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Association between circulating cell adhesion molecules and risk of type 2 diabetes: A meta-analysis

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HIGHLIGHTS

- Elevated ICAM-1 and E-selectin increased type 2 diabetes risk dose-dependently.
- Elevated VCAM-1 or P-selectin did not significantly predict type 2 diabetes risk.
- ICAM-1 showed comparable ability to E-selectin in predicting type 2 diabetes.
- CAMs exhibited limited incremental value beyond traditional prediction algorithms.

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ABSTRACT

Background and aims: Cell adhesion molecules (CAMs) are implicated in the initiation and progression of atherosclerosis, but their association with risk of type 2 diabetes remains inconsistent. This meta-analysis aimed to quantify this association with dose-response analysis in the general population without type 2 diabetes at baseline.

Methods: Prospective studies, investigating the association of circulating (plasma/serum) CAMs, such as intercellular adhesion molecule-1 (ICAM-1), E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and P-selectin, with risk of type 2 diabetes, were included. The overall relative risks (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model.

Results: Sixteen datasets from 15 studies were included. The overall RR was 1.88 (95% CI 1.59 to 2.23) per 1-ln μg/ml increase in ICAM-1, and 2.44 (95% CI 1.90 to 3.12) per 1-ln μg/ml increase in E-selectin. These associations were log-linearly shaped (both $p_{non\text{-}linearity} > 0.05$) and independent of traditional cardiovascular risk factors (all $p < 0.05$). ICAM-1 had comparable predictive ability as E-selectin (2.22 *versus* 2.66, $p = 0.40$). However, no significant association was observed for VCAM-1 (RR 1.20, 95% CI 0.73 to 1.98) or P-selectin (RR 1.01, 95% CI 0.64 to 1.59), and the added predictive value of circulating CAMs assessed by Integrated Discrimination Improvement to the basic prediction models was small (0.01 for ICAM-1, 0.003 for E-selectin, and 0.007 for VCAM-1).

Conclusions: Elevated circulating CAMs, especially ICAM-1 and E-selectin, led to increased risk of type 2 diabetes in a dose-dependent manner, supporting the assumption that endothelial dysfunction contributes to the development of diabetes.

1. Introduction

As the surrogate markers of endothelial function, cell adhesion molecules (CAMs) are a subset of cell surface proteins released from cell membranes upon proteolytic shedding or cleavage [1–3]. Accumulating evidence suggests that CAMs play a crucial role for the initiation and progression of atherosclerosis [3,4], mediating leukocytes recruitment to vessel wall and leukocytes transmigration across the endothelial

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surface in response to inflammatory stimuli [2–4]. Apart from being a possible contributing factor to atherosclerosis, it is suggested that CAMs are closely linked to the development of insulin resistance [2,5,6], which is considered the pathophysiological hallmark featured by type 2 diabetes [6]. This has recently led to an ongoing interest in exploring the association of circulating (plasma/serum) CAMs with risk of type 2 diabetes [7–22], since it may theoretically help refine diabetes risk stratification and diversify the options for diabetes prevention and/or treatment.

In studies that assessed the association of circulating CAMs with risk of type 2 diabetes, soluble forms of intercellular adhesion molecule-1 (ICAM-1), E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and P-selectin were found to be the most commonly detected CAMs in blood circulation [1,12]. Yet, evidence regarding their relationships with risk of type 2 diabetes has not reached a consensus. For example, some studies showed that elevated ICAM-1 or E-selectin was associated with significantly increased risk of type 2 diabetes [10–12], while others argued that these association might not exist or showed limited predictive value [16,17]. Despite several narrative reviews were in favor of the usefulness of these markers in predicting type 2 diabetes [2,5,23], they did not provide quantified analyses accounting for existing heterogeneity across studies (e.g., variations in scaling or adjusted variables), nor specified which CAM may carry stronger power [2,5].

Given these inconsistencies, this meta-analysis of prospective studies was aimed to quantify the association of circulating CAMs represented by ICAM-1, E-selectin, VCAM-1, and P-selectin with risk of type 2 diabetes, along with analyses exploring the heterogeneity and the effort to identify the most sensitive marker to detect diabetes. Moreover, to have a better understanding of the predictive abilities of CAMs for type 2 diabetes, we also attempted to examine whether they would produce any incremental benefit assessed by Integrated Discrimination Improvement (IDI) index, if they were added to the referent prediction algorithm incorporating traditional cardiometabolic risk factors such as age, body mass index (BMI), glycemic control, and/or lipid profiles.

2. Materials and methods

This study was conducted according to the guideline of Meta-analysis Of Observational Studies in Epidemiology [24], and its protocol was registered in PROSPERO as CRD42018116107. Literature search, study selection, data extraction, and quality assessment were initially performed by one investigator (S.Q), and later cross-checked by another investigator (X.C.). Disagreements were solved by discussion or consultation with a third investigator (U.S.).

2.1. Search strategy

A literature search of PubMed, the Cochrane Library of Controlled Trials, and the Web of Science was performed from their inception to October 22, 2018, using the words or terms associated with "cell adhesion molecules" and "diabetes" (Supplementary Table 1). In addition, the reference lists of identified articles or relevant systematic reviews or meta-analyses were manually checked for additional studies.

2.2. Selection criteria

To be included, an individual study had to: i) have a cohort, case-cohort, or nested case-control design conducted in adult population without baseline type 2 diabetes; ii) report incident type 2 diabetes as the outcome; iii) select any of the circulating CAMs, which include ICAM-1, E-selectin, VCAM-1, or P-selectin, as the exposure; iv) provide risk estimates such as hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs); and v) be published in English. Studies were excluded if they were letters, comments, or reviews, focused on gestational diabetes, or utilized a cross-sectional design. Studies were also excluded if they enrolled only populations with specific diseases using specific medications, or did not provide sufficient information to obtain the risk estimates after contacting with the corresponding authors (if any).

2.3. Data collection

Data were collected using a standardized form, which includes information as follows: author, publication year, study design, country, sample size, numbers of cases/controls, mean age, proportion of women, mean BMI, follow-up length, mean and/or standard deviation (SD) of CAM levels at baseline and different exposure levels, RR and 95% confidence interval (CI), IDI (if any), assays for measuring CAMs, methods for type 2 diabetes ascertainment, and covariables adjusted. If a study reported multiple HRs/ORs, the one adjusted for the largest number of covariables was selected [25,26]. If a single cohort generates multiple studies, data were abstracted from the study with the biggest number of incident type 2 diabetes. If means or SDs were not reported, they were imputed using the methods described previously [25–28]. In brief, for studies reporting medians and/or interquartile ranges, means were considered equal to medians [25], and SDs were calculated by dividing the width of the interquartile ranges by 1.35 [26]. In studies that reported the individual means or SDs for different groups instead, the overall ones were obtained by combining them [26]. In studies analysing circulating CAMs in tertiles without specifications on exposure levels, it is assumed that the difference for standard normal distribution mean values of the top tertile *versus* bottom one is 2.18 SD units [27,28].

2.4. Quality assessment

Study quality of included studies was assessed using the validated Newcastle-Ottawa Scale [29]. It has 3 main domains: selection category (0-4 stars), comparability category (0-2 stars), and outcome/exposure category (0-3 stars). Studies receiving ≥7 stars were considered of high quality.

2.5. Statistical analysis

RRs were used as the main effect size, and HRs and ORs were assumed to be equal to RRs in this meta-analysis. To obtain a consistent approach for meta-analysis, the risk estimate for each study was transformed into RR per 1-ln μg/ml increase in each of the circulating CAMs that include ICAM-1, E-selectin, VCAM-1, and P-selectin. If this study-specific RR was not provided initially, it was estimated using the generalized least squares for trend estimation analysis by assuming a log-linear relationship [30–32]. To plot the dose-response relationship, the method described by Orsini et al. was referred to Ref. [33], in which the non-linear association was assessed using Wald test by hypothesizing that the coefficient of the second spline is equal to zero.

The random-effects model, which better accounts for between-study heterogeneity than the fixed-effects model [26], was applied to obtain the summary RRs or IDI and corresponding 95% CIs. A two-tailed $p < 0.05$ was considered statistically significant. Heterogeneity was assessed using I^2 statistic mainly, with the core > 50% indicative of significant heterogeneity [26]. Subgroup and meta-regression analyses were conducted to investigate the difference in RRs according to mean age and BMI, location (country), risk estimates, blood samples, proportion of women, follow-up length, and adjustment for confounders (e.g., smoking, drinking, physical activity, C-reactive protein), or for potential intermediates (e.g., glycemic control, blood pressure, lipid profile). Sensitivity analysis by omitting a study at a time was performed to evaluate the influence of each individual study. Publication bias was assessed by Egger's test and Begg's test, with either $p < 0.10$ being the threshold of significance. All analyses were performed using STATA (Version 14.0, StataCorp, College Station, Texas).

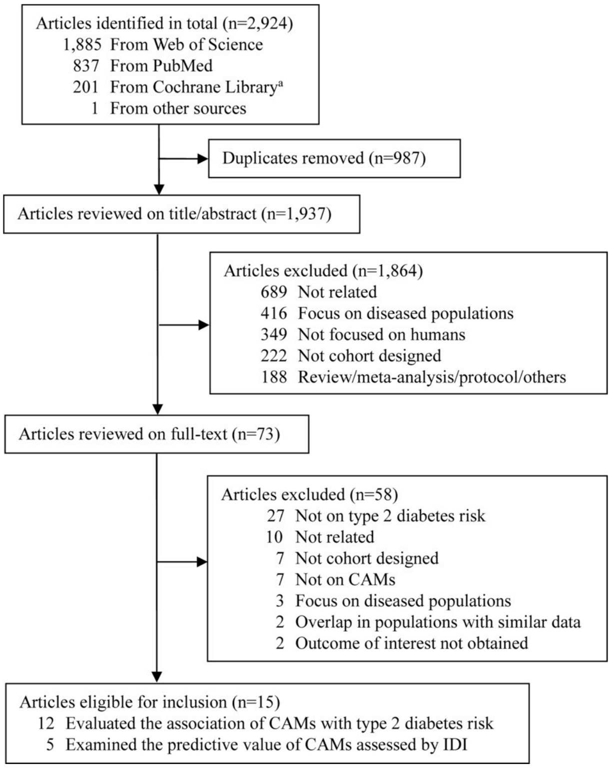

Fig. 1. Study selection process.
[a] Studies were searched in the Cochrane Central Register of Controlled Trials. CAMs, cell adhesion molecules; IDI, Integrated Discrimination Improvement.

3. Results

3.1. Characteristics of identified studies

The literature search yielded 1937 unique publications upon the removal of duplicates, and 15 of them were identified as suitable, following screening of titles/abstracts and review of full-texts (Fig. 1) [7–21]. Among them, one study reported sex-specific data [15], and was treated as 2 separate datasets when performing the meta-analyses.

Among the prospective studies investigating the association of circulating CAMs with risk of type 2 diabetes [7–18], there were 6 cohort studies, 2 case-cohort studies, and 4 nested case-control studies. The sample size ranged from 142 to 4945, and the length of follow-up varied from 3.2 to 13 years. The mean age of enrolled participants at entry was from 32.3 to 75.4 years, with their mean BMI differing from 26.3 to 36.3 kg/m^2 (Table 1). For studies that reported results on IDI associated with circulating CAMs [8,9,19–21], the main characteristics are summarized in Supplementary Table 2, in which the sample size differed from 821 to 3782, and the mean age ranged from 35.4 to 62.5 years.

Of the 15 studies included, 11 were from USA [7,9–14,16,17,19,21], and the other 4 from Europe [8,15,18,20]. All circulating CAMs were measured using ELISA kits, which were majorly purchased from R&D Systems (Minneapolis, MN, USA), with the assay coefficients of variation reported to be less than 10% for almost all circulating CAMs. More than half of the studies collected fasting blood samples and used plasma for CAMs measurement (Supplementary Table 3). The study quality of included studies was judged to be high.

3.2. Association of ICAM-1 with risk of type 2 diabetes

Thirteen datasets from 12 studies with 4,673 incident cases among 23,191 participants were included in the meta-analysis for the association between ICAM-1 and risk of type 2 diabetes [7–18]. The summary RR of type 2 diabetes was 1.88 (95% CI 1.59 to 2.23) per 1-ln μg/ml increase in ICAM-1 (Fig. 2A), along with low heterogeneity ($I^2 < 1\%$). Dose-response analysis from 9 datasets with at least 3 categories of ICAM-1 [7,8,10–15] indicated that there was no evidence of a non-linear association between ICAM-1 and risk of type 2 diabetes (p for non-linearity = 0.73, Fig. 2B).

Subgroup analyses showed that this association was not significantly affected by study location or blood sample resources, but turned to be stronger among studies using fasting samples (RR 2.00, 95% CI 1.66 to 2.40) than non-fasting ones to measure ICAM-1 (Table 2). Notably, despite smaller magnitudes observed, this association remained significant but became more conservative with adjustment for confounders or potential intermediates than without, in general (Table 2). Meta-regression analysis suggested that none of the variables including mean age, BMI, proportion of women, or length of follow-up could predict changes in the summary RRs (all $p > 0.24$). Sensitivity analysis showed none of the individual studies had a large influence on the summary RRs. No evidence of publication bias was detected by Egger's test ($p = 0.62$) or Begg's test ($p = 0.86$).

3.3. Association of E-selectin with risk of type 2 diabetes

Nine datasets from 8 studies that included 3,325 incident cases from 12,275 participants were available for the analysis on the association between E-selectin and risk of type 2 diabetes [8,10–15,17]. The summary RR of type 2 diabetes was 2.44 (95% CI 1.90 to 3.12) per 1-ln μg/ml increase in E-selectin (Fig. 2C), with significant heterogeneity ($I^2 = 52\%$). There was evidence of departure from a non-linear association between E-selectin and risk of type 2 diabetes (7 datasets [10–15], p for non-linearity = 0.07, Fig. 2D).

The positive association of E-selectin with risk of type 2 diabetes persisted across all subgroup analyses (Table 2), but the magnitude was larger in studies adjusting for confounders, whilst smaller in studies controlling for potential intermediates compared with those not. None of the variables such as mean age, BMI, proportion of women, or length of follow-up could predict any significant change in the summary RRs based on the meta-regression analysis (all $p > 0.48$). Sensitivity analysis revealed that none of the individual studies substantially affected the summary RRs. No evidence of publication bias was observed ($p = 0.73$ for Egger's test, and $p > 0.99$ for Begg's test).

3.4. Association of other circulating CAMs with risk of type 2 diabetes

Seven datasets from 7 studies including 2,895 incident cases among 11,257 participants were pooled for the association of VCAM-1 with risk of type 2 diabetes [8–13,17]. The summary RR of type 2 diabetes was 1.20 (95% CI 0.73 to 1.98, $I^2 = 70\%$) per 1-ln μg/ml increase in VCAM-1, and there was no evidence of a non-linear association (5 datasets [8,10–13], p for non-linearity = 0.54) (Supplementary Figs. 1A and B). Subgroup analysis showed that this association was non-significant after adjustment for confounders. Yet, it became significant and stronger after controlling for potential intermediates, along with reduced heterogeneity (Supplementary Table 4). No evidence of publication bias was detected ($p = 0.89$ for Egger's test, and $p > 0.99$ for Begg's test).

Three datasets from 3 studies with 566 incident cases from 6,863 participants gave information on the association of P-selectin with risk of type 2 diabetes [11,12,16]. Yet, only 2 of them were included in this meta-analysis [11,12,16], because one study did not report the outcome with comparable units as the others [16]. The summary RR of type 2 diabetes was pooled to be 1.01 (95% CI 0.64 to 1.59) per 1-ln μg/ml increase in P-selectin, with low heterogeneity ($I^2 = 25\%$).

3.5. Association of ICAM-1 versus E-selectin with risk of type 2 diabetes

Nine datasets from 8 studies reported results on both ICAM-1 and E-

Table 1
Characteristics of studies examining the association of circulating CAMs with risk of type 2 diabetes.

Author, year, location	Study name	Study design[a]	Age[b], year	BMI[b], kg/m^2	Women, %	Follow up, year	Diabetes		CAMs measured
							Yes	No	
Hoogeveen et al., 2007 [7]; USA	ARIC	A	53.1	28.7	60.4	9	581	572	ICAM-1
Julia et al., 2014 [8];France	SU.VI.MAX 2	C	51.5	26.3	50.9	13	82	1,263	ICAM-1 E-selectin VCAM-1
Kulkarni et al., 2016 [9]; USA	SAFHS	C	35.4	28.9	62.2	11.9	134	687	ICAM-1 VCAM-1
Meigs et al., 2004 [10]; USA	NHS	B	56.3	28.2	100	10	666	712	ICAM-1 E-selectin VCAM-1
Odegaard et al., 2016 [11]; USA	CARDIA	C	40.1	28.3	58	10	222 222 186 220	2,117 2,117 1,796 2,111	ICAM-1 E-selectin VCAM-1 P-selectin
Pankow et al., 2016 [12]; USA	MESA	C	59 59 62.3 62.3	27.8 28.3 27.3 27.3	92.2 79.8 53.3 54	8.1 8.1 6.5 6.5	286 107 172 184	1,899 719 1,626 1,710	ICAM-1 E-selectin VCAM-1 P-selectin
Song et al., 2007 [13]; USA	WHIOS	B	62.3	29.1	100	5.9	1,584	2,198	ICAM-1 E-selectin VCAM-1
Stranges et al., 2008 [14]; USA	WNYS	B	59	30.8	47.5	5.9	61	158	ICAM-1 E-selectin
Thorand et al. 2006A[c] [15]Germany	MONICA/KORA	A	54	28.4	0	10.5	310	902	ICAM-1 E-selectin
Thorand et al. 2006B[c] [15]Germany	MONICA/KORA	A	54	28.7	100	10.5	222	810	ICAM-1 E-selectin
Dallmeier et al., 2012 [16]; USA	FHS	C	59	27.7	56	6.6	162	2,476	ICAM-1 P-selectin
Krakoff et al., 2003 [17]; USA	MGRIC	B	32.3	36.3	66.2	5.7	71	71	ICAM-1 E-selectin VCAM-1
Sattar et al., 2009 [18];UK	PSPER	C	75.4	27.7	53	3.2	292	4,653	ICAM-1

CAMs, cell adhesion molecules; BMI, body mass index; ARIC, Atherosclerosis Risk in Communities Study; ICAM-1, intercellular adhesion molecule-1; SU.VI.MAX 2; SUpple'-mentation en VItamines et Mine'raux AntioXydants study 2; VCAM-1, vascular cell adhesion molecule-1; SAFHS, San Antonio Family Heart Study; NHS, Nurses' Health Study; CARDIA, Community-Based Coronary Artery Risk Development in Young Adults; MESA, Multi-Ethnic Study of Atherosclerosis; WHIOS, Women's Health Initiative Observational Study; WNYS, Western New York Study; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease/Cooperative Research in the Region of Augsburg studies; FHS, Framingham Heart Study; MGRIC, Members of the Gila River Indian Community; PSPER, Prospective Study of Pravastatin in the Elderly at Risk trial.

[a] A, case-cohort; B, nested case-control; C, cohort.
[b] It represented the average mean value at baseline.
[c] This study had sex-specific groups, with A on men and B on women.

selectin, and were included in the meta-analysis comparing the association of ICAM-1 *versus* E-selectin with risk of type 2 diabetes [8,10–15,17]. The summary RR of type 2 diabetes was 2.22 (95% CI 1.57 to 3.16) per 1-ln μg/ml increase in ICAM-1, and 2.66 (95% CI 2.14 to 3.31) per 1-ln μg/ml increase in E-selectin, with the difference being nonsignificant ($p = 0.40$ for the test of interaction, Supplementary Fig. 2).

3.6. *Improvement in the prediction ability of type 2 diabetes by circulating CAMs*

Five studies with a total of 2,758 incident cases among 8,842 participants explored the incremental predictive value for type 2 diabetes by adding a single CAM to the referent prediction models that included age and parameters related to obesity, glycemic control, blood pressure, and lipid profiles in general [8,9,19–21] (Supplementary Table 2). Meta-analyses showed that the index of IDI, which represents the improvement in prediction ability, was pooled to be 0.01 (95% CI 0.004, 0.015), 0.003 (95% CI -0.001, 0.007), and 0.007 (95% CI -0.001, 0.015) by adding ICAM-1, E-selectin, and VCAM-1 individually to the referent models, respectively (Fig. 3).

4. Discussion

4.1. *Summary of the main findings*

This meta-analysis of 15 prospective studies showed that the risk of type 2 diabetes was increased by 88% per 1-ln μg/ml increase in ICAM-1, and 144% per 1-ln μg/ml increase in E-selectin among the general population, both of which acted in a log-linear dose-dependent manner. However, no significant association was observed for VCAM-1 or P-selectin. This meta-analysis also showed that ICAM-1 was comparable to E-selectin in predicting type 2 diabetes, yet both exhibited limited value to improve the predictive ability of the basic prediction models, as evidenced by the very small or nonsignificant changes in IDI.

4.2. *Interpretation and implication*

In line with our findings, the systematic review conducted in 2012 found an increased risk of type 2 diabetes for a higher level of ICAM-1 or E-selectin, but not for VCAM-1 [34]. However, the conclusions from that study were derived from 3 individual studies with less than 10,000 participants only. Our current analyses summarized evidence from a total of 13 prospective datasets with more than 4,600 incident cases from about 23,200 participants, and therefore provides a more robust

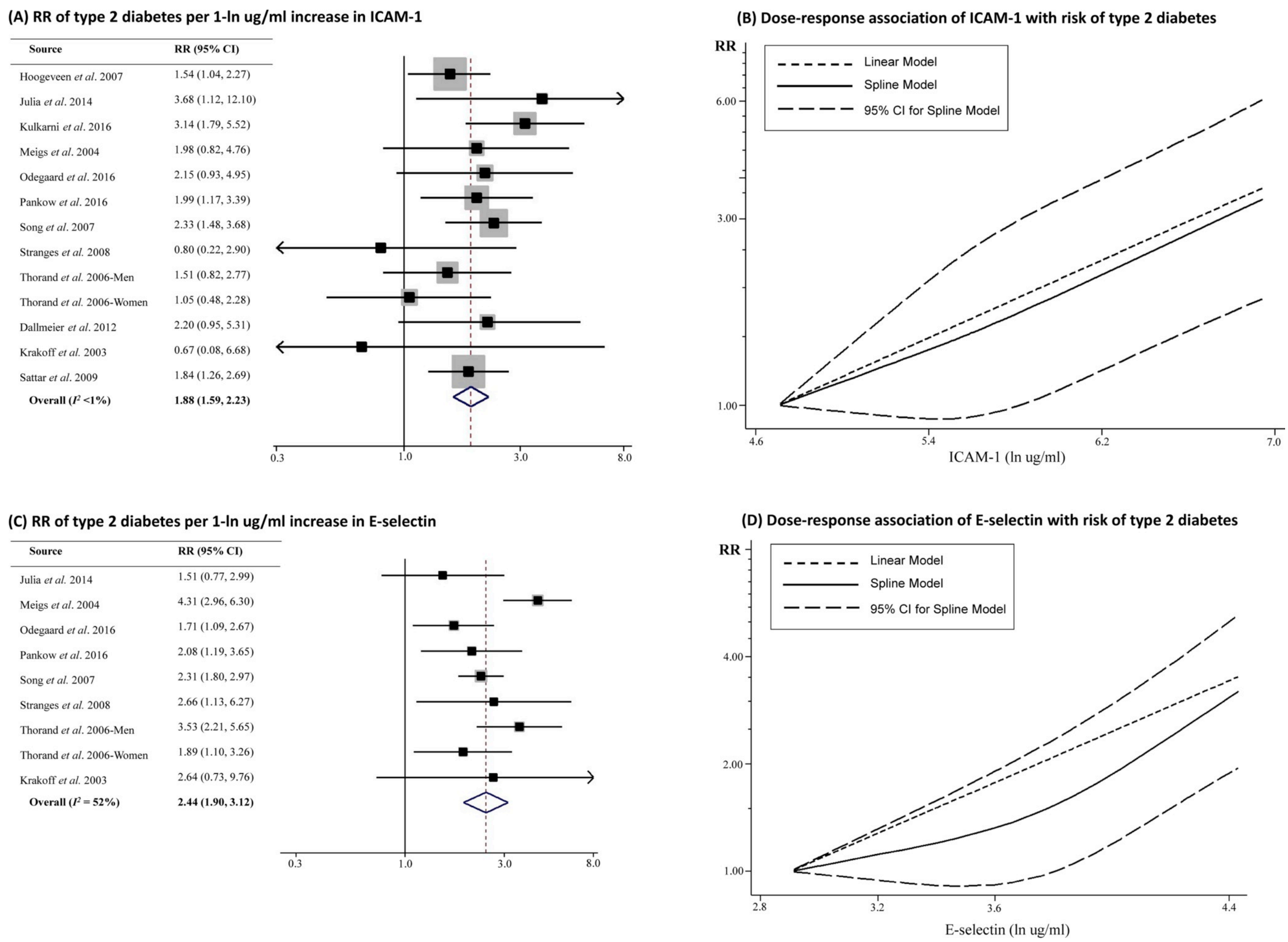

Fig. 2. Association of ICAM-1 and E-selectin with risk of type 2 diabetes.
(A) RR per 1-ln μg/ml increase in ICAM-1; (B) dose-response analysis for ICAM-1; (C) RR per 1-ln μg/ml increase in E-selectin; (D) dose-response analysis for E-selectin. ICAM-1 and E-selectin were modeled with restricted cubic splines with 3 knots. ICAM-1, intercellular adhesion molecule-1; RR, relative risk; CI, confidence interval.

and less biased overall estimate of the association for ICAM-1, E-selectin, and VCAM-1. Moreover, our study expanded the analyses beyond the previous one by using dose-response analysis, from which a linear dose-response relationship was noted for the first time for the risk of type 2 diabetes in relation to the increases in VCAM-1 or E-selectin. In addition, our study pooled results on the predictive value for P-selectin, a CAM that is less frequently examined in epidemiological studies [11,12,16], albeit showing a negative finding.

Several potential mechanism may help explain the association of elevated circulating CAMs with risk of type 2 diabetes. Firstly, elevated circulating CAMs might indicate the dysfunction of vascular endothelium [4], leading to reduced vascular permeability and a subsequently decreased insulin delivery to insulin sensitive peripheral tissues, along with impaired insulin-mediated glucose metabolism [35,36]. In addition, elevated circulating CAMs may also represent the dysfunction of islet endothelial cells, which may contribute to the loss of β-cell function [37,38]. Secondly, it is recognized that CAMs play an important role in leukocytes recruitment and migration in response to inflammatory stimuli [2]. Elevated circulating CAMs may therefore reflect a chronic inflammatory status that could be induced by advanced glycation end-products [39] or oxidative stress [40], which are believed to be associated with increased risk of type 2 diabetes [11,41]. Finally, epidemiological studies show that circulating CAMs such as ICAM-1 or E-selectin are positively related to several independent risk factors for type 2 diabetes like central obesity [42,43] or increased red meat intake [44].

Our study, as indicated by subgroup analyses, further showed that the association of ICAM-1 and E-selectin with increased risk of type 2 diabetes might be independent of factors suggested to be associated with or mediating the development of diabetes, such as smoking, drinking, physical inactivity, C-reactive protein, glycemic control, blood pressure, or lipid profiles [45]. Yet, this was not consistently observed for VCAM-1. The significant association of VCAM-1 with increased risk of type 2 diabetes was evident only after adjustment for glycemic control, blood pressure, or lipid profiles, but not for factors including smoking, drinking, physical activity, or C-reactive protein. These may, at least partly, suggest that ICAM-1 and E-selectin are more sensitive and stable than VCAM-1 in predicting type 2 diabetes. Notably, there is evidence that E-selectin might be a better surrogate biomarker for early endothelial dysfunction than other circulating CAMs (including ICAM-1) in the context that E-selectin is expressed exclusively on endothelial cells [2]. Furthermore, several epidemiological studies have observed that E-selectin is more recommended as a marker for diabetes prediction [11,13–15]. However, our comparisons did not provide support for these notions, but rather suggested that ICAM-1 was comparable to E-selectin in predicting type 2 diabetes.

The findings may help improve the understanding of the pathogenesis of diabetes, enriching the approaches for diabetes risk stratification. In addition, the findings may suggest that circulating CAMs (e.g., ICAM-1 and E-selectin) could serve as targets for lifestyle

Table 2
Subgroup analysis on the association between circulating CAMs and risk of type 2 diabetes.

Variable	ICAM-1 (for every 1-ln μg/ml increase)				E-selectin (for every 1-ln μg/ml increase)			
	N	RR (95% CI)	I^2 (%)	$p_{heterogeneity}$	N	RR (95% CI)	I^2 (%)	$p_{heterogeneity}$
Location (Country)								
Americans	9	1.99 (1.61, 2.45)	< 1	0.48	6	2.51 (1.84, 3.43)	57	0.04
Europeans	4	1.69 (1.22, 2.33)	12	0.33	3	2.25 (1.34, 3.76)	61	0.08
Measure of association								
HR/RR/IRR	10	1.87 (1.57, 2.23)	< 1	0.47	7	2.54 (1.93, 3.34)	59	0.02
OR	3	1.96 (0.91, 4.25)	33	0.22	2	1.88 (1.10, 3.23)	3	0.31
Blood sample collection time								
Fasted	9	2.00 (1.66, 2.40)	< 1	0.45	5	2.11 (1.74, 2.55)	< 1	0.63
Nonfasted	4	1.41 (0.93, 2.13)	< 1	0.66	4	3.14 (2.11, 4.68)	0.51	0.10
Blood sample resources[a]								
Plasma	6	1.87 (1.50, 2.33)	< 1	0.56	4	2.61 (1.64, 4.14)	71	0.02
Serum	6	1.96 (1.45, 2.64)	16	0.31	4	2.22 (1.58, 3.11)	45	0.14
Adjustment for confounders								
Smoking Yes	8	1.88 (1.53, 2.31)	< 1	0.80	6	2.53 (1.89, 3.39)	66	0.01
No	5	1.91 (1.12, 3.26)	50	0.09	3	1.97 (1.21, 3.23)	< 1	0.53
Drinking Yes	5	1.84 (1.38, 2.46)	< 1	0.46	5	2.60 (1.86, 3.64)	72	0.01
No	8	1.93 (1.52, 2.44)	14	0.32	4	2.02 (1.39, 2.92)	< 1	0.73
PA Yes	6	1.87 (1.45, 2.42)	< 1	0.60	6	2.53 (1.89, 3.39)	66	0.01
No	7	1.93 (1.44, 2.59)	26	0.23	3	1.97 (1.21, 3.23)	< 1	0.53
CRP Yes	7	1.69 (1.38, 2.07)	< 1	0.84	5	2.57 (1.74, 3.80)	71	0.01
No	6	2.37 (1.70, 3.31)	9	0.36	4	2.24 (1.79, 2.80)	< 1	0.67
Adjustment for potential intermediates								
Glucose Yes	7	1.76 (1.41, 2.20)	< 1	0.60	4	2.02 (1.39, 2.92)	< 1	0.73
No	6	2.02 (1.50, 2.72)	21	0.28	5	2.60 (1.86, 3.64)	72	0.01
BP Yes	7	1.81 (1.46, 2.25)	13	0.33	3	2.41 (1.71, 3.40)	62	0.02
No	6	2.11 (1.51, 2.94)	< 1	0.51	6	2.46 (1.65, 3.67)	43	0.17
Lipid Yes	7	1.85 (1.43, 2.39)	26	0.23	3	2.25 (1.34, 3.76)	61	0.08
No	6	2.01 (1.50, 2.68)	< 1	0.65	6	2.51 (1.84, 3.43)	57	0.04

CAMs, cell adhesion molecules; ICAM-1, intercellular adhesion molecule-1; RR, relative risk; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; PA, physical activity; CRP, C-reactive protein; BP, blood pressure.
[a] The study by Stranges et al. did not specify the source of blood and was not included [14].

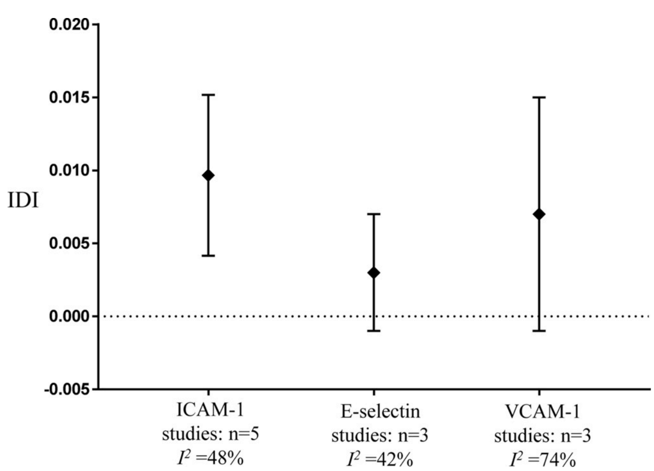

Fig. 3. Added value of circulating CAMs to basic prediction models.
Data were the summary IDI with 95% confidence intervals, and I^2 represents the degree of heterogeneity. Data from the study by Chao et al. were imputed using the 2-sided p value at 0.05 [19]. CAMs, cell adhesion molecules; ICAM-1, intercellular adhesion molecule-1; IDI, Integrated Discrimination Improvement; VCAM-1, vascular cell adhesion molecule-1.

interventions designed to prevent diabetes, since such interventions (e.g., exercise training) are found to be effective in reducing ICAM-1 and E-selectin levels [22,46]. However, as shown in our study and by others [8,19], it should be noted that circulating CAMs exhibited limited incremental value beyond the referent prediction models for type 2 diabetes that include obesity, blood pressure, or lipid profiles for the general population. Future studies might be required to assess whether this would apply to other target populations (e.g., individuals at risk for diabetes [22]) or for other disease prediction (e.g., peripheral arterial disease [47]).

4.3. Strengths and limitations

This study is to date the most comprehensive meta-analysis with dose-response analysis that examined the association of several circulating CAMs with risk of type 2 diabetes from more than 23,000 participants. Moreover, the inclusion of only prospective studies may help avoid recall bias and reduce selection bias for the conclusions observed. However, this study has some limitations. Firstly, almost all circulating CAMs were only measured once at baseline. The lack of repeated measures may underestimate true association. Yet, there is evidence that changes in circulating CAMs (e.g., E-selectin) over years are also related to increased risk of type 2 diabetes [22]. Secondly, although a consistent association for risk of type 2 diabetes was observed in different geographic regions (that is, America *versus* Europe), our study could not address the issue of ethnical difference. However, Song et al. suggested that circulating CAMs like ICAM-1 or E-selectin might be less sensitive to predict type 2 diabetes in Blacks compared with Whites, Hispanics, or Asian/Pacific Islanders [13], which is indicative of such a potential difference. Thirdly, the possibility of residual confounding cannot be ruled out, and the association of circulating CAMs with risk of type 2 diabetes might be attenuated because of the unmeasured factors or confounders. Fourthly, the ascertainment of incident diabetes was generally based on glucose levels, anti-diabetic medication use, or patient medical records, while the failure of using glycated HA1c to define diabetes in most included studies may potentially weaken the robustness of our findings. Fifthly, some heterogeneity was noted in our analyses, which could be only partly explained by some variables (e.g., blood sample collection time or blood sample resources). Finally, the inclusion of published studies in English only may result in selection bias.

4.4. Conclusion

In conclusion, this study showed that elevated circulating CAMs, in particular ICAM-1 and E-selectin, increased the risk of type 2 diabetes in the general population, which supports the notion that endothelial dysfunction contributes to the pathogenesis of type 2 diabetes. However, evidence regarding this positive association for VCAM-1 and P-selectin remains inadequate. Future studies investigating whether circulating CAMs could be used as therapeutic targets associated with interventions for type 2 diabetes prevention might be required.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Authors contributions

S.Q. designed the study, collected the data, analysed the data, and wrote the manuscript. X.C. collected the data and contributed to the discussion. J.L., B.Y., and M.Z. contributed to the introduction and reviewed the manuscript. J.S. contributed to the discussion and reviewed/edited the manuscript. Z.S., and U.S. designed the study and contributed to the introduction and the discussion. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.06.908.

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