Microvascular Dysfunction Is Associated With a Higher Incidence of Type 2 Diabetes Mellitus A Systematic Review and Meta-Analysis

Microvascular Dysfunction Is Associated With a Higher Incidence of Type 2 Diabetes Mellitus

A Systematic Review and Meta-Analysis

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Objective—Recent data support the hypothesis that microvascular dysfunction may be a potential mechanism in the development of insulin resistance. We examined the association of microvascular dysfunction with incident type 2 diabetes mellitus (T2DM) and impaired glucose metabolism by reviewing the literature and conducting a meta-analysis of longitudinal studies on this topic.

Methods and Results—We searched Medline and Embase for articles published up to October 2011. Prospective cohort studies that focused on microvascular measurements in participants free of T2DM at baseline were included. Pooled relative risks were calculated using random effects models. Thirteen studies met the inclusion criteria for this meta-analysis. These studies focused on T2DM or impaired fasting glucose, not on impaired glucose tolerance. The pooled relative risks for incident T2DM (3846 cases) was 1.25 (95% confidence interval, 1.15; 1.36) per 1 SD greater microvascular dysfunction when all estimates of microvascular dysfunction were combined. In analyses of single estimates of microvascular dysfunction, the pooled relative risks for incident T2DM was 1.49 (1.36; 1.64) per 1 SD higher plasma soluble E-selectin levels; 1.21(1.11; 1.31) per 1 SD higher plasma soluble intercellular adhesion molecule-1 levels; 1.48 (1.03; 2.12) per 1 SD lower response to acetylcholine-mediated peripheral vascular reactivity; 1.18 (1.08; 1.29) per 1 SD lower retinal arteriole-to-venule ratio; and 1.43 (1.33; 1.54) per 1 logarithmically transformed unit higher albumin-to-creatinine ratio. In addition, the pooled relative risks for incident impaired fasting glucose (409 cases) was 1.15 (1.01–1.31) per 1 SD greater retinal venular diameters.

Conclusion—These data indicate that various estimates of microvascular dysfunction were associated with incident T2DM and, possibly, impaired fasting glucose, suggesting a role for the microcirculation in the pathogenesis of T2DM. **(*Arterioscler Thromb Vasc Biol*. 2012;32:3082-3094.)**

Key Words: diabetes mellitus ■ meta-analysis ■ microcirculation

Insulin resistance and β cell dysfunction are key features of the pathophysiology of type 2 diabetes mellitus (T2DM), the prevalence of which is rapidly increasing. Central obesity and low physical activity, in turn, are main underlying causes of insulin resistance. We[1] and others[2] have recently advanced the hypothesis that microvascular dysfunction, by impairing the timely access of glucose and insulin to their target tissues, is an additional cause of insulin resistance. In addition, microvascular dysfunction may function as an intermediate step linking central obesity, low physical activity, and chronic low-grade inflammation to insulin resistance[3] (Figure 1).

There is substantial evidence in support of this hypothesis. For example, it has been demonstrated that insulin can redirect blood flow in skeletal muscle from nonnutritive capillaries to nutritive capillaries and thereby increase insulin-mediated glucose uptake without increasing total blood flow.[4] This process, so-called capillary recruitment, is impaired in insulin-resistant individuals.[5,6] In addition, experimental studies have demonstrated impairments in glucose disposal after blocking insulin-mediated capillary recruitment,[7] suggesting that microvascular dysfunction directly affects insulin-mediated glucose disposal. It is not clear, however, whether there is consistent prospective evidence to support this hypothesis, although, since the early 2000s, a growing number of prospective studies have investigated the association between various estimates of microvascular dysfunction and incident T2DM and impaired fasting glucose (IFG).

In view of these considerations, we conducted a systematic review and meta-analysis of these prospective studies to investigate whether microvascular dysfunction is associated with incident T2DM and IFG in population-based settings

Materials and Methods

Search Strategy

We conducted a search in Medline and Embase for studies published from inception (1977) to October 2011. We considered 4 types of

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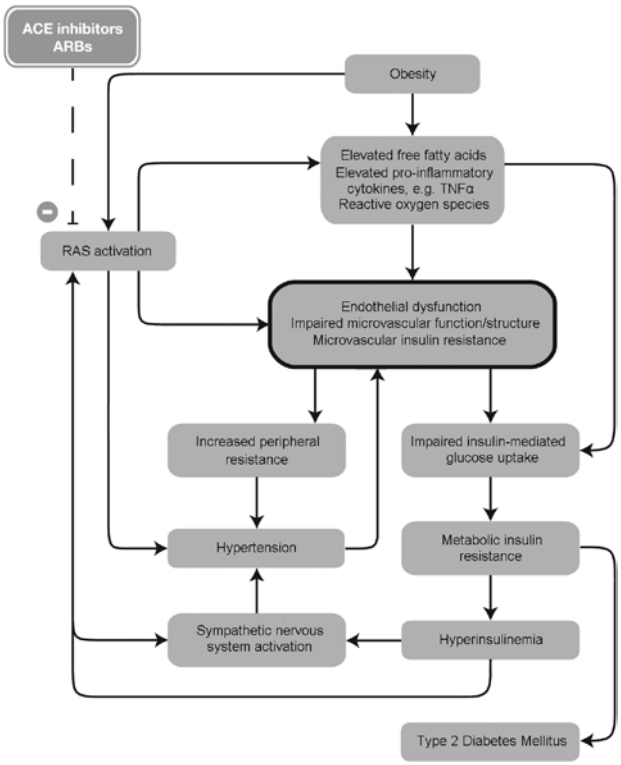

Figure 1. Hypothesis which states that microvascular dysfunction may function as an intermediate step linking central obesity and low physical activity to insulin resistance (and, downstream, type 2 diabetes mellitus) and hypertension (adapted from Jonk[3]). ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blockers; RNF, renin angiotensin factor; TNF-α, tumor necrosis factor.

estimates of microvascular function. First, we included plasma markers of endothelial dysfunction, defined as markers that are synthesized to an important extent by the endothelium (regardless of whether they are also synthesized by other cell types), including soluble E-selectin (sE-selectin), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), and von Willebrand factor (vWF).[8] Higher concentrations of these markers are associated with cardiovascular disease[9] and are thought to be derived mainly from microcirculatory endothelium,[10] which makes it plausible that higher concentrations of these markers reflect greater microvascular endothelial dysfunction. Second, we included assessment of skin and muscle microcirculation (by capillaroscopy and laser-Doppler fluxmetry, and plethysmography, respectively), with lower responses reflecting microcirculatory dysfunction. Third, we included retinal diameters, as evaluated by retinal photography. We defined greater venular diameters and both lower arteriolar diameters and lower arteriole-to-venule ratios (AVRs) as markers of microvascular dysfunction, because greater retinal venular diameters are associated with atherosclerosis, inflammation, and cholesterol levels, and both lower AVRs and generalized arteriolar narrowing are associated with incident cardiovascular disease.[11] Finally, we included microalbuminuria, which is thought to reflect a generalized increase in endothelial permeability.[8] Therefore, higher values of urinary albumin excretion (UAE; expressed as albumin–to–creatinine ratio [ACR] or as UAE per time) are thought to reflect greater microvascular endothelial dysfunction.

To identify the studies of interest, we used the following terms: plasma markers of endothelial dysfunction (*sE-selectin, sICAM-1, sVCAM-1, vWF*); peripheral vascular reactivity (*forearm blood flow, plethysmography, acetylcholine, sodium nitroprusside, L-NMMA*); skin microvascular endothelium-dependent or -independent reactivity (*iontophoresis, intracutaneous injection, acetylcholine, sodium nitroprusside, L-NMMA*); capillary density (*capillary density, capillary recruitment, capillaroscopy, capillaries*); retinal diameters (*retinal vessels, arteriovenous ratio, AVR, venular diameter, arteriolar diameter, retinal arteriolar diameter*); and microalbuminuria (*microalbuminuria, macroalbuminuria, albuminuria, ACR, UAE*). These search strategies were combined with the terms (*risk of*) *diabetes, glucose tolerance, cohort, follow-up, longitudinal.* The search was limited to studies within humans and to studies written in English. Finally, we examined the reference lists of the selected papers to find other relevant articles.

Selection Criteria and Data Extraction

Three authors (D.M.J.M., A.J.H.M.H., and M.T.S.) independently selected articles. Prospective cohort studies that measured microvascular function in participants free of T2DM at baseline were included. First, titles and abstracts of the retrieved studies were scanned and excluded if they were irrelevant. After title and abstract selection, the full text of the included articles was read to identify whether the studies met the prespecified inclusion criteria. After the selection procedure, the following data were extracted: characteristics of the study population, number of participants without T2DM at baseline, incident cases of T2DM or IFG, mean follow-up, definition of T2DM or IFG, the crude and adjusted odds ratios (OR), relative risks (RR) or hazard ratios (HR) with 95%CI, confounding variables included in the analyses, and the incidence and cumulative incidence of T2DM and IFG. When these data were missing, the principal investigator of the selected study was contacted for further information. If the investigator could not provide the requested information or did not respond, the available data were used.

Statistical Analysis

Incidences and Cumulative Incidences

When incidence data were not presented in the original article, cases per 1000 person-years and cumulative incidences were calculated. We used the following formulas: cases per 1000 person-years = ([T2DM or IFG cases/person-years]×1000), person-years = (participants×follow-up time), and cumulative incidence = ([T2DM or IFG cases/controls×100%). If the person-years were not specified in the article, T2DM or IFG cases were set at half of the duration of the follow-up.

Statistical Analysis for the Meta-Analysis

Meta-analysis was performed by use of RevMan5,[12] using the generic inverse variance method with a random effects model. One SD difference of the independent variable in the fully adjusted models was used to estimate the pooled RRs and 95%CI. The pooled effect sizes were estimated by calculating the logarithm of the RR and the standard error. In this analysis, larger studies with smaller standard errors have a greater weight than smaller studies with larger standard errors. A forest plot was made to show the pooled RRs and 95%CIs. We assumed that the populations in the different studies share the same underlying distribution of the microvascular markers. Therefore, different SDs of the microvascular markers are likely to be the result of measurements errors, and risk per 1SD can be compared without conversion.[13] Heterogeneity was assessed visually by forest plots, by means of Cochran's Q test, of which the null hypothesis assumes homogeneity,[14] and by I^2 statistics, which indicates the percentage of variability across trials that is explained by heterogeneity rather than chance.[15]

Because of the highly skewed distribution, the continuous variables ACR and UAE were logarithmically transformed, and results on the association of microalbuminuria with incident T2DM are expressed per logarithmically transformed unit higher ACR or UAE. All logarithmic transformations were to the base e.

Results

Study Selection and Characteristics

The literature search resulted in 2722 articles (Figure I in the online-only Data Supplement). After title, abstract, and

full text selection, 23 articles were found that investigated the association of plasma markers of endothelial dysfunction (n=11), peripheral vascular reactivity (n=1), retinal diameters (n=5), and microalbuminuria (n=6), respectively, with incident T2DM or IFG. These studies focused on T2DM or IFG, not on impaired glucose tolerance (IGM). We did not find any articles that prospectively investigated the association of skin microvascular endothelium-dependent or -independent reactivity and capillary density or recruitment with incident IGM or T2DM.

Table 1 shows the characteristics of the selected studies. All articles were published in English after 1994. We found 15 prospective population-based cohort studies,[16–30] 3 prospective nested case-control studies,[31–33] and 5 prospective case–cohort studies.[34–38] The studies examined mainly white participants from Europe, the United States, and Australia. As expected, subjects who developed T2DM during follow-up were slightly older and had a higher body mass index (BMI) at baseline. In addition, 10.2% to 70.2% of the subjects had hypertension at baseline and 9.3% to 72.6% of the subjects were current smokers. The follow-up time of the studies ranged from 2.6 to 12 years. The included studies used different measures to diagnose T2DM and IFG, mainly based on the American Diabetes Association (1997 and 2003) and World Health Organization (1985 and 2006) criteria. Most studies compared incident T2DM with a combined sample of non-T2DM and incident IFG. Two studies[20,21] compared incident T2DM and IFG with non-T2DM.

Plasma samples of sE-selectin, sVCAM-1, sICAM-1, and vWF were analyzed by use of ELISAs. Peripheral vascular reactivity was assessed by a dose-response curve to intra-arterial infusion of acetylcholine (7.5, 15, and 30 $\mu g \cdot mL^{-1} \cdot min^{-1}$).[25] Retinal diameters were evaluated offline by the use of fundus photos (Retinal Analysis; Optimate, Madison, WI). ACR or UAE were calculated to determine microalbuminuria. Five studies assessed microalbuminuria in a morning fasting spot urine sample,[18,19,23,27,33] whereas 1 study assessed microalbuminuria by use of two 24-hour urine collections.[16]

Microvascular Dysfunction and Risk of T2DM

Eleven studies[17,22,26,28,31,32,34–38] investigated the association of microvascular dysfunction as measured by plasma markers of endothelial dysfunction and incident T2DM. Table I in the online-only Data Supplement shows a higher incidence of T2DM at higher levels of sE-selectin, sICAM-1, and vWF at baseline. Only the Western New York Study[37] showed a lower incidence of T2DM at a higher level of sICAM-1 at baseline. Table 2 illustrates the associations of plasma markers of endothelial dysfunction with incident T2DM, comparing the upper with the lower tertile/quartile. Plasma markers of sE-selectin, sICAM-1, sVCAM-1, and vWF were positively and significantly associated with incident T2DM. After adjustment for confounders, including age, sex, race, and body composition, sE-selectin and sICAM-1 remained associated with incident T2DM, with RRs ranging from 1.34 (95%CI, 0.91; 1.99) to 4.61 (2.85; 7.46) and from 1.03 (0.64; 1.67) to 1.84 (1.26; 2.69) respectively.

One study investigated the association of peripheral vascular reactivity with incident T2DM.[25] An attenuated endothelium-dependent vasoreactivity response was significantly associated with incident T2DM; the association remained present after adjustment for age, sex, BMI, smoking, systolic blood pressure, total cholesterol, fasting glucose, fasting insulin, homeostasis model of assessment-insulin resistance, and C-reactive protein (HR 1.30 [1.01; 1.64]).

Five studies assessed the relationship between retinal diameters and incident T2DM.[20,21,24,29,30] Table I in the online-only Data Supplement shows a higher incidence of T2DM with smaller baseline arteriolar diameters and AVR. In contrast, venular diameters were not significantly associated with the incidence of T2DM. Table 2 illustrates that lower AVRs were significantly associated with incident T2DM in all 3 studies,[20,29,30] with RRs ranging from 1.53 (1.03; 2.27) to 1.92 (1.10; 3.36). No significant associations were found between either venular or arteriolar diameters and the development of T2DM, except in the AusDiab Study,[24] which showed a significant association for arteriolar diameters (OR, 2.21 [1.02; 4.80]). All studies adjusted for age, sex, smoking, systolic blood pressure, and fasting plasma glucose levels. The studies additionally adjusted for ethnicity, study center, BMI, waist circumference, physical activity, alcohol consumption, diastolic blood pressure, hypertension, family history of diabetes mellitus, total cholesterol, high density lipoprotein cholesterol, fasting insulin levels, IFG/impaired glucose tolerance, cholesterol-lowering medication, follow-up time, HbA1c, carotid plaque score, retinopathy, and ACR, although not all studies used the same variables in the fully adjusted models (Table 2).

Six studies investigated the association between microalbuminuria with incident T2DM.[16,18,19,23,27,33] The incidence of T2DM was higher at higher levels of UAE and ACR, or in presence of microalbuminuria at baseline (Table I in the online-only Data Supplement). In addition, all 6 studies showed that the presence of microalbuminuria was significantly associated with incident T2DM. After adjustment for potential confounders, the associations remained present in 5 studies, with RRs ranging from 1.40 (0.82; 2.39) to 2.36 (1.01; 5.50), although studies adjusted for different variables in the analyses (Table 2).

Meta-Analysis

With regard to plasma markers, 2 studies[34,36] presented their results in figures and therefore did not report exact RR. Five studies presented their data in units that we could not transform into SDs (either tertiles[28,35,37,38] or quintiles.[31]) The remaining 4 studies[22,26,32,36] were included in the meta-analysis. With regard to peripheral vascular reactivity, only 1 study[25] was available (Figure 2). With regard to retinal diameters, all 5 studies[20,21,24,29,30] were included in the meta-analysis and are presented in Figure 2. For microalbuminuria, 3 studies presented UAE[16] and ACR[18,33] as a continuous variable. These studies are presented in Figure 2.

Figure 2 shows that 1 SD greater microvascular dysfunction was associated with a 25% (15; 36%) higher incidence of T2DM. In addition, 1 SD higher levels of plasma markers of endothelial function were associated with a 21% (5; 39%) higher incidence of T2DM. In analyses of single estimates of microvascular dysfunction (Figure 2), 1 SD higher levels of sE-selectin and sICAM-1 were significantly associated with a 49% (36; 64%) and 21% (11; 31%) higher incidence of T2DM, respectively. sVCAM-1 (2% [−9; 16%]) and vWF

Table 1. Characteristics of Selected Studies

Study	Etnicity	Age, y		BMI, kg/m^2		Hypertension, %		Current Smokers, %		No. of Participants Without Diabetes Mellitus at Baseline	Incident Cases of Mean Diabetes Mellitus/IFG, y	Follow-Up	Definitions of IFG or Diabetes Mellitus
		Developed T2DM											
		Yes	No	Yes	No	Yes	No	Yes	No				
Plasma markers of endothelial dysfunction													
The Atherosclerosis Risk in Communities study*[17]	White (78%) and black (22%)	54		26.4		30		25		12330	1335	7	ADA guidelines use of antidiabetic medication physicians diagnosis
The Framingham offspring study*[22]	Primarily white	54		25.3		38.6		18.5		924	153	7	ADA guidelines use of antidaibetic medication
The British regional heart study*[28]	White	68	69	29.7	26.6	NA		9.3	13.3	3562	162	7	WHO guidelines physicians diagnosis
The prospective study of pravastatin in the elderly at risk*[26]	White	75	75	26.5	26.8	70.2	61.9	22.3	29.0	4945	292	3.2	ADA guidelines self-reported history
The Atherosclerosis Risk in Communities study†[35]	White (47%) and black (53%)	54	53	30.5	26.8	40.5	23.6	19.8	21.9	1153	581	9	ADA guidelines use of antidiabetic medication physicians diagnosis
The women's health initiative observational study‡[32]	White (51%), blacks(29%), hispanics(12%) and Asian/ Pacific(8%)	64	64	33	26	NA		NA		3782	1584	5.9§	Use of antidiabetic medication self-reported history
The nurses health study†[31]	Primarily white	56	56	30.2	26.2	NA		14.0	13.4	1522	737	10	ADA guidelines use of antidiabetic medication
The Monitoring of Trends and Determinants in Cardiovascular Disease and Cooperative Research in the Region of Augsburg studies‡[38]	White	56	52	29.7	27.1	65.8	43.9	35.1	29.4	2244	532	12	Physicians diagnosis self-reported history
The Western New York study†[37]	Primarily white	58	60	32.2	29.5	55.9	35.1	19.7	10.8	219	61	5.9	ADA guidelines
Longitudinal health study in Pima Indians†[36]	Prime Indians	33	32	36.3	36.3	NA		NA		142	71	4.6|6.8||	WHO guidelines
The Monitoring of Trends and Determinants in Cardiovascular Disease and Cooperative Research in the Region of Augsburg studies‡[34]	White	57	52	30.3	26.7	69.5	39.5	23.9	23.3	1846	436	10.5	Physicians diagnosis Self-reported history
Peripheral vascular reactivity													
Peritone, 2008*[25]	White#	50	48	27.6	27.5	100	100	14	19	400	44	4.5	ADA guidelines use of antidiabetic medication
Retinal diameters													
The Rotterdam study*[20]	White	5		26.2%		NA		21.8		2309	118/305	6.4	ADA guidelines use of antidiabetic medication physicians diagnosis

(*Continued*)

Table 1. (Continued)

Study	Etnicity	Age, y		BMI, kg/m^2		Hypertension, %		Current Smokers, %		No. of Participants Without Diabetes Mellitus at Baseline	Incident Cases of Mean Diabetes Mellitus/IFG, y	Follow-Up	Definitions of IFG or Diabetes Mellitus
		Developed T2DM											
		Yes	No	Yes	No	Yes	No	Yes	No				
The blue mountains eye study*[21]	White	NA		NA		NA		NA		2123	165/104	10	ADA guidelines physicians diagnosis
The AusDiab study*[24]	White	58	56	30.2	27.5	55.7	44.2	12.4	8.8	803	108	4.98	WHO guidelines use of antidiabetic medication
The Atherosclerosis Risk in Communities study*[29]	White (82.9%) and black (17.1%)	59		27.9		NA		16.6		7993	291	3.5§	ADA guidelines Use of antidiabetic medication physicians diagnosis
The beaver dam eye study*[30]	White	50		28.7		NA		NA		3252	249	10	Postload plasma glucose>11.1 mmol/L use of antidiabetic medication or diet therapy physician diagnosis
Microalbuminuria													
The strong heart study*[27]	Americans Indians**	56		31.5	30.1	32.6	34.2	30.4	38.5	1079	391	7.8§	ADA guidelines
The Data from an Epidemiological Study on the Insulin Resistance Syndrome study*[19]	White	47		24.0	25.3	29.4	42.0	13.3	26.3	3842	171	9	ADA guidelines use of antidiabetic medication
Wang,2006‡[33]	Aboriginals	36	36	26.7	26.2	NA		72.6	66.7	234	117	11	WHO guidelines
The Prevention of Renal and Vascular End Stage Disease Study*[16]	White	57	49	29.6	25.8	25.4	10.2	NA		5654	185	4.2	ADA guidelines use of antidiabetic medication
Diabetes mellitus prevention program*[18]	All races**	50		33		NA		7.9		3188	674	3.2§	ADA guidelinesWHO guidelines
Mykkanen, 1994*[23]	White	69		27.4		49.7		10.0		891	92	3.5	WHO guidelines†† physician diagnosis††

ACR indicates albumin-to-creatinine ratio; UAE, urinary albumin excretion; ADA, American Diabetes Association; WHO, World Health Organization; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; NA, not applicable.

ACR milligrams of albumin per gram of creatinine. ACR:30 to 300 mg/day=microalbuminuria; UAE : milligrams albumin per litre urine. UAE: 20 to 200 mg/L=microalbuminuria; ADA guidelines:incident IFG if fasting glucose values reach 6.1 to 7.0 mmol/L. Incident T2DM if fasting glucose values reach ≥7.0 mmol/L;
WHO guidelines:incident IFG if fasting glucose values reach 6.1 to 6.9 mmol/L. Incident T2DM if fasting glucose values reach ≥7.0 mmol/L.

*Cohort study.
†Case–cohort study.
‡Nested-case–cohort study.
§Follow-up described in median.
‖Mean follow-up for control subjects.
¶Mean follow-up for case subjects.
#Hypertension at baseline.
**Prediabetes at baseline.
††Definition of Non-insulin–dependent diabetes mellitus(NIDDM).

Table 2. Unadjusted and Fully Adjusted Association of Plasma Markers of Endothelial Dysfunction, Peripheral Vascular Reactivity, Retinal Diameters, and Microalbuminuria With T2DM and IFG

Study	Risk Marker	Crude IFG Risk	Crude T2DM Risk	Fully Adjusted IFG Risk	Fully Adjusted T2DM Risk	Adjustment for Confounders[e]
Plasma markers of endothelial dysfunction						
The Atherosclerosis Risk in Communities study[17]	vWF	NA	1.20, ns [a**] 1.50 (P<0.001)[a§§]	NA	0.95, ns[a**] 1.30, ns[a††]	1, 3, 4, 6, 9, 10, 15, 16, 19, 21, 22, 26
The Framingam offspring study[22]	vWF	NA	1.40 (1.12–1.77)[b†]	NA	1.33 (1.03–1.72)[b†]	2, 7, 9, 10, 11, 13, 14, 16, 19, 21, 24, 27, 28, 29, 30, 31
The British regional heart study[28]	vWF	NA	1.39 (0.94–2.03)[b]	NA	1.01 (0.67–1.53)[b]	1, 2, 5, 7, 9, 10, 11, 16, 33, 34, 35, 36
The prospective study of pravastatin in elderly at risk[26]	sICAM-1	NA	1.60 (1.14–2.25)[c‡]	NA	1.84 (1.26–2.69)[c‡]	1, 2, 6, 13, 14, 19, 21, 22, 27
The Atherosclerosis Risk in Communities study[35]	sICAM-1	NA	1.91 (1.45–2.50)[c]	NA	1.50 (1.02–2.23)[c]	1, 2, 3, 4, 7, 15, 19, 21, 22, 27
The woman's health initiative observational study[32]	sE-selectin	NA	5.48 (4.33–6.94)[b††]	NA	2.89 (2.11–3.96)[b††]	1, 3, 4, 6, 9, 10, 11, 16, 29, 37, 38
	sVCAM-1		2.05 (1.62–2.59)[b††]		1.05 (0.74–1.50)[b††]	
	sICAM-1		3.32 (2.67–4.11)[b††]		1.85 (1.35–2.52)[b††]	
The nurse's health study[31]	sE-selectin	NA	7.50 (5.05–11.14)[b††]	NA	4.61 (2.85–7.46)[b††]	1, 3, 6, 9, 10, 11, 16, 22, 27, 29, 39
	sVCAM-1		1.54 (1.10–2.15)[b††]		0.64 (0.41–1.00)[b††]	
	sICAM-1		4.29 (2.95–6.23)[b††]		1.75 (1.05–2.92)[b††]	
The Monitoring of Trends and Determinants in Cardiovascular Disease and Cooperative Research in the Region of Augsberg studies[38]	sE-selectin	NA	3.01(2.18–4.17)[c**] 3.29 (2.25–4.83)[c††]	NA	2.63 (1.79–3.88)[c**] 1.71 (1.07–2.75)[c††]	1, 4, 6, 9, 10, 11, 13, 16, 19, 21, 27
	sVCAM-1		2.16 (1.59–2.93)[c**] 2.24 (1.55–3.25)[c††]		1.32 (0.89–1.96)[c**] 1.03 (0.64–1.67)[c††]	
	vWF		1.43 (0.85–2.40)[c**] 1.31 (0.69–2.49)[c††]		0.87 (0.44–1.74)[c**] 1.10 (0.42–2.90)[c††]	
The Western New York study[37]	sE-selectin	NA	3.39 (1.47–7.83)[b]	NA	2.77 (1.13–6.79)[b]	1, 2, 3, 6, 10, 11, 16, 22, 40
	sICAM-1		0.08 (0.42–1.87)[b]		NA	
Longitudinal health study in Pima Indians[36]	sE-selectin	NA	1.12 (0.82–1.55)[d]	NA	1.39 (0.91–1.99)[d]	1, 7, 22, 23, 41, 42
	sVCAM-1		0.70, ns[d¶]		0.90, ns[d¶]	
	sICAM-1		0.70, ns[d¶]		0.80, ns[d¶]	
	vWF		0.67 (0.45–1.00)[d]		0.73 (0.46–1.16)[d]	
The Monitoring of Trends and Determinants in Cardiovascular Disease and Cooperative Research in the Region of Augsberg studies[34]	sE-selectin	NA	1.80 (P<0.001)[c*¶]	NA	1.60 (P<0.001)[c*¶]	1, 2, 4, 6, 9, 10, 11, 13, 16, 18, 19
	sICAM-1		1.45 (P<0.001)[c*¶]		1.30 (P=0.031)[c*¶]	
Peripheral vascular reactivity						
Petricone, 2008[25]	Acetyl-chrorine simulated forearm blood flow	NA	1.47 (1.16–1.85)[c#]	NA	1.30 (1.01–1.64)[c¶]	1, 2, 6, 10, 13, 18, 22, 23, 24, 27

(*Continued*)

Table 2. (Continued)

Study	Risk Marker	Crude IFG Risk	Crude T2DM Risk	Fully Adjusted IFG Risk	Fully Adjusted T2DM Risk	Adjustment for Confounders[e]
Retinal diameters						
The Rotterdam study[20]	arteriole-to-venule ratio	NA	NA	1.93 (1.35–2.77)[a]	1.80 (1.05–3.08)[a]	1, 2, 6, 10, 13, 14, 18, 19, 27, 38, 46
	Venular diameter	NA	NA	1.46 (1.02–2.08)[a]	1.41 (0.83–2.38)[a]	
	Arteriolar diameter	NA	NA	1.17 (0.82–1.66)[a]	1.29 (0.73–2.28)[a]	
The blue mountains eye study[21]	Venular diameter	1.28 (1.04–1.59) [a*]	1.26 (1.06–1.50)[a*]	1.16 (0.91–1.47)[a*]	1.06 (0.87–1.29)[a*]	1, 2, 6, 10, 11, 13, 16, 19, 22, 32
	Arteriolar diameter	0.96 (0.77–1.18) [a*]	1.06 (0.89–1.26)[a*]	1.02 (0.80–1.30)[a*]	1.07 (0.88–1.30)[a*]	
The AusDiab study[24]	Venular diameter	NA	1.11 (0.61–2.01)[a]	NA	0.82 (0.40–1.69)[a]	1, 2, 5, 6, 7, 9, 10, 13, 15, 16, 19, 21, 22, 23, 28, 47, 48
	Arteriolar diameter	NA	2.14 (1.13–4.05)[a]		2.21 (1.02–4.80)[a]	
The Atherosclerosis Risk in Communities study[29]	AV ratio	NA	2.76 (1.67–4.58)[a]	NA	1.92 (1.10–3.36)[a]	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 15, 16, 18, 19, 21, 22, 23
The beaver dam eye study[30]	AV ratio	NA	1.71 (1.17–2.51)[b]	NA	1.53 (1.03–2.27)[b]	1, 2, 9, 10, 11, 13, 14, 18, 19, 22, 41
	Venular diameter	NA	1.10 (0.71–1.43)[b]		1.03 (0.73–1.46)[b]	
	Arteriolar diameter	NA	1.67 (1.14–2.46)[b]		1.47 (0.99–2.18)[b]	

(*Continued*)

Table 2. (Continued)

Study	Risk Marker	Crude IFG Risk	Crude T2DM Risk	Fully Adjusted IFG Risk	Fully Adjusted T2DM Risk	Adjustment for Confounders[e]
Microalbuminuria						
The strong heart study[27]	ACR	NA	NA	NA	1.46 (1.08–1.98)[c§]	1, 2, 6, 7, 9, 10, 16, 43
The Data from an Epidemiological Study on the Insulin Resistance Syndrome study[19]	UAE	NA	2.28 (1.39–3.73)[c]	NA	2.12 (1.76–9.54)[c]	1, 6, 9, 10, 15, 16, 22, 23, 24, 26, 27, 28, 33, 44
Wang, 2006[33]	ACR	NA	2.22 (1.11–4.48)[b]	NA	2.36 (1.01–5.50)[b]	1, 6, 18, 22, 27
	Microalbuminuria		2.22 (1.15–4.29)[b§]		1.90 (0.88–4.06)[b§]	
The Prevention of Renal and Vascular End Stage Disease study[16]	UAE	NA	1.59 (1.42–1.79)[b]	NA	1.53 (1.25–1.88)[b]	1, 2, 7, 13, 14, 16, 17, 19, 21, 22, 23, 27, 31, 32
Diabetes mellitus prevention program[10]	ACR	NA	1.07 (1.00–1.10)[c‖]	NA	0.98 (0.91–1.06)[c‖]	1, 2, 3, 9, 45
Mykkanen,1994[23]	ACR	NA	1.76 (1.07–2.90)[b§]	NA	1.40 (0.82–2.39)[b§]	1, 2

NA indicates not applicable, effect on incident IFG not investigated; ns, not significant; sE, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1 vWF, von Willebrand factor; IFG, impaired fasting glucose; ACR, albumin-to-creatinine ratio; UAE, urinary albumin excretion; T2DM, type 2 diabetes mellitus.

IFG and T2DM risk were calculated by the comparison of the upper and lower tertile/quartile, unless otherwise indicated. The fully adjusted models were extracted from the articles.

[a]Odds ratio.

[b]Relative risk.

[c]Hazard ratio.

[d]Incidence rate ratio.

[e]1, age; 2, sex; 3, race; 4, study center; 5, education; 6, body mass index; 7, waist circumference; 8, waist–to–hip ratio; 9, physical activity; 10, smoking; 11, alcohol consumption; 13, systolic blood pressure; 14, diastolic blood pressure;15, hypertension;16, family history of diabetics mellitus ; 17, family history of cardiovascular disease; 18, total cholesterol; 19, HDL cholesterol; 20, LDL cholesterol; 21, triglycerides; 22, fasting glucose; 23, fasting insulin; 24, homeostasis model of assessment-insulin resistance; 25, social class; 26, fibrinogen; 27, CRP; 28, IFG,IGT; 29, postmenopausal hormone therapy; 30, use of aspirin; 31, blood pressure therapy; 32, cholesterol lowering medication; 33, history of cardiovascular disease; 34, use of statins; 35, adiponectin; 36, IL-6; 37, time of blood draw; 38, follow-up time; 39, diet score; 40, yr of baseline visit; 41, HbA 1c; 42, 2-h glucose levels; 43, albuminuria; 44, leucocytes; 45, weight loss; 46, carotid plaque score; 47, retinopathy; 49, micro albumin-to-creatinine ratio.

*Risk IFG and T2DM per 1SD change in risk marker.

†Risk T2DM per 1QR higher level of vWF.

‡Risk T2DM per 1U higher log[sICAM-1].

§(Micro)albuminuria absent vs present.

‖Risk diabetes mellitus with every doubling of ACR.

¶No exact data, risks estimated from the figure.

#Risk diabetes mellitus per 100% lower vasodilatory response to acetylcholine.

**Association in men.

††Association in women.

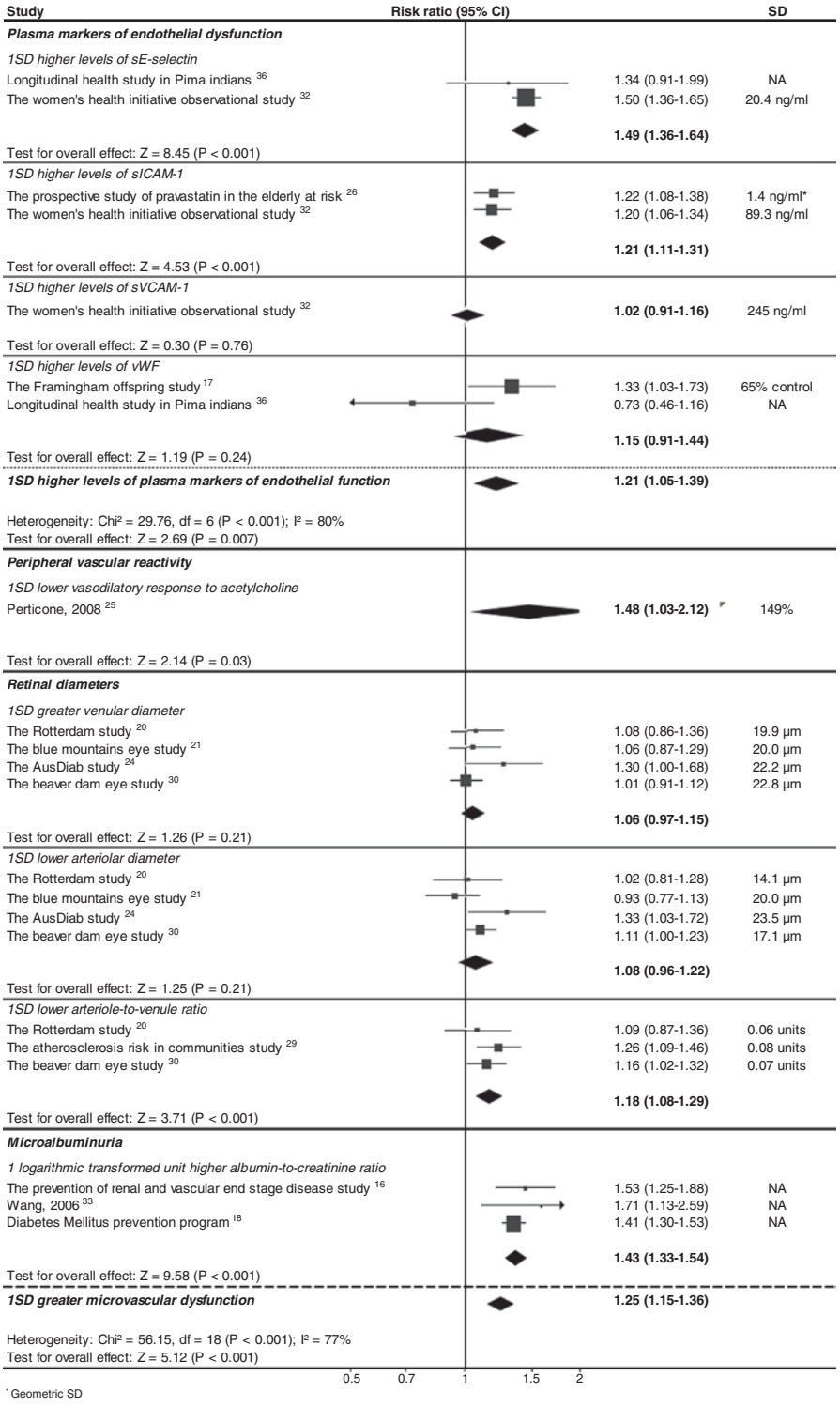

Figure 2. Forest plot showing the relative risk (RR) and 95%CI for each study, and the pooled RR and 95%CI for risk of type 2 diabetes mellitus. sE-selectin indicates soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; vWF, von Willebrand factor.

(15% [−9; 44%]) were not significantly associated with incident T2DM. One SD lower vasodilatory response to acetylcholine was associated with a 48% (3; 102%) higher incidence of T2DM. In addition, 1 SD lower AVR was associated with an 18% (8; 29%) higher incidence of T2DM. Greater venular diameters and 1 SD lower arteriolar diameters were positively, but not significantly, associated with a 6% (−3; 15%) and 8% (−4; 22%) higher incidence of T2DM, respectively. Finally,

1 logarithmically transformed unit higher UAE or ACR was associated with a 43% (33; 54%) higher incidence of T2DM.

Microvascular Dysfunction and Risk of IFG

Two studies, the Rotterdam Study[20] and the Blue Mountains Eye Study,[21] investigated the relationship between microvascular dysfunction as measured by retinal diameters and incident IFG. These studies did not specify cumulative incidences per tertile/quartile (Table I in the online-only Data Supplement). Table 2 illustrates the associations of retinal diameters with incident IFG, comparing the upper to the lower tertile/quartile. The Rotterdam Study[20] showed a significant association between both larger venular diameters (OR, 1.46 [1.02; 2.08]) and smaller AVR (OR, 1.93 [1.35; 2.77]), and the development of IFG. The Blue Mountains Eye Study[21] showed a positive association between larger venular diameters (OR, 1.16 [0.91; 1.47]) and the development of IFG. Both studies adjusted for age, sex, BMI, smoking, systolic blood pressure, and high density lipoprotein cholesterol. The Rotterdam Study[20] additionally adjusted for diastolic blood pressure, total cholesterol, C-reactive protein, follow-up time, and carotid plaque score. In contrast, the Blue Mountains Eye Study[21] additionally adjusted for alcohol consumption, family history of diabetes mellitus, fasting plasma glucose levels, and cholesterol-lowering medication.

Meta-Analysis

One SD greater venular diameters were associated with a 15% (1; 31%) higher incidence of IFG (Figure 3). Arteriolar diameter was not associated with incident IFG. The Rotterdam Study[20] also showed that 1SD lower AVR was associated with a 14% (−2; 32%) higher incidence of IFG.

Discussion

This study represents the first systematic overview regarding microvascular dysfunction as a risk factor for incident T2DM and IFG. This review had 2 main findings. First, several markers of microvascular dysfunction, including plasma markers, peripheral vascular reactivity, AVR, and microalbuminuria were associated with incident T2DM. Second, greater venular diameters were associated with incident IFG. These findings are consistent with the hypothesis that microvascular dysfunction is causally linked with T2DM.

Our meta-analysis confirms that microvascular dysfunction was associated with a 10% to 49% higher incidence of T2DM and an 8% to 15% higher incidence of IFG. Several mechanisms, not mutually exclusive, may explain the association between microvascular dysfunction with both T2DM and IFG. First, one underlying mechanism is likely to involve the concept that insulin normally can redirect blood flow in skeletal muscle from nonnutritive capillaries to nutritive capillaries and thereby increase insulin-mediated glucose uptake without increasing total blood flow,[39] and that these processes are impaired in states of microvascular dysfunction, such as obesity, low physical activity, and chronic low-grade inflammation.[3] Notably, specific inhibition of insulin-mediated microvascular effects has been shown to cause a 30% to 40% reduction in glucose disposal.[7] Second, it has been suggested that (pancreatic) microvascular endothelial dysfunction causes apoptosis of β cells in the pancreas.[40] This process decreases insulin secretory capacity and thus may lead to hyperglycemia, which, in addition, can further impair endothelial (microvascular) function, thus leading to a vicious cycle that may play a crucial role in the development of T2DM.[40]

Our analysis demonstrated consistent positive associations across all markers of microvascular endothelial dysfunction used. An important assumption in this reasoning is that these markers are valid indicators of microvascular endothelial dysfunction.[41] The endothelium is a key regulator of permeability, vascular tone, and hemostasis. Thus, endothelial dysfunction can be manifested as increased microvascular permeability and impaired balance between vasodilatation and vasoconstriction, as well as between thrombotic and antithrombotic properties.[8] Likewise, plasma markers of endothelial dysfunction, peripheral vascular reactivity, retinal diameters, and microalbuminuria may reflect different manifestations of these disturbances of the microvascular endothelium. First, E-selectin, ICAM-1, and VCAM-1 are thought to increase endothelial

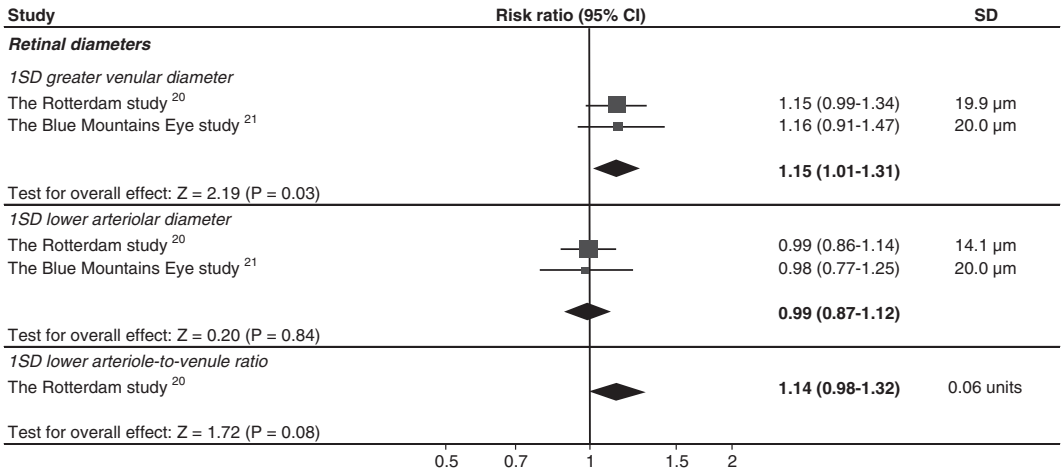

Figure 3. Forest plot showing the relative risks (RR) and 95%CI for each study and the pooled RR and 95%CI for risk of impaired fasting glucose.

permeability to leucocytes, initiated by rolling and endothelial adhesion,[8] and their soluble forms are thought to reflect the concentration of membrane-bound adhesion molecules on the endothelium.[42] In addition, vWF is thought to increase prothrombotic and procoagulant activity.[8] These markers are synthesized by endothelial cells,[8] and the microvascular endothelium, with its large surface area and production capacity (ie, the microvasculature covers 98% of the total vascular surface area),[43] is likely to be the most important determinant of these plasma concentrations.[8] In addition, according to a previously described concept, endothelial dysfunction in large arteries is paralleled by endothelial dysfunction in resistance vessels that contributes to the development of T2DM.[44] For these reasons, it is plausible that higher circulating concentrations of these markers reflect microvascular endothelial dysfunction. Second, acetylcholine is an endothelium-dependent vasodilator because of the release of NO and the production of prostaglandins and endothelium-derived hyperpolarizing factor.[45] Consequently, a lower response in the peripheral microvasculature after stimulation with acetylcholine suggests a defect in the release of NO, endothelium-derived hyperpolarizing factor or prostaglandins, and thus impaired endothelium-dependent vasodilatation. Third, retinal venular dilation and retinal arteriolar narrowing have been associated with endothelial dysfunction.[46,47] Hence, both alterations may represent a directly microvascular phenotype of endothelial dysfunction.[48] In addition, it has been hypothesized that higher intraluminal retinal venular diameters reflect a disrupted endothelial surface layer and thereby increase leukocyte adhesion.[11] This assumption is in line with our meta-analysis, which suggests an association between higher venular diameters and incident IFG. However, because of the use of static fundus photos it is uncertain whether retinal diameters reflect structural or functional microvascular changes. Fourth, microalbuminuria is considered to reflect various aspects of endothelial dysfunction in many vascular beds.[8] This concept is derived from data showing that microalbuminuria is associated with a greater transcapillary escape rate of albumin, that is, with greater microvascular permeability[8] and from data showing that microalbuminuria is strongly associated with risk of cardiovascular disease, that this association cannot be explained by conventional risk factors, and that changes in microalbuminuria are paralleled by changes in cardiovascular risk (reviewed elsewhere).[49]

Strengths of our study include its systematic approach and the evaluation of population-based studies. To identify all studies that assessed the association of microvascular dysfunction with both T2DM and IFG, we extensively searched Medline and Embase. Given the fact that we searched for relatively large population-based studies, it seems unlikely that these studies will have been published and not identified by our search. Therefore, it is likely that we retrieved all published data. All studies included in this systematic review adjusted for multiple confounders, which makes it unlikely that residual confounding may have influenced the results, although we cannot completely exclude this. In contrast, overcorrection may have occurred, as microvascular dysfunction may link central obesity, low physical activity, and chronic, low-grade inflammation to insulin resistance, and be an intermediate step in the pathophysiologic process.[3] Adjustment for these factors could therefore result in an underestimation of the actual association. In fact, some studies[17,37,38] specifically adjusted for BMI and were able to quantify the exact influence of adjusting for BMI or waist-to-hip ratio (Table II in the online-only Data Supplement). Interestingly, the significant associations among sICAM-1,[37,38] vWF,[17] and sE-selectin[37,38] with incident T2DM decreased after adjustment for BMI or waist-to-hip ratio. Because adjustment for BMI or waist-to-hip ratio may be an over adjustment, we conclude that the reported risks possibly underestimate the true risk for incident T2DM associated with microvascular dysfunction. Another important issue to address is whether the association is different among different subgroups (ie, whether there is effect modification). Three studies included in this systematic review demonstrated significant associations between microvascular dysfunction with incident T2DM in the general population group as well as obese,[31] inflammation,[32] and hypertensive[30] population groups. In addition, at every level of increasing BMI,[31] C-reactive protein,[32] and blood pressure[30] there was a stepwise increase in the association of markers of microvascular dysfunction with incident T2DM. Taken together, these studies suggest that there are significant associations between microvascular dysfunction and incident T2DM in all populations groups, with stronger associations in the obese, inflammation, and hypertensive groups. However, other studies included in this review did not investigate effect modification. Therefore, we cannot definitively conclude that the association is stronger in obese or hypertensive individuals, or at higher levels of inflammation.

The studies included in this review had several limitations. First, because most studies examined mainly white individuals (Table 1), the results of our meta-analysis are not necessarily valid for other ethnicities. For instance, the Longitudinal Health Study[36] examined very obese Pima indians, who had higher sE-selectin levels as compared with other studies,[31,32,34,37,38] and found no significant associations between plasma markers of endothelial dysfunction and T2DM. The authors concluded that the substantially higher plasma levels might reduce the power to detect an effect of such markers.[36] However, ethnic differences (eg, different population risks) may also explain the variations in T2DM risk. However, the Women's Health Initiative Observational Study[32] showed no major differences between ethnic groups with respect to plasma markers of endothelial dysfunction. In addition, the Monitoring of Trends and Determinants in Cardiovascular Disease and Cooperative Research in the Region of Augsberg studies[38] demonstrated no clear differences between men and women (Table 2 and Table I in the online-only Data Supplement). Second, power problems could explain the lack of significant results in some studies. Mykkänen et al[23] examined 92 incident T2DM cases and demonstrated a positive but nonsignificant relationship between microalbuminuria and incident T2DM, which suggests a lack of power. In contrast, other studies that did demonstrate significant associations,[16,19,27,33] included between 117 and 391 cases of incident T2DM (Table 1). Third, different methods for the assessment of microalbuminuria were used. The Prevention of Renal and Vascular End Stage Disease study[16] assessed microalbuminuria by use of the mean of two

24-hour urine collections (the accepted standard), whereas other studies[18,19,23,27,33] used less precise morning urine samples. Although morning urine samples are a good screening test for albuminuria,[50] its lesser precision may have resulted in less strong associations with wider CI.

Our meta-analysis had some additional limitations. First, the concept that high plasma levels of endothelial dysfunction reflect endothelial dysfunction requires that endothelial cells are the major source of the plasma markers and that higher plasma levels are caused more by increased synthesis than by decreased clearance.[8,41] Indeed, sE-selectin is exclusively synthesized by endothelial cells,[51] which may explain the strong association between sE-selectin and incident T2DM. In addition, in T2DM, higher plasma vWF levels are determined by synthesis rather than clearance.[52] However, sICAM-1, sVCAM-1, and vWF are expressed by several other cell types.[51] Furthermore, except for vWF there is no information on the clearance of these markers. Consequently, the validity of these assumptions remains uncertain.[8,41] Second, we acknowledge the limited availability of prospective studies that could be included in analyses of single estimates of microvascular dysfunction. Because of this low number we could not formally test for heterogeneity,[53] and we could not perform meta-regression analyses. As a consequence, we cannot exclude statistical heterogeneity, although all CIs overlapped (Figures 2 and 3). Third, microvascular function is strongly tissue-dependent.[54] In this systematic overview, we searched for all available prospective population-based studies that focused on any marker of microvascular function. Probably because of the difficulties of microvascular measurements in population-based studies, we only found studies investigating the microcirculation in skin, eye, and kidney. On the one hand, this could limit the generalizability of the data, because the association of microvascular dysfunction and incident T2DM may be tissue-specific (eg, be limited to skeletal muscle microcirculation). On the other hand, the meta-analysis in fact demonstrated that all markers of microvascular dysfunction (skin, eye, as well as kidney) are associated with incident T2DM. This suggests that microvascular function in quite different tissues does have common properties, a notion supported by other data. For example, it has been demonstrated that skeletal muscle microvascular dysfunction was associated with brain microvascular damage among individuals with hypertension.[55]

This systematic review underscores the importance of microvascular dysfunction in the pathogenesis of T2DM. However, this systematic review cannot prove any causal relationship. Therefore, more studies are needed to investigate this. These findings may contribute to more precise assessment of risk of T2DM. In addition, unraveling how microvascular dysfunction is determined and how it leads to T2DM may lead to new treatment targets as well as to a better understanding of why certain existing treatments are associated with decreased risk of developing T2DM (ie, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and physical activity).

In conclusion, we demonstrated that microvascular dysfunction, assessed by use of different methods, was associated with incident T2DM and even IFG. Our findings are consistent with the hypothesis that microvascular dysfunction is causally linked with T2DM.

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Disclosures

None.

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