C-reactive Protein, Body Mass Index, and Diabetic Retinopathy

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Purpose. C-reactive protein (CRP) is an inflammatory biomarker that may be associated with diabetic retinopathy (DR), but body mass index (BMI) is an important confounder of this relationship. The purpose of this study was to determine the relationship between CRP, BMI, and existing DR.

Methods. This was a population-based, cross-sectional study on 718 persons with diabetes in the Singapore Malay Eye Study (SiMES). Diabetes was defined as random glucose ≥ 11.1 mmol/L, on diabetic medication or a history of physician-diagnosed diabetes. CRP was measured in frozen plasma. DR was graded from retinal photographs.

Results. Higher CRP and BMI were associated with lower prevalence of DR. After adjustment for age, sex, HbA1c level, hypertension, smoking, total cholesterol level, cholesterol-lowering medication, and insulin use, persons with the highest quartiles of CRP were less likely to have any DR (odds ratio [OR] 0.5; 95% CI, 0.3–0.9, comparing the fourth with the first quartile of CRP), vision-threatening DR (OR 0.3; 95% CI, 0.1–0.7), or CSME (OR 0.2; 95% CI, 0.1–0.6). Similarly, persons with the highest quartiles of BMI were less likely to have any DR (OR 0.5; 95% CI, 0.3–0.7), moderate DR (OR 0.4; 95% CI, 0.2–0.7), vision-threatening DR (OR 0.4; 95% CI, 0.1–0.8) or CSME (OR 0.2; 95% CI, 0.0–1.0). No significant interactions between CRP and BMI on DR were seen.

Conclusions. Persons with diabetes who had higher levels of CRP and BMI were less likely to have DR. Further research is needed to understand the interrelationship role of inflammation, body weight, and microvascular complications. (*Invest Ophthalmol Vis Sci.* 2010;51:4458–4463) DOI:10.1167/iovs.09-4939

Diabetic retinopathy (DR) is a major cause of visual loss worldwide, with vision-threatening DR present in 10% of persons with diabetes.[1–9] Although hyperglycemia and hypertension are clearly involved in the pathogenesis of DR, other risk factors and pathogenetic pathways are not fully elucidated despite substantial research.[10–14]

C-reactive protein (CRP) is an inflammatory biomarker[15] involved in endothelial dysfunction and atherogenesis[16–18] and has been associated with macrovascular disease[19–21] and the nonocular microvascular[22,23] complications of diabetes. Data on a possible association of CRP with DR, however, are sparse, and results from limited studies have been inconsistent. In the Hoorn study,[10] a large population-based cohort study of 625 adults, higher CRP was associated with the prevalence of any DR. Spijkerman et al.,[11] however, reported that CRP levels were not associated with DR progression over 10 years in a prospective clinic-based study of 328 subjects with type 2 diabetes, and Le et al.[24] also did not find an association between CRP levels and the severity of DR in 163 young Pima Indians with early-onset type 2 diabetes. Recent reports from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and the Multi-ethnic Study of Atherosclerosis (MESA) also did not find any associations between CRP and DR.[25,26]

The association of body mass index (BMI) and DR has also been equivocal. Some studies have demonstrated a relationship between obesity or higher BMI and an increased risk of DR,[27–31] but others, including the WESDR, have reported contradictory results, in which higher BMI levels may be protective of DR.[30,32–35]

As CRP and BMI levels are intimately related,[36–40] and BMI may have significant confounding influences on the relationships between CRP levels and DR,[11,41] we aimed to determine the relationship between CRP, BMI, and the presence and severity of DR, in persons with diabetes mellitus from a population-based study in Asian Malays.

Methods

Study Population

The Singapore Malay Eye Study (SiMES) is a population-based, cross-sectional study of urban Malay adults aged 40 to 80 years residing in Singapore. Study design and population details have been described elsewhere.[1,42–45] In brief, Malay subjects were selected from a national database by using an age-stratified random sampling process. Of those eligible, 3280 (78.7% participation rate) were examined between 2004 and 2006. Diabetes mellitus was identified from plasma glucose ≥200 mg/dL (11.1 mmol/L); self reported use of diabetic medication, or physician-diagnosed diabetes. These criteria were met by 718 (21.9%) of the subjects, and they were included in the analysis.

All study procedures were performed in accordance with the tenets of the Declaration of Helsinki as revised in 1989. Written informed consent was obtained from the subjects, and the study was approved by the Institutional Review Board of the Singapore Eye Research Institute.

Measurement of BMI

All participants had a standardized systemic and eye examination. Height was measured in centimeters using a wall-mounted measuring

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tape, and weight was measured in kilograms using a digital scale (SECA, model 782 2321009; Vogel & Halke, Hamburg, Germany). Height and weight were measured without shoes and with the subject standing. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.[46]

Measurement of C-reactive Protein Levels

A 40-mL sample of venous blood was collected from the participants, who had not fasted. Serum CRP was measured in frozen plasma that had been stored at −80°C at the National University Hospital Reference laboratory by using an immunoturbidimetric assay (intra-assay precision 0.6%–1.3%, interassay precision 2.3%–3.1%) implemented on a chemistry analyzer (COBAS Integra 400; Roche Diagnostics, Mannheim, Germany). The detection limit of this assay is 0.07 mg/L, and the coefficient of variation is 2.9% at a mean of 6.3 mg/L and 3.9% at a mean of 108 mg/L.

Assessment of Diabetic Retinopathy

Retinal photography was performed according to a standard protocol, the details of which have been described in other publications regarding the same cohort.[1,43,47] Briefly, after pupil dilation, two retinal photographs, centered at the optic disc and macula, were obtained from both eyes of each participant by digital retinal camera (CR-DGi with a 10-D SLR; Canon, Tokyo, Japan). Photographs then were sent to the Centre for Vision Research, the University of Sydney, where retinopathy and other retinal diseases were graded by trained graders in the Blue Mountains Eye Study retinal photographic center.[48,49] Retinopathy was considered present if any characteristic lesions were detected, according to the Early Treatment Diabetic Retinopathy Study (ETDRS) standard set of images (microaneurysms [MA], hemorrhages, cotton wool spots, intraretinal microvascular abnormalities [IRMA], hard exudates [HE], venous beading, and new vessels).[47] For each eye, a retinopathy severity score was assigned according to the modified Airlie House classification system.[47] Retinopathy severity was categorized as minimal nonproliferative diabetic retinopathy (NPDR; ETDRS levels 15 through 20), mild NPDR (level 35), moderate NPDR (levels 43 through 47), severe NPDR (level 53), and proliferative retinopathy (level, >60). If an eye was ungradable, it was excluded from the analysis. Macular edema (ME) was defined by hard exudates in the presence of MA and blot hemorrhage within 1 disc diameter from the foveal center or the presence of focal photocoagulation scars in the macular area. Clinically significant macular edema (CSME) was deemed to be present when the ME was within 500 mm of the foveal center or if focal laser photocoagulation scars were present in the macular area.

Assessment and Definitions of Risk Factors

Physical examination included anthropometry and blood pressure measurement. Blood pressure was measured with an automated sphygmomanometer (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies Inc., Milwaukee, WI), with the patient seated after 5 minutes of rest. Systolic and diastolic blood pressures (BPs) were taken.[50] Two readings were taken 5 minutes apart, with a third reading taken if the two differed by >10 mm Hg systolic or >5 mm Hg diastolic. The mean of the two closest readings was then used for the analysis. Hypertension was defined as a systolic pressure of >140 mm Hg, a diastolic pressure >90 mm Hg, or a self-reported history of hypertension.

All participants underwent a standardized interview[43,51,52] that covered socioeconomic measures (e.g., income, education), lifestyle risk factors (e.g., smoking), medication use, and a self-reported history of systemic diseases. Nonfasting venous blood samples were drawn and sent for analysis of serum lipid levels (total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), hemoglobin A1c (HbA_{1c}), and glucose at the National University Hospital Reference Laboratory on the same day. Urine samples were collected to determine levels of microalbuminuria and creatinine at the Alexandra Hospital Laboratory. Chronic kidney disease (CKD) was defined as the estimated glomerular filtration rate of less than 60 mL/min per 1.73 m^2.[52]

Statistical Analysis

Four DR outcomes were defined for analyses (SPSS ver. 16.0; SPSS Inc., Chicago, IL). Any DR was defined as minimal NPDR or worse, moderate DR as moderate NPDR or worse, and vision-threatening retinopathy as the presence of severe NPDR, proliferative retinopathy, or CSME, according to the Eye Diseases Prevalence Research Group definition.[7] Any CSME was also analyzed as a separate outcome. Linear trend in the mean characteristics and proportions across the CRP quartiles was tested based on the χ^2 or ANOVA. Multivariate logistic regression models were constructed with the DR outcomes as the dependant variables, to assess the relationship with CRP, initially adjusting for age and sex. HbA1c level, hypertension, smoking, total cholesterol level, intake of cholesterol-lowering medication, insulin use, and BMI were added in the subsequent multivariate models. Subgroup analyses were conducted stratified by the overweight and CRP status as follows: BMI was dichotomized as overweight (BMI ≥ 25 kg/m^2) and not overweight (BMI < 25 kg/m^2), and CRP was as classified as >2.15 and ≤2.15 mg/dL. Odds ratio (OR) and 95% confidence interval (CI) are presented.

Results

A total of 718 subjects (309 [43%] men) with diabetes were included in the analysis. The mean (SD) values for age and CRP were 62.5 (9.4) years and 4.4 (8.3) mg/dL, respectively. Table 1 summarizes the demographic and systemic characteristics of study participants, stratified by sex and quartiles of CRP level. In unadjusted analyses, higher quartiles of CRP levels were associated with younger age and higher BMI in both the men and the women ($P = 0.005$ and <0.001 respectively in males; $P = 0.001$ and <0.001 respectively in females), and with shorter duration of diabetes in the women ($P = 0.002$).

In age-sex adjusted models, subjects with highest levels of CRP were significantly less likely to have any DR (0.8, per log unit increase in CRP levels) and vision-threatening DR (OR 0.8; Table 2). Similarly, subjects with the highest levels of BMI were significantly less likely to have any DR (OR 0.95, per unit increase in BMI), moderate DR (OR 0.93), vision-threatening DR (OR 0.92), or CSME (OR 0.91).

Table 3 shows that after adjustment for age, sex, HbA1c level, hypertension, smoking, total cholesterol level, cholesterol-lowering medication, insulin and aspirin use, the significant and negative associations of CRP levels with nearly all DR outcomes assessed persisted. However, there were no significant interactions between CRP and obesity for any DR, moderate DR, vision-threatening DR, or CSME (*P* interaction terms = 0.25, 0.82, 0.30, and 0.66, respectively).

After adjustment for age, sex, HbA1c level, hypertension, smoking, total cholesterol level, and cholesterol-lowering medication, insulin and aspirin use, subjects in the highest quartiles of BMI were less likely to have any DR (*P* for trend = 0.001), moderate DR (*P* for trend = 0.001), vision-threatening DR (*P* for trend = 0.005), or any CSME (*P* for trend = 0.04; Table 3). There were no significant interactions between CRP and obesity for any DR, moderate DR, vision-threatening DR, or CSME (*P* interaction terms = 0.18, 0.87, 0.47, and 0.91, respectively).

Stratification by sex revealed that women with the highest levels of CRP were less likely to have any DR (OR 0.7; 95% CI, 0.5–0.9, per log unit increase in CRP levels), moderate DR (OR 0.7; 95% CI, 0.5–0.9), vision-threatening DR (OR 0.6; 95% CI, 0.4–0.8), or CSME (OR 0.5; 95% CI, 0.3–0.9). In the men, we did not find significant associations between CRP and DR (data not shown). When stratified according to treatment, the asso-

Table 1. Characteristics of the Participating Diabetic Malay Adults, by Quartiles of CRP

	CRP				
	1st Quartile (n = 95)	2nd Quartile (n = 85)	3rd Quartile (n = 78)	4th Quartile (n = 46)	P for Trend*
Male subjects					
Age, y	65.6 (9.6)	63.7 (9.7)	62.0 (10.2)	60.9 (10.1)	**0.005**
BMI, kg/m^2	21.8 (2.1)	25.6 (0.8)	28.4 (1.0)	33.9 (3.1)	**<0.001**
Hypertension, yes vs. no	76 (80.0)	74 (87.1)	70 (89.7)	41 (89.1)	0.071
Total cholesterol, mmol/L	5.3 (1.3)	5.2 (1.2)	5.2 (1.1)	5.2 (0.9)	0.735
Blood glucose, mmol/L	11.3 (5.8)	10.8 (4.9)	10.9 (5.6)	10.2 (4.6)	0.318
HbA1c, %	8.4 (2.3)	8.3 (1.9)	8.4 (1.7)	7.8 (1.4)	0.128
Duration of diabetes, y	11.3 (11.8)	9.2 (9.1)	8.0 (6.9)	7.8 (6.9)	0.041
Current smoking, yes vs. no	28 (29.5)	17 (20.0)	22 (28.2)	15 (32.6)	0.645
Aspirin use, yes vs. no	11 (11.6)	10 (11.8)	12 (15.4)	5 (10.9)	0.790
Statin use, yes vs. no	23 (24.2)	29 (34.1)	18 (23.1)	16 (34.8)	0.486
Female subjects	(n = 81)	(n = 92)	(n = 99)	(n = 131)	
Age, y	64.3 (8.8)	61.9 (9.0)	62.0 (8.6)	59.8 (9.0)	**0.001**
BMI, kg/m^2	21.8 (2.0)	25.5 (0.8)	28.7 (1.1)	33.9 (3.1)	**<0.001**
Hypertension, yes vs. no	68 (84.0)	77 (83.7)	82 (82.8)	119 (90.8)	0.141
Total cholesterol, mmol/L	5.9 (1.3)	5.8 (1.3)	5.6 (1.3)	5.6 (1.3)	0.080
Blood glucose, mmol/L	11.3 (5.7)	11.3 (5.9)	10.8 (5.3)	11.1 (5.0)	0.606
HbA1c, %	8.5 (2.2)	8.7 (2.2)	8.5 (2.0)	8.4 (2.0)	0.615
Duration of diabetes, y	10.7 (9.5)	9.2 (8.4)	8.5 (7.7)	6.8 (6.3)	**0.002**
Current smoking, yes vs. no	2 (2.5)	2 (2.2)	1 (1.0)	4 (3.1)	0.820
Aspirin use, yes vs. no	9 (11.1)	6 (6.5)	12 (12.1)	10 (7.6)	0.678
Statin use, yes vs. no	17 (21.0)	28 (30.4)	30 (30.3)	39 (29.8)	0.247

Data presented are means (SD) or number (%), as appropriate.

* P-value for linear trend in mean characteristics across quartiles based on χ^2 or ANOVA. Bold denotes a significant trend.

ciations were stronger in subjects who were treated (i.e., subjects with a self reported history of diabetes medication).

Discussion

We report an association between higher levels of CRP and BMI and reduced prevalence of DR in an Asian Malay population with diabetes. Subjects with both high BMI and high serum CRP were less likely to have any of the DR outcomes assessed, including any DR, moderate DR, vision-threatening DR, and CSME.

There are substantial data supporting the role of CRP as a risk marker for diabetes and macrovascular disease.[15,53] In our cohort, consistent with previous reports, higher CRP levels were positively associated with classic cardiovascular risk factors including overweight or obese status and an adverse lipid profile. However, the associations of CRP with the microvascular complications of diabetes, or DR in particular, have been inconsistent from the few studies that examined this association (Table 4). In the EURODIAB study,[41] CRP was found to be positively associated with DR severity after adjustment for age, sex, HbA_{1c}, diabetes duration and SBP, but when BMI was added to the model, the association was no longer significant. Similarly, in a longitudinal study of patients with type 2 diabetes, Spijkerman et al.[11] reported that CRP was cross-sectionally associated with baseline prevalence of DR, but this association was not independent of HbA_{1c} levels and BMI and there were also no associations between CRP levels and DR progression. Other studies, however, reported no association between CRP and DR.[10,24,25] For example, prospective data from the WESDR

Table 2. Association of CRP, BMI, and DR, in Persons with Diabetes

	At Risk (n)	Any DR		Moderate DR		Vision-Threatening DR		Any CSME	
		n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
CRP									
1st quartile	164	69 (42.1)	1.0	32 (19.6)	1.0	25 (15.2)	1.0	12 (7.2)	1.0
2nd quartile	180	66 (36.7)	0.8 (0.5–1.2)	29 (16.4)	0.8 (0.4–1.4)	18 (10.1)	0.6 (0.3–1.2)	8 (4.4)	0.5 (0.2–1.4)
3rd quartile	167	50 (29.9)	**0.5 (0.3–0.9)**	22 (13.4)	0.6 (0.3–1.1)	15 (9.0)	0.5 (0.2–1.0)	4 (2.4)	0.3 (0.1–1.0)
4th quartile	202	65 (32.2)	**0.6 (0.4–0.9)**	30 (15.0)	0.6 (0.3–1.1)	18 (9.0)	**0.5 (0.2–0.9)**	7 (3.5)	0.4 (0.1–1.1)
P for trend			0.01		0.09		0.04		0.05
LogCRP	713	250 (35.1)	**0.8 (0.7–0.9)**	113 (16.1)	0.8 (0.7–1.0)	76 (10.7)	0.8 (0.6–1.0)	31 (4.3)	0.7 (0.5–1.0)
BMI									
1st quartile	174	71 (40.8)	1.0	35 (20.6)	1.0	22 (12.7)	1.0	8 (4.6)	1.0
2nd quartile	177	67 (37.9)	0.8 (0.5–1.3)	30 (17.1)	0.7 (0.4–1.2)	24 (13.6)	1.0 (0.5–1.9)	12 (6.8)	1.5 (0.6–3.7)
3rd quartile	176	53 (30.1)	**0.5 (0.3–0.9)**	21 (12.1)	**0.4 (0.2–0.8)**	13 (7.4)	0.5 (0.2–1.0)	7 (4.0)	0.8 (0.3–2.3)
4th quartile	175	51 (29.1)	**0.5 (0.3–0.8)**	22 (12.6)	**0.4 (0.2–0.7)**	12 (6.9)	**0.4 (0.2–0.8)**	2 (1.1)	0.2 (0.0–1.0)
P for trend			0.001		0.002		0.005		0.038
Per kg/m^2	702	242 (34.5)	**0.95 (0.92–0.98)**	108 (15.6)	**0.93 (0.88–0.97)**	71 (10.1)	**0.92 (0.87–0.97)**	29 (4.1)	**0.91 (0.84–1.00)**

Models adjusted for age and sex, presented as OR with 95% CI. Bold denotes significance.

TABLE 3. Association of CRP and BMI with DR in Persons with Diabetes

	At Risk (*n*)	Any DR		Moderate DR		Vision-Threatening DR		Any CSME	
		n (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
CRP									
1st quartile	163	69 (42.3)	1.0	32 (19.8)	1.0	25 (15.3)	1.0	12 (7.3)	1.0
2nd quartile	178	66 (37.1)	0.7 (0.4–1.1)	29 (16.6)	0.7 (0.4–1.3)	18 (10.2)	0.5 (0.2–1.0)	8 (4.5)	0.3 (0.1–1.0)
3rd quartile	165	49 (29.7)	0.5 (0.3–0.8)	21 (13.0)	0.5 (0.3–1.1)	14 (8.5)	0.4 (0.2–0.8)	4 (2.4)	0.1 (0.0–0.6)
4th quartile	192	57 (29.7)	0.5 (0.3–0.8)	26 (13.7)	0.5 (0.2–1.0)	14 (7.3)	0.3 (0.1–0.6)	5 (2.6)	0.1 (0.0–0.5)
P for trend			0.006		0.046		0.003		0.002
LogCRP	698	241 (34.5)	0.8 (0.6–0.9)	108 (15.7)	0.8 (0.6–1.0)	71 (10.2)	0.7 (0.5–0.9)	29 (4.1)	0.5 (0.3–0.7)
BMI									
1st quartile	173	71 (41.0)	1.0	35 (20.7)	1.0	22 (12.8)	1.0	8 (4.6)	1.0
2nd quartile	177	67 (37.9)	0.8 (0.5–1.2)	30 (17.1)	0.6 (0.3–1.1)	24 (13.6)	0.9 (0.5–1.8)	12 (6.8)	1.4 (0.5–3.6)
3rd quartile	174	52 (29.9)	0.5 (0.3–0.8)	21 (12.2)	0.4 (0.2–0.8)	13 (7.5)	0.4 (0.2–1.0)	7 (4.0)	0.8 (0.2–2.4)
4th quartile	174	51 (29.3)	0.5 (0.3–0.7)	22 (12.7)	0.4 (0.2–0.7)	12 (6.9)	0.4 (0.1–0.8)	2 (1.1)	0.2 (0.0–1.0)
P for trend			0.001		0.001		0.005		0.040
Per kg/m^2	698	241 (34.5)	0.95 (0.91–0.98)	108 (15.7)	0.92 (0.87–0.96)	71 (10.2)	0.91 (0.86–0.97)	29 (4.1)	0.90 (0.82–0.99)

Multivariate models adjusted for age; sex; HbA1c level; hypertension; smoking; total cholesterol level; use of cholesterol-lowering medication, insulin, or aspirin; and BMI (in CRP models only), presented as OR with 95% CI.

found that CRP levels were not associated with DR incidence or progression. Our study is the first to report an inverse (or protective) association of high CRP levels with low prevalence of any DR and vision-threatening DR, even after adjustment for BMI.

The relationship of BMI and DR has similarly been examined in epidemiologic studies, but again has shown inconsistent results. Most studies have reported positive associations between high BMI or obesity with DR.[27–31] The Diabetes Control and Complications Trial (DCCT) reported that high BMI was associated with DR after adjustment for metabolic control.[54] The EURODIAB Prospective Complications Study likewise reported that waist-hip ratio was an independent risk factor for incident DR after 7 years or more of follow-up.[29] Many explanations and mechanisms have been proposed to account for this association, including associations of DR with the metabolic syndrome,[55] and increased oxidative stress in persons with obesity as well as in those with DR.[28] Other studies have reported contradictory findings.[30,32–35] The WESDR found that the associations between obesity and DR progression and severity were not statistically significant and were limited only to individuals with older-onset insulin-independent diabetes,[35] whereas underweight subjects had a threefold increase in risk of DR.[30] Similarly, Dowse et al.[27] and Chaturvedi and Fuller[29] reported that decreasing BMI is associated with a higher prevalence of DR. Our results are in agreement with those in these latter studies.

Our findings of an association of higher CRP and BMI with lower prevalence of DR, while consistent across the different DR endpoints, were unexpected. Although the function of CRP in the systemic vasculature has been extensively studied,[56] little is known as to whether CRP function varies in the retinal microvasculature. One possible explanation is that CRP has proangiogenic properties and stimulates monocytic cells to upregulate expression of vascular endothelial growth factor A.[57] Thus, elevated CRP levels may be beneficial in the preproliferative stages of DR by increasing retinal perfusion and relieving ischemia. CRP has also been reported to have anti-inflammatory effects in monocytes through downregulation of α2-macroglobulin expression and upregulation of liver X receptor α expression.[58]

TABLE 4. Comparison of Data on the Associations between CRP and DR

Study	*n*	Age (y)	Study Population	Definition of Diabetic Retinopathy	Main Findings
EURODIAB[41]	543	≥36	Type 1 diabetes diagnosed before 36 years of age	Retinal photography	Higher CRP associated with DR in analyses adjusting for age, sex, HbA1c, diabetes duration, and systolic blood pressure. Associations not significant with further adjustment for BMI.
Hvidöre Hospital, Denmark[11]	363	<66	Type 2 diabetes	Baseline: dilated ophthalmoscopy, follow-up: retinal photography	Higher CRP associated with higher baseline risk of DR, but not independent of HbA1c, BMI, or urinary albumin excretion rate.
Hoorn study[10]	625	50–74	Type 2 diabetes	Direct ophthalmoscopy and retinal photography	Higher CRP associated with DR, but not with adjustment for BMI.
Wisconsin Epidemiologic Study of Diabetic Retinopathy[26]	671	Mean age, 37.4	Type 1 diabetes using insulin diagnosed before 30 years of age	Retinal photography	CRP levels not associated with prevalence, severity or progression of DR.
Multi-Ethnic Study of Atherosclerosis[25]	921	45–84	Type 2 diabetes	Retinal photography	CRP levels not associated with any DR or vision threatening DR.
Pima Indians[24]	163	25–39	Type 2 diabetes	Direct ophthalmoscopy	CRP levels not associated with severity of DR.

Another possible explanation for our findings is indication bias. In other words, persons with DR could have adopted positive behavioral modifications that led to lower CRP and BMI levels. This possibility is supported by the finding that the associations were stronger in the subjects with a history of diabetic medication use. However, most subjects with DR have mild DR, which is largely asymptomatic,[1] and 85% of subjects in our cohort were unaware that they had DR (Wong TY, unpublished data, 2009). Also, the only class of oral hypoglycemic agents that has been shown to reduce CRP levels so far are the thiazolidinediones,[59] but these agents are generally avoided in subjects with DR due to the possible aggravation of CSME.[60]

The strengths of our study design include the standardized assessments of serum biochemistry, retinal photography, anthropometric measures, and blood pressure and a large population-based sample with a relatively high prevalence of DR. We also had data to account for a wide range of potential confounding factors in statistical models. The limitations of our study include the possibility of selection bias, although only a small proportion of participants were excluded because of missing data. The cross-sectional design of our study restricts any inferences of causality and also subjects it to indication and other potential biases. Survival bias may also have lead to underrepresentation of subjects with high CRP and severe DR in our cohort, as these subjects could have been more likely to have had severe systemic comorbidities or even mortality that precluded their participation. Diabetes was defined using random blood glucose for those without a previously diagnosed history of diabetes, which could have led to a misclassification of diabetes status. Use of nonstereoscopic fundus photography could also have led to a misclassification of CSME. CRP levels may also have been influenced by a variety of infectious and inflammatory conditions, and our analyses were based on only a single measurement of CRP levels. These potential misclassification errors are nondifferential and therefore would only bias our results toward the null.

In conclusion, we report that Asian diabetic patients with higher levels of CRP and BMI were less likely to have DR. The results in our study compared with those in other studies (largely in white populations) may reflect racial or ethnic differences in CRP and BMI levels, and diabetes status, reflecting complex genetic and environmental variation. These associations suggest the further research is needed to understand the role of inflammation, body weight, and their interaction on the pathogenesis of DR.

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