2 cohort, similar to the main results in Table 3, a positive association was observed between CRP and prediabetes within subgroups of sex, race–ethnicity and BMI categories; however, the association was stronger in females (*p* for interaction=

0.03); although the association was stronger in Chinese and Malays and among those with BMI <25 kg/m², there was no significant interaction by race–ethnicity (*p* for interaction=0.2) or by BMI (*p* for interaction=0.2). In the SiMES cohort, the association was significant in females (*p* for interaction=0.02) and those with BMI <25 kg/m² (*p* for interaction=0.02).

Table 2 Characteristics of the study participants by prediabetes status

Characteristic	SP2 cohort			SiMES cohort		
	Prediabetes absent (<i>n</i> =3,866)	Prediabetes present (<i>n</i> =386)	<i>p</i> value ^a	Prediabetes absent (<i>n</i> =1,106)	Prediabetes present (<i>n</i> =1,231)	<i>p</i> value ^a
Age (years)	48.2 (11.4)	55.9 (10.5)	<0.0001	56.5 (11.5)	58.1 (10.8)	0.001
Sex, female (%)	56.1	43.8	<0.0001	54.7	48.1	0.001
Education, primary/below (%)	23.6	36.5	<0.0001	70.1	72.6	0.2
Current smoking (%)	12.1	9.8	0.2	21.5	22.3	0.7
Alcohol consumption (%)	38.4	27.2	<0.0001	2.6	1.5	0.07
Systolic BP (mmHg)	129.2 (19.4)	144.1 (21.5)	<0.0001	143.5 (24.3)	145.8 (22.6)	0.02
Diastolic BP (mmHg)	76.9 (10.7)	82.4 (10.9)	<0.0001	79.4 (11.5)	80.3 (11.1)	0.05
BMI (kg/m ²)	23.5 (4.1)	26.0 (4.8)	<0.0001	25.7 (5.2)	26.5 (5.1)	0.0004
Total cholesterol (mmol/l)	5.2 (0.9)	5.3 (0.9)	0.3	5.6 (1.1)	5.8 (1.1)	<0.0001
HDL-cholesterol (mmol/l)	1.4 (0.4)	1.3 (0.3)	<0.0001	1.4 (0.3)	1.4 (0.3)	0.2
Fasting plasma glucose (mmol/l)	4.7 (0.4)	6.0 (0.4)	<0.0001	–	–	–
HbA _{1c} (%)	–	–	<0.0001	5.7 (0.8)	6.0 (0.2)	<0.0001
CRP (mg/l)	2.3 (5.1)	4.2 (9.0)	<0.0001	3.7 (7.6)	4.2 (8.5)	0.1

Data are mean (SD) unless stated otherwise

^a The *p* value represents difference in characteristics by ethnicity based on analysis of variance or χ^2 test as appropriate

Table 3 Association between CRP and prediabetes

Serum CRP categories (mg/l)	Number at risk (cases)	Prediabetes (%)	Age–sex adjusted OR (95% CI)	Multivariable OR (95% CI) ^a
SP2 population (<i>n</i> =4,252)				
<1	1,943 (105)	5.4	1.00 (referent)	1.00 (referent)
1–3	1,379 (130)	9.4	1.70 (1.30–2.23)	1.31 (0.99–1.74)
>3	930 (151)	16.2	3.35 (2.56–4.38)	2.17 (1.61–2.92)
<i>P</i> _{trend}			<0.0001	<0.0001
Log-transformed CRP, mg/l			1.48 (1.35–1.62)	1.28 (1.16–1.42)
SiMES population (<i>n</i> =2,337)				
<1	645 (301)	46.7	1.00 (Referent)	1.00 (Referent)
1–3	889 (479)	53.9	1.35 (1.10–1.65)	1.23 (1.00–1.52)
>3	803 (451)	56.2	1.51 (1.22–1.86)	1.31 (1.06–1.64)
<i>P</i> _{trend}			0.0002	0.02
Log transformed CRP, mg/l			1.15 (1.08–1.24)	1.11 (1.03–1.19)

^a Adjusted for age (years), sex (female, male), race–ethnicity (Chinese, Malay, Indian) in SP2, education (primary/below, secondary/higher), BMI (kg/m²), current smoker (absent, present), ever drinker (absent, present), hypertension (absent, present), total cholesterol (mmol/l)

Table 4 Association between serum CRP and prediabetes within selected subgroups

Subgroups	CRP categories (mg/l)						<i>P</i> _{trend}
	<1		1–3		>3		
	<i>n</i> (cases)	Multivariable OR (95% CI) ^{a,b}	<i>n</i> (cases)	Multivariable OR (95% CI) ^a	<i>n</i> (cases)	Multivariable OR (95% CI) ^a	
<hr/>							
SP2 population							
Sex ^b							
Male (<i>n</i> =1,914)	881 (73)	1.00	668 (80)	1.22 (0.86–1.74)	365 (64)	1.72 (1.16–2.55)	0.007
Female (<i>n</i> =2,338)	1,062 (32)	1.00	711 (50)	1.51 (0.94–2.45)	565 (87)	2.84 (1.75–4.59)	<0.0001
Race–ethnicity ^b							
Chinese (<i>n</i> =2,900)	1,556 (72)	1.00	898 (70)	1.23 (0.86–1.76)	446 (71)	2.51 (1.72–3.67)	<0.0001
Malay (<i>n</i> =737)	229 (18)	1.00	286 (33)	1.40 (0.74–2.65)	222 (37)	2.11 (1.09–4.09)	0.02
Indian (<i>n</i> =615)	158 (15)	1.00	195 (27)	1.19 (0.59–2.40)	262 (43)	1.33 (0.66–2.68)	0.4
BMI ^b							
<25 kg/m ² (<i>n</i> =2,875)	1,645 (70)	1.00	855 (63)	1.30 (0.90–1.88)	375 (49)	2.17 (1.43–3.30)	0.0005
≥25 kg/m ² (<i>n</i> =1,377)	298 (35)	1.00	524 (67)	1.01 (0.65–1.59)	555 (102)	1.49 (0.94–2.34)	0.05
SiMES population							
Sex ^b							
Male (<i>n</i> =1,140)	336 (176)	1.00	452 (265)	1.25 (0.93–1.68)	352 (198)	1.11 (0.82–1.52)	0.5
Female (<i>n</i> =1,197)	309 (125)	1.00	437 (214)	1.20 (0.88–1.64)	451 (253)	1.48 (1.07–2.03)	0.02
BMI ^b							
<25 kg/m ² (<i>n</i> =1,041)	424 (174)	1.00	360 (189)	1.45 (1.08–1.96)	257 (145)	1.58 (1.14–2.20)	0.004
≥25 kg/m ² (<i>n</i> =1,296)	221 (127)	1.00	529 (290)	0.89 (0.65–1.23)	546 (306)	0.91 (0.66–1.27)	0.7

^a Adjusted for age (years), sex (female, male), race–ethnicity (Chinese, Malay, Indian) in SP2, education (primary/below, secondary/higher), BMI (kg/m²), current smoker (absent, present), ever drinker (absent, present), hypertension (absent, present), total cholesterol (mmol/l)

^b *p* interaction for serum CRP categories and female is equal to 0.03 in SP2 and 0.02 in SiMES; CRP categories and race–ethnicity=0.2 in SP2; CRP categories and BMI=0.2 in SP2 and 0.02 in SiMES

Figure 1 shows the dose–response relationship between serum hsCRP levels and prediabetes employing nonparametric models without linearity assumptions. A continuous positive association was observed between serum hsCRP levels and prediabetes in both the study cohorts; however, the dose–response curve was steeper in the SP2 cohort.

In a supplementary analysis, when we repeated the main analysis in Table 3 using quartiles of CRP, the

Fig. 1 Multivariable-adjusted odds of prediabetes according to serum CRP level (mg/l) in SP2 (a) and SiMES (b) populations. The black line represents the predicted odds of prediabetes from non-parametric logistic regression; the dashed lines represent 95% confidence limits for the nonparametric logistic regression estimates. The non-parametric logistic regression was adjusted for age (years), sex (male, female), race–ethnicity (Chinese, Malay, Indians) in SP2, education (primary/below, secondary/higher), BMI (kg/m^2), current smoker (absent, present), ever drinker (absent, present), hypertension (absent, present), total cholesterol (mmol/l)

results were largely similar; in the SP2 cohort, compared with quartile 1 (referent) of hsCRP, the multivariable OR (95% CI) of prediabetes was 1.15 (0.81–1.62) in quartile 2, 1.21 (0.84–1.74) in quartile 3 and 2.25 (1.59–3.20) in quartile 4; $p_{\text{trend}} < 0.0001$. In the SiMES cohort, compared with quartile 1 (referent) of hsCRP, the multivariable OR (95% CI) of prediabetes was 1.13 (0.86–1.48) in quartile 2, 1.15 (0.88–1.51) in quartile 3 and 1.39 (1.06–1.82) in quartile 4; $p_{\text{trend}} = 0.01$. Additional supplementary analyses are shown in Table 5. Excluding those with evidence of clinical inflammation ($>10 \text{ mg}/\text{l}$) and a history of CVD did not materially alter the results. When we repeated the main analysis in Table 3 using log-binomial regression, the effect estimates (prevalence ratios, PR) were slightly attenuated, but the association still remained positive and significant.

Discussion

The current study, analysing data from two large population-based Asian cohorts, showed that higher hsCRP levels were associated with prediabetes among participants without diabetes. This association was found to be independent of age, sex, race–ethnicity, education, current smoking, alcohol consumption, hypertension, BMI, and total cholesterol, and a positive dose–response trend was observed between increasing categories of hsCRP and prediabetes. The positive association between hsCRP and prediabetes was found to be stronger in women, Chinese and Malays, and participants with BMI $<25 \text{ kg}/\text{m}^2$. Finally, despite using two different populations with different ways of measuring glycaemia, the results for the association between hsCRP and prediabetes were similar.

A higher level of hsCRP is a sensitive marker of subclinical inflammation. Our finding of an association between CRP and prediabetes is largely consistent with previous studies that report an association between CRP and diabetes [6, 7, 12, 26] or elevated blood glucose levels [11, 13, 14] or HbA_{1c} [14]. It is also consistent with previous studies that report an association between CRP and prediabetes among specific populations [12, 19, 20, 27] and extends the association to a multi-ethnic Asian population. A positive association between elevated CRP and prediabetes was reported among the Chinese Han population ($n=1,730$) in a clinic-based study [20], 3,075 well-functioning black and white participants aged 70–79 years in the Health, Aging and Body Composition Study in the USA [12], 2,127 middle-aged Japanese men and women in the Hisayama Study [19] and among 232 non-smoking elderly Korean women [27].

Table 5 Supplementary analyses for association between CRP and prediabetes

Model	Multivariable OR (95% confidence interval) ^a			<i>P</i> _{trend}
	CRP categories (mg/l)			
	<1 ^b	1–3	>3	
SP2 population				
Using log binomial model instead of logistic regression	1.00	1.28 (0.98–1.67)	1.94 (1.47–2.55)	<0.0001
Excluding those with clinical inflammation, CRP >10 mg/l (<i>n</i> =4,084)	1.00	1.27 (0.96–1.68)	1.86 (1.35–2.57)	0.0002
Excluding those with history of CVD (<i>n</i> =4,127)	1.00	1.27 (0.95–1.69)	1.86 (1.36–2.55)	0.0001
SiMES population				
Using log binomial model instead of logistic regression	1.00	1.12 (0.97–1.29)	1.21 (1.05–1.40)	0.01
Excluding those with clinical inflammation, CRP >10 mg/l (<i>n</i> =2,174)	1.00	1.24 (1.00–1.53)	1.31 (1.04–1.65)	0.03
Excluding those with history of CVD (<i>n</i> =2,126)	1.00	1.28 (1.03–1.60)	1.34 (1.07–1.69)	0.02

^a Adjusted for age (years), sex (female, male), race–ethnicity (Chinese, Malay, Indian) in SP2, education (primary/below, secondary/higher), BMI (kg/m²), current smoker (absent, present), ever drinker (absent, present), hypertension (absent, present), total cholesterol (mmol/l)

^b Referent

The mechanism linking elevated CRP levels and prediabetes could be partially explained by its association with insulin resistance [28]. Treatment with insulin-sensitising agents has been shown to lower CRP levels in type 2 diabetic patients [29]. Subclinical inflammation leads to endothelial dysfunction and increased peripheral resistance that promotes insulin resistance further [30, 31].

Our finding of a stronger association between CRP and prediabetes in women is consistent with previous reports [13, 14, 21, 32]. Nakanishi et al. [13] reported a stronger association between CRP and fasting plasma glucose in Japanese women compared with men [13]. Few previous studies found an association between CRP and fasting plasma glucose in women only [14, 21]. In the KORA study in Germany, the positive association between CRP and diabetes disappeared in men after adjustment for BMI, whereas it persisted in women [32]. It could be speculated that the stronger association between CRP and prediabetes in women could be as a result of higher insulin resistance resulting from higher body fat composition [32]. At comparable BMI levels, women tend to have higher body fat than men [33, 34]. Also, endogenous sex hormones modulate glucose metabolism differently in men and women [35]. Lower levels of oestrogens and higher levels of androgens increase the risk of diabetes in women [36, 37].

In the current study, the association between CRP and prediabetes was significantly present among Chinese and Malays. Although the association was in the same direction as other ethnic groups, the association was weaker and not statistically significant in Indians. This is in contrast to previous reports from the UK [38] and India [39, 40] that have reported an association between CRP and diabetes

among Indians. The exact reason for this lack of association among Indians is not clear. It may be because of the relatively smaller sample size of the Indian cohort. Further studies with larger sample sizes are warranted to explore the association between CRP and prediabetes among Indians.

We found that the association between CRP and prediabetes was stronger among those with BMI <25 kg/m². Similar to our report, few previous studies [41, 42] including a Japanese study [32], have shown that the association between CRP and diabetes is stronger among lean individuals, whereas some studies have shown that this association is consistently present among those with normal BMI and overweight individuals [20]. Adipose cells produce proinflammatory cytokines that play a role in the development of insulin resistance and glucose intolerance [43, 44]. Our finding of an association between CRP and prediabetes could be owing to the association between BMI and prediabetes in those with BMI <25 kg/m². Consistent with our findings, previous studies have reported that Asians have higher visceral adipose tissue and higher per cent of body fat despite a lean BMI resulting in a higher risk for insulin resistance [45, 46].

Our study has some limitations. The cross-sectional nature of the study limits making causal inferences. Strengths of the study include its large sample size, population-based nature and the use of two separate Asian cohorts.

In conclusion, data from two large-population based Asian cohorts show that elevated CRP levels are associated with prediabetes. If confirmed by future prospective studies, CRP evaluation may be a useful tool in clinical practice for assessing future risk of diabetes in Asian populations.

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Duality of Interest The authors declare that there is no duality of interest associated with this manuscript.

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