

# Uric acid and skin microvascular function: the Maastricht study

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# Uric acid and skin microvascular function: the Maastricht study

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**Objective:** Microvascular dysfunction has been suggested as a possible underlying mechanism for the association between uric acid and various diseases, such as hypertension, renal disease and cardiomyopathies. We therefore analysed the association between serum uric acid and skin microvascular function, a model of generalized microvascular function.

**Methods:** A cross-sectional study was performed in 610 individuals [51.8% men; mean age  $58.7 \pm 8.6$  years; 23.6% with type 2 diabetes (by design)] from The Maastricht Study. We assessed skin capillary density (capillaries/mm<sup>2</sup>) by capillaroscopy at baseline, after 4 min of arterial occlusion, and after 2 min of venous congestion. Capillary recruitment after arterial occlusion and during venous congestion was expressed as the absolute change in capillary density after recruitment and as the percentage change in capillary density from baseline.

**Results:** Crude linear regression analyses showed that serum uric acid [per +1 standard deviation (SD) of 74  $\mu\text{mol/l}$ ] was not associated with baseline capillary density [ $\beta = -0.21$  (95% confidence interval, 95% CI  $-1.61$  to  $1.19$ )  $P = 0.765$ ], while an inverse association was found between uric acid and absolute change in capillary density after arterial occlusion [ $\beta = -1.15$  (95% CI  $-2.36$  to  $0.06$ )  $P = 0.062$ ] and during venous congestion [ $\beta = -1.41$  (95% CI  $-2.68$  to  $-0.14$ )  $P = 0.029$ ]. However, after adjustment for sex, age and glucose metabolism status, these associations were no longer statistically significant. In addition, we found no association between uric acid and percentage capillary recruitment after arterial occlusion [ $\beta = -1.66$  (95% CI  $-3.97$  to  $0.65$ )  $P = 0.159$ ] or during venous congestion [ $\beta = -2.02$  (95% CI  $-4.46$  to  $0.42$ )  $P = 0.104$ ] in unadjusted analyses; multivariable analyses gave similar results.

**Conclusion:** These results do not support the hypothesis that generalized microvascular dysfunction (as estimated in skin microcirculation) is the underlying mechanism for the association between uric acid and cardiovascular and renal diseases. The possibility that uric acid is associated with microvascular dysfunction in specific end-organs, for example heart or kidney, needs further investigation.

**Keywords:** capillaries, microcirculation, uric acid

**Abbreviations:** eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGM, impaired glucose metabolism; IGT, impaired glucose tolerance; NGM, normal glucose metabolism; OGTT, oral glucose tolerance test; OTC, over-the-counter; T2DM, type 2 diabetes mellitus

## INTRODUCTION

High uric acid concentrations may induce endothelial dysfunction by decreasing nitric oxide availability [1], and stimulate vascular smooth muscle cell proliferation through activation of the renin-angiotensin system [2,3]. These processes can eventually result in microvascular damage [4]. Therefore, uric acid-mediated microvascular dysfunction has been brought forward as a potential mechanism underlying the association between uric acid and various diseases, such as hypertension [5], renal disease [6] and cardiomyopathies [7], a hypothesis that is supported by animal models [8,9]. However, epidemiological evidence from population-based studies is still scarce.

A limited number of small studies have reported an association between uric acid and coronary microcirculatory function as determined by coronary flow reserve in patients with cardiomyopathy [10–12]. Furthermore, prior work has shown that uric acid was associated with retinal arteriolar narrowing [13] and the development of microalbuminuria in healthy men after 5-year follow-up [14]. As microvascular dysfunction may occur in various vascular beds simultaneously, it has been suggested that

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microvascular dysfunction is part of a systemic process [15]. The cutaneous microcirculation is considered a representative model of microvascular function in general [16]. An important advantage of the skin is that noninvasive techniques can be used to assess mechanisms of microvascular dilation and constriction [16]. Furthermore, alterations in the cutaneous microcirculation have been identified in patients with type 2 diabetes mellitus (T2DM) [17], chronic heart failure [18] and hypertension [19]. Although the microcirculation of the skin may be a representative model to study generalized microcirculatory function, only one previous study assessed the association with uric acid [20]. This study showed that higher uric acid concentrations were associated with a reduced endothelium-dependent vasodilator response in patients with type 1 diabetes [20].

In view of the above, the aim of the present study was to assess the association between serum uric acid concentration and cutaneous microcirculatory function as determined by capillary density. As it has been suggested that uric acid has a more pronounced detrimental effect in women [21], younger individuals [5,22] and individuals with normal glucose metabolism [23,24], possibly because of the primary involvement of uric acid in the early or less severe stages of cardiovascular diseases [22,25], we additionally investigated potential differences related to sex, age and glucose metabolism status.

## MATERIALS AND METHODS

### Study population and design

In this study, we used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously [26]. In brief, the study focuses on the aetiology, pathophysiology, complications and comorbidities of T2DM and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status for reasons of efficiency. The present report includes cross-sectional data from the first 866 participants, who completed the baseline survey between November 2010 and March 2012. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Netherlands Health Council under the Dutch 'Law for Population Studies' (Permit 131088–105234-PG). All participants gave written informed consent.

For the present study, we excluded individuals without data on uric acid ( $N=13$ ), capillary density ( $N=44$ ), systolic blood pressure (SBP) ( $N=2$ ), BMI ( $N=1$ ), waist ( $N=3$ ), cholesterol concentration ( $N=8$ ), smoking status ( $N=17$ ) and/or estimated glomerular filtration rate (eGFR) ( $N=9$ ). We also excluded individuals with type 1 diabetes ( $N=4$ ) or a history of cardiovascular disease ( $N=152$ ). A history of cardiovascular disease was defined as self-reported myocardial infarction; cerebrovascular infarction or haemorrhage; and/or percutaneous artery angioplasty or

vascular surgery of the coronary, abdominal, peripheral or carotid arteries according to the Rose questionnaire [27]. Furthermore, individuals taking any uric acid-lowering medication (i.e. allopurinol or benzbromarone;  $N=21$ ) were excluded. The total study population thus consisted of 610 participants.

### Skin capillaroscopy

Skin capillaroscopy was conducted as described elsewhere [28]. In short, measurements were performed in a temperature-controlled ( $24^{\circ}\text{C}$ ) room after a standardized breakfast or lunch, which included restrictions for caffeine, fatty products and smoking. A digital video microscope (Capi-scope; KK Technology, Honiton, UK) was used to record capillaries in the dorsal skin of the distal phalanges of the right-hand third and fourth finger. Capillaries were visualized 4.5 mm proximal to the terminal row of capillaries in the middle of the nailfold, after which a region of interest of  $1\text{ mm}^2$  skin area was selected. Capillary density (mean of two fields) was measured under three conditions. First, baseline capillary density was assessed. Second, capillary recruitment after 4 min of arterial occlusion was measured. Finally, capillary density after 2 min of venous congestion was examined. These measures are thought to reflect functional and/or structural capillary reserve capacity [4]. The number of continuously perfused capillaries within the region of interest was counted with a semi-automatic image analysis application (CapiAna) by two investigators who were both blinded to the characteristics of the participants. As described elsewhere, the intraobserver and interobserver variability was 2.5 and 5.6%, respectively [28].

### Covariates

After an overnight fast, venous blood samples were collected at The Maastricht Study research centre. Plasma glucose was measured with a standard enzymatic hexokinase reference method, and serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine and uric acid concentrations were measured with standard (enzymatic and/or colorimetric) methods by an automatic analyser (Beckman Synchron LX20; Beckman Coulter Inc., Brea, California, USA) at Maastricht University Medical Centre (the Netherlands). Measurement of creatinine was based on the Jaffé method traceable to isotope dilution mass spectrometry (Synchron LX20; Beckman Coulter Inc.). Weight and height were measured without shoes and wearing light clothing using a scale and stadiometer to the nearest 0.5 kg or 0.1 cm (Seca, Hamburg, Germany). BMI was calculated as body weight (kg) divided by height squared ( $\text{m}^2$ ). Waist circumference was measured in duplicate midway between the lower rib margin and the iliac crest at the end of expiration, to the nearest 0.5 cm, with a flexible plastic tape measure (Seca). Participants were requested to bring all the medication they used at the time of measurement or a list from their pharmacists to the research centre. During a medication interview generic name, dose and frequency, and additional over-the-counter (OTC) medication use were registered by trained staff. All participants received an extensive web-based questionnaire in which smoking behaviour (never, former, current) and years of diabetes duration were self-reported. SBP and

diastolic blood pressure (DBP) was determined three times on the right arm after a 10-min resting period, using a blood pressure monitor (Omron 705 IT; Omron, Japan). The average of the three measurements was calculated. Hypertension was defined as office SBP more than 140 mmHg, DBP more than 90 mmHg and/or current antihypertensive medication use. Renal function as estimated by eGFR (in ml/min per 1.73 m<sup>2</sup>) was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula [29]. To determine glucose metabolism, all participants (except those who used insulin) underwent a standardized 2-h, 75 g oral glucose tolerance test (OGTT) after an overnight fast. For safety reasons, participants with a fasting glucose level above 11.0 mmol/l, as determined by a finger prick, did not undergo the OGTT (*N*=13). Glucose metabolism status was classified according to the WHO 2006 criteria [30] as normal glucose metabolism (NGM) in case of fasting plasma glucose concentrations less than 6.1 mmol/l and 2-h post-glucose concentrations less than 7.8 mmol/l; impaired glucose tolerance (IGT) in case of fasting plasma glucose less than 7.0 mmol/l and 2-h post-glucose at least 7.8 and less than 11.1 mmol/l; impaired fasting glucose (IFG) in case of fasting plasma glucose 6.1–6.9 mmol/l and (if measured) 2-h post-glucose less than 7.8 mmol/l; and T2DM in case of fasting plasma glucose at least 7.0 mmol/l and/or 2-h post-glucose at least 11.1 mmol/l. For this study, we defined having either IFG or IGT as impaired glucose metabolism (IGM).

### Statistical analysis

All analyses were performed using IBM SPSS version 19 (SPSS, Chicago, Illinois, USA). General characteristics of the study population were compared across tertiles of uric acid concentrations using analysis of variance (ANOVA) for continuous variables and  $\chi^2$  test for discrete variables. Multivariable linear regression analyses were used to determine the association between uric acid [per +1 standard deviation (SD), SD=74  $\mu$ mol/l] and measures of skin microvascular function, that is capillary density at baseline (capillaries/mm<sup>2</sup>) and capillary recruitment after arterial occlusion and during venous congestion. Capillary recruitment after arterial occlusion and during venous congestion was expressed as the absolute change in capillary density after recruitment and as the percentage change in capillary density from baseline. The crude model (model 1) was first adjusted for age, sex and glucose metabolism status (model 2). Subsequently, the associations were adjusted for SBP, BMI, waist, smoking habits (current, ever, and never smoker), total cholesterol to HDL cholesterol ratio, triglycerides, eGFR and use of lipid-modifying and antidiabetic medication, renin–angiotensin–aldosterone system inhibitors and other antihypertensives (including beta-blockers) that have no known uricosuric properties, and antihypertensive and lipid-modifying medication that may have a uricosuric effect, that is secondary uricosurics [including losartan (*N*=13) [31,32], amlodipine (*N*=17) [33], atorvastatin (*N*=35) [34], rosuvastatin (*N*=37) [34]] (model 3). None of the individuals used fenofibrate [35]. Because high blood pressure and (or) low eGFR can theoretically acts as intermediates linking uric acid to microvascular dysfunction, adjustment for these variables may represent

overadjustment. We therefore specifically investigated whether model 3 was affected by the inclusion of SBP, antihypertensives and/or eGFR.

Finally, we tested interactions between uric acid and sex, age or glucose metabolism status (three categories: NGM, IGM and T2DM) in model 3, both with and without adjustment for SBP and eGFR. A *P* value of less than 0.05 was considered statistically significant, except for the interaction analyses, wherein we used *P* value less than 0.10.

## RESULTS

Table 1 summarizes the characteristics of the study population. This study included 610 individuals with a mean age of 58.7  $\pm$  8.6 years of whom 51.8% were men. By design, individuals with type 2 diabetes were oversampled (23.6% of our study population). A large percentage of individuals had hypertension (50.5%), and among those individuals, 11.7% used diuretics. Mean capillary density at baseline was 73.7  $\pm$  17.6 capillaries/mm<sup>2</sup>; density increased to 103.8  $\pm$  17.5 capillaries/mm<sup>2</sup> after arterial occlusion and to 104.2  $\pm$  18.0 capillaries/mm<sup>2</sup> during venous congestion. Consequently, the average percentages of recruitment after arterial occlusion or during venous congestion were 45.5  $\pm$  29.1 and 46.2  $\pm$  30.7%, respectively. Capillary density and percentage of recruitment were not significantly different between uric acid tertiles. However, individuals in the third uric acid tertile were more often male and did have a worse metabolic profile, including significantly higher BMI, triglyceride concentrations and higher total cholesterol to HDL ratio. Individuals excluded due to missing values had higher uric acid concentrations, slightly higher BMI and waist, and more often had T2DM (supplementary table, <http://links.lww.com/HJH/A478>).

### Uric acid, baseline capillary density and capillary recruitment

Crude linear regression analysis showed that a 1 SD (74  $\mu$ mol/l) higher serum uric acid concentration was not associated with baseline capillary density [ $\beta$  = -0.21 (95% confidence interval, 95% CI -1.61 to 1.19) *P* = 0.765] (Table 2, model 1; Fig. 1). The association remained non-significant after adjustment for sex, age and glucose metabolism status, as well as further adjustments (Table 2, models 2 and 3). Excluding SBP and eGFR from model 3 did not change the results (data not shown). In contrast, higher uric acid was borderline associated with decreased capillary recruitment expressed as absolute change in density after arterial occlusion [ $\beta$  = -1.15 (95% CI -2.36 to 0.06) *P* = 0.062] and significantly associated with change in capillary density during venous congestion [ $\beta$  = -1.41 (95% CI -2.68 to -0.14) *P* = 0.029] (Table 2, model 1; Fig. 1) in unadjusted analyses. However, after adjustment for sex, age and glucose metabolism status, the associations with change in capillary density after arterial occlusion [ $\beta$  = 0.01 (95% CI -1.32 to 1.35) *P* = 0.983] and during venous congestion [ $\beta$  = -0.04 (95% CI -1.44 to 1.36) *P* = 0.952] were no longer statistically significant (Table 2, model 2); further adjustment gave similar results (model 3). Results did not change after excluding SBP, antihypertensives and/or eGFR from model 3 (data not shown).

**TABLE 1. Baseline characteristics of The Maastricht Study population according to tertiles of uric acid**

	Uric acid tertiles				P <sup>a</sup>
	Overall (N = 610)	Lowest (N = 196)	Middle (N = 212)	Highest (N = 202)	
Uric acid (μmol/l)	346 ± 74	267 ± 30	339 ± 20	430 ± 47	<0.001
Age (years)	58.7 ± 8.6	57.3 ± 8.1	58.6 ± 8.8	60.1 ± 8.5	0.004
Male sex (%)	51.8	23.5	57.1	73.8	<0.001
BMI (kg/m <sup>2</sup> )	26.9 ± 4.4	25.0 ± 3.7	26.8 ± 4.0	28.8 ± 4.5	<0.001
Waist circumference (cm)	95.5 ± 13.0	88.8 ± 12.0	95.1 ± 11.8	102.5 ± 11.3	<0.001
Smoking (%)					0.417
Never	32.5	34.2	30.7	32.7	
Past	52.0	47.4	53.3	55.0	
Current	15.6	18.4	16.0	12.4	
Total cholesterol to HDL ratio	4.2 ± 1.3	3.7 ± 1.1	4.2 ± 1.3	4.7 ± 1.4	<0.001
Triglycerides (mmol/l)	1.19 (0.83; 1.74)	0.93 (0.67; 1.34)	1.26 (0.85; 1.69)	1.48 (1.05; 2.24)	<0.001
Use of lipid-modifying medication (%)	27.2	18.9	29.7	32.7	0.005
Use of lipid-modifying medication that have no known uricosuric properties (%)	15.9	9.2	18.4	19.8	0.007
eGFR (ml/min per 1.73 m <sup>2</sup> )	85.9 ± 14.2	89.2 ± 12.1	87.3 ± 13.6	81.3 ± 15.4	<0.001
eGFR <60 ml/min per 1.73 m <sup>2</sup> (%)	4.9	1.0	3.3	10.4	<0.001
Glucose metabolism status (%)					<0.001
Normal glucose metabolism	59.7	76.5	59.4	43.6	
Impaired glucose metabolism	16.7	8.2	17.5	24.3	
Type 2 diabetes	23.6	15.3	23.1	32.2	
Diabetes treatment among patients with type 2 diabetes <sup>b</sup> (%)					0.358
No medication	24.3	26.7	26.5	21.5	
Oral medication	60.4	46.7	59.2	67.7	
Insulin with or without oral medication	15.3	26.7	14.3	10.7	
Diabetes duration <sup>b</sup> (years)	6.0 (3.0; 10.3)	6.0 (3.0; 11.8)	6.0 (3.0; 11.0)	6.0 (2.0; 10.0)	0.510
Hypertension (%)	50.5	31.6	54.2	64.9	<0.001
Use of antihypertensives among patients with hypertension <sup>c</sup> (%)					
Use of RAAS inhibitors	44.2	43.5	39.1	48.9	0.307
Use of RAAS inhibitors that have no known uricosuric properties	39.9	37.1	33.9	46.6	0.114
Use of other antihypertensives	41.6	27.4	37.4	51.9	0.003
Use of other antihypertensives that have no known uricosuric properties	38.6	25.8	34.8	48.1	0.007
Use of secondary uricosurics (%)	15.2	13.3	16.0	16.3	0.643
Capillary density (capillaries/mm <sup>2</sup> )					
Baseline	73.7 ± 17.6	72.4 ± 17.2	75.6 ± 17.7	72.9 ± 17.7	0.110
Arterial occlusion	103.8 ± 17.5	104.0 ± 16.0	105.3 ± 18.1	102.1 ± 18.3	0.166
Venous congestion	104.2 ± 18.0	104.7 ± 16.6	105.6 ± 18.6	102.2 ± 18.5	0.121
Capillary recruitment (%)					
Arterial occlusion	45.5 ± 29.1	48.7 ± 29.8	43.4 ± 29.3	44.6 ± 28.0	0.151
Venous congestion	46.2 ± 30.7	49.9 ± 31.9	44.0 ± 30.4	44.9 ± 29.7	0.116

eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system. Data are reported as mean ± SD, median (interquartile range), or percentage as appropriate.

<sup>a</sup>Based on ANOVA for continuous variables and Chi-square tests for categorical variables.

<sup>b</sup>Individuals with type 2 diabetes: overall N = 144; lowest tertile N = 30; middle tertile N = 49; highest tertile N = 65.

<sup>c</sup>Individuals with hypertension: overall N = 308; lowest tertile N = 62; middle tertile N = 115; highest tertile N = 131.

In unadjusted analyses, no significant association was found between uric acid and the percentage of capillary recruitment after arterial occlusion [ $\beta = -1.66$  (95% CI  $-3.97$  to  $0.65$ )  $P = 0.159$ ] or during venous congestion

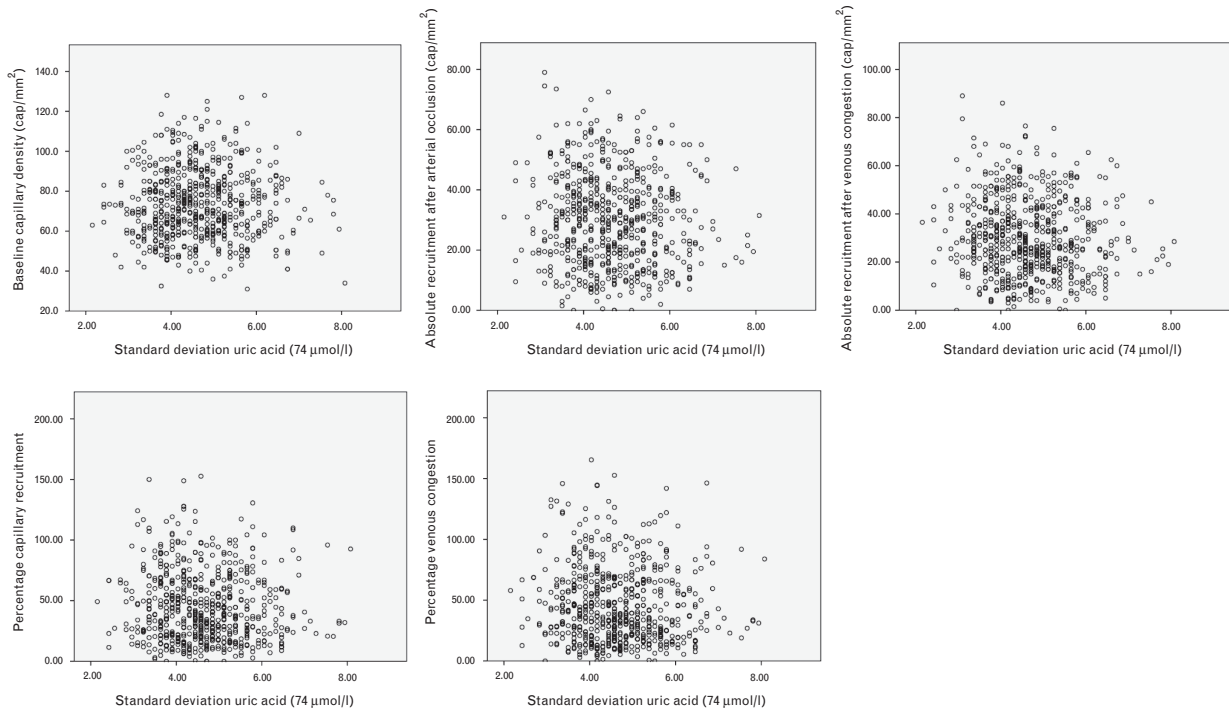
[ $\beta = -2.02$  (95% CI  $-4.46$  to  $0.42$ )  $P = 0.104$ ] (Table 3, model 1; Fig. 1); multivariable analyses gave similar results. Excluding SBP, antihypertensives and/or eGFR from model 3 did not change the results (data not shown).

**TABLE 2. Association between uric acid, capillary density (cap/mm<sup>2</sup>) at baseline and absolute recruitment after arterial occlusion and during venous congestion**

	Capillary density (cap/mm <sup>2</sup> )								
	Baseline			Arterial occlusion			Venous congestion		
	$\beta^a$	95% CI	P	$\beta^a$	95% CI	P	$\beta^a$	95% CI	P
Model 1	-0.21	-1.61 to 1.19	0.765	-1.15	-2.36 to 0.06	0.062	-1.41	-2.68 to -0.14	0.029
Model 2	-0.23	-1.80 to 1.34	0.773	0.01	-1.32 to 1.35	0.983	-0.04	-1.44 to 1.36	0.952
Model 3	-0.25	-2.16 to 1.65	0.794	0.53	-1.08 to 2.14	0.516	0.80	-0.88 to 2.48	0.352

Model 1: crude. Model 2: adjusted for sex, age, glucose metabolism status. Model 3: model 2 and adjusted for SBP, BMI, waist, smoking, total:HDL cholesterol ratio, triglycerides, eGFR and use of lipid-modifying and antidiabetic medication, renin-angiotensin-aldosterone system inhibitors, other antihypertensives and use of secondary uricosurics. CI, confidence interval.

<sup>a</sup>Uric acid expressed as standard deviation (74 μmol/l).



**FIGURE 1** Scatterplots of measures of skin microvascular function against serum uric acid concentrations (expressed as standard deviation).

**Additional analyses**

Sex modified the association between uric acid and baseline capillary density (*P* for interaction = 0.009), with an inverse nonsignificant association among men [ $\beta = -2.19$  (95% CI -4.67 to 0.30) *P* = 0.084] compared with a positive nonsignificant association among women [ $\beta = 1.78$  (95% CI -1.26 to 4.82) *P* = 0.251] after full adjustments. Similarly, age modified the association between uric acid and baseline capillary density (*p* for interaction = 0.079), with an inverse association in the lowest age tertile (mean age 48.7 ± 4.4 years) [ $\beta = -3.73$  (95% CI -6.80 to -0.67) *P* = 0.017] compared with nonsignificant associations in the middle (mean age 59.7 ± 2.2 years) [ $\beta = 1.75$  (95% CI -1.69 to 5.20) *P* = 0.317] and highest age tertiles (mean age 67.7 ± 3.0 years) [ $\beta = 0.29$  (95% CI -3.47 to 4.06) *P* = 0.878]. Sex and age did not modify the associations between uric acid and any of the other skin microvascular function measures (*P* for interaction > 0.10).

No significant interactions between uric acid and glucose metabolism status (three categories: NGM, IGM and T2DM) were identified in any of the investigated associations (*P* for interaction > 0.10).

Finally, excluding SBP, antihypertensives and/or eGFR from model 3 gave similar results (data not shown).

**DISCUSSION**

The present study showed that, in middle-aged individuals, uric acid was not significantly associated with skin microvascular function as determined by baseline capillary density and capillary recruitment. To the best of our knowledge, this study is the first to assess the relation between uric acid and microvascular function of the skin in the general population.

Our results are in contrast with prior research on the association between uric acid and markers of microvascular dysfunction in the eye (i.e. retinal arteriolar narrowing) [13], kidney (i.e. microalbuminuria) [14] and of the coronary arteries (i.e. coronary flow reserve) [10–12]. These studies showed significant associations between higher uric acid and altered microvascular structure or decreased microvascular function. Reasons for these contrasting findings are not apparent, especially as microvascular dysfunction appears to be part of a systemic process [15]. The contrasting findings

**TABLE 3. Association between uric acid and capillary recruitment (%) after arterial occlusion and during venous congestion**

	Capillary recruitment (%)					
	Arterial occlusion			Venous congestion		
	$\beta^a$	95% CI	<i>P</i>	$\beta^a$	95% CI	<i>P</i>
Model 1	-1.66	-3.97 to 0.65	0.159	-2.02	-4.46 to 0.42	0.104
Model 2	0.14	-2.43 to 2.71	0.915	0.04	-2.67 to 2.75	0.976
Model 3	0.89	-2.22 to 3.99	0.576	1.23	-2.04 to 4.50	0.461

Model 1: crude. Model 2: adjusted for sex, age, glucose metabolism status. Model 3: model 2 and adjusted for SBP, BMI, waist, smoking, total:HDL cholesterol ratio, triglycerides, eGFR, and use of lipid-modifying and antidiabetic medication, renin-angiotensin-aldosterone system inhibitors, other antihypertensives and use of secondary uricosurics. CI, confidence interval. <sup>a</sup>Uric acid expressed as standard deviation (74 µmol/l).

may, therefore, be caused by methodological differences, such as demographics and cardiovascular risk profile of the study populations, or the methods used to assess microvascular function.

A possible pathophysiological explanation for our findings may relate to the heterogeneous mechanisms underlying arterial reactivity in various vascular beds [36]. Autoregulation of blood flow is achieved by metabolic, tissue pressure and myogenic control, but the degree to which they participate in the vascular response may differ [37]. Indeed, it has been suggested that the myogenic response is most pronounced in renal, cerebral and coronary vessels [37,38]. Animal studies that assessed the underlying mechanism of the association between uric acid and microcirculatory function point towards a primary role of smooth muscle cell proliferation [8,9]. Therefore, it is possible that uric acid mainly affects the kidney and/or coronary microcirculation. However, uric acid has also been associated with endothelial dysfunction [39]. A study in individuals with type 1 diabetes showed that uric acid was associated with a reduced endothelium-dependent vasodilator response, but not with the endothelium-independent response of the skin microcirculation [20].

We hypothesized that uric acid may have a more pronounced effect in individuals with a lower cardiovascular risk profile [22,25], that is women, younger individuals and individuals with normal glucose metabolism. However, no strong effect of sex on the association between uric acid and microvascular function could be identified. These data thus seem to contradict previous studies showing a stronger relation between uric acid, cardiovascular disease [21] and coronary microvascular dysfunction [11] in women. The effect of sex on the association between uric acid and microvascular function needs further exploration, and also the mechanism of a possible differential effect of sex needs to be elucidated. In addition, we assessed the interaction between uric acid and age, but were unable to clearly confirm the hypothesis of Feig [22], who suggested that elevated uric acid concentrations may have a more pronounced effect in the young. We did, however, find a significant inverse association between uric acid and baseline capillary density in the lowest age tertile. This result should be interpreted with caution in view of the number of associations we studied. On the contrary, we cannot exclude that uric acid affects microcirculatory function in individuals younger than those we studied (i.e. mean age = 58.7 years). In addition, we found no support for the hypothesis that uric acid may affect microcirculatory function especially in individuals with normal glucose metabolism [23,24]. These issues deserve further study before firm conclusions can be drawn.

A limitation of our study may be the mean age of the study population. If uric acid is indeed only associated with microvascular function in young individuals, the age range of our study population may have contributed to the lack of statistical significance of the results of the present study. Furthermore, we used skin microcirculation as a model of generalized microvascular function. However, the generalizability to other vascular beds still needs further examination [40].

In conclusion, our results suggest that the previously reported association between uric acid and various diseases, such as hypertension [5], renal disease [6] and cardiomyopathies [7], cannot be explained by generalized microvascular dysfunction. However, this does not exclude the possibility that uric acid is associated with microvascular dysfunction in specific vascular beds. Especially the association between uric acid and microvascular function of vascular beds in which the myogenic response plays a primary role needs further investigation.

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## Conflicts of interest

A.B. receives research grants for the department from Pfizer, AbbVie, Merck, Amgen and occasionally speakers' honoraria from Pfizer and UCB. For the remaining authors, none were declared.

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