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# Vascular risk factors for optical coherence tomography-detected macular cysts: The Maastricht Study

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**ABSTRACT.**

***Purpose:*** **To investigate whether higher blood pressure and greater arterial stiffness are associated with the presence of macular cysts and whether this association is already present in the absence of micro-aneurysms in individuals with and without type 2 diabetes.**

***Methods:*** **Using spectral domain optical coherence tomography (OCT), we performed a macular volume scan in 2647 individuals (mean age 60 ± 8 years, 50% men, 27% type 2 diabetes). The association between macular cysts and 24-hour systolic and diastolic blood pressure, pulse pressure, mean arterial blood pressure, carotid-femoral pulse wave velocity and carotid distensibility was assessed by use of logistic regression.**

***Results:*** **Twenty-four hours systolic blood pressure was associated with the presence of macular cysts [OR = 1.03 (95% CI 1.00–1.05) per 1 mmHg, p = 0.03]. 24 hr pulse pressure [OR = 1.61 (95% CI 1.11–2.34) per 10 mmHg, p = 0.01] and carotid-femoral pulse wave velocity [OR = 1.16 (95% CI 1.02–1.32) per 1 m/s, p = 0.02] were associated with macular cysts, while carotid distensibility was not [OR = 1.03 (95% CI 0.96–1.11) per $1.0*10^{-3}$/kPa, p = 0.45]. Associations were similar in individuals with and without type 2 diabetes and were already present in the absence of micro-aneurysms.**

***Conclusion:*** **Twenty-four hours systolic blood pressure, 24 hr pulse pressure and carotid-femoral pulse wave velocity are associated with the presence of OCT-detected macular cysts in individuals with and without type 2 diabetes, even in the absence of micro-aneurysms. Therefore, blood pressure and aortic stiffness are potential factors contributing to macular cysts.**

**Key words:** macular cysts – optical coherence tomography – type 2 diabetes – vascular risk factors

The corresponding author is a member of the Dutch Ophthalmological Societies only.

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## Introduction

Macular oedema commonly leads to vision loss and is a main cause of visual impairment (Ferris et al. 1987). Leakage of fluid into the extracellular space of the neurosensory retina due to loss of endothelial cells in retinal vessels with subsequent altered blood–retina barrier is thought to play an important role in the formation of macular cysts in individuals with arterial hypertension and/or diabetes (Augustin et al. 2010; Staurenghi et al. 2010; Bhargava et al. 2012). Furthermore, hypertension increases the risk of development of macular oedema in individuals with diabetes (Fenwick et al. 2017). However, proposed mechanisms may not only include local microvascular alterations in the retinal vessels, but also systemic macrovascular alterations such as arterial stiffening (Rema et al. 2004).

Large artery stiffening leads to a high pulsatile energy that is transmitted distally and may damage the microcirculation in organs such as the kidney and brain, resulting in nephropathy and cerebral damage (O'Rourke & Safar 2005; Mitchell 2008; Mitchell et al. 2011; van Sloten et al. 2015).

Also in the retinal microcirculation, which is characterized by low impedance, the increased pulsatile load could penetrate deeply into the small retinal vessels promoting vascular leakage (Rema et al. 2004) and formation of cystoid oedema (O'Rourke & Safar 2005; Mitchell 2008). Large artery stiffening is one of the long-term complications of diabetes mellitus (Henry et al. 2003; Stehouwer et al. 2008). In addition, the ability of retinal vessels to withstand this increased pulsatile load could be decreased in individuals with type 2 diabetes (Schram et al. 2002; Schram et al. 2003; Rema et al. 2004; O'Rourke & Safar 2005), which could render these subjects susceptible to development of macular oedema.

Traditionally, fundoscopy allows visualization of micro-aneurysms and the presence of significant macular oedema. With the development of optical coherence tomography (OCT), macular cysts as part of the macular oedema, and even small cysts without obvious macular thickening as an early sign of macular oedema formation, can currently be assessed with high sensitivity (Frank 2004). Therefore, macular cysts already occur in the absence of micro-aneurysms, before structural damage can be observed (Coscas et al. 2017).

The aim of the present study was to assess whether higher blood pressure and greater arterial stiffness are associated with the presence of macular cysts detected with optical coherence tomography (OCT) and whether this association is already present in the absence of micro-aneurysms in individuals with and without type 2 diabetes.

# Materials and Methods

### Study population and design

We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously (Schram et al. 2014). In brief, the study focuses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus (DM2) 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 DM2 status, with an oversampling of individuals with DM2, for reasons of efficiency. The present report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. OCT measurements were included in the protocol from 8 December 2011 onwards. The examinations of each participant were performed within a time window of three months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

### Glucose metabolism status

To determine glucose metabolism status, all participants, except those who used insulin, underwent a standardized 2-hr 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. For these individuals ($n = 13$), fasting glucose level and information about diabetes medication were used to determine glucose metabolism status. Glucose metabolism status was defined according to the World Health Organization (2006) criteria into normal glucose metabolism (NGM), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and DM2 (World Health Organization 2006). Individuals without type 1 diabetes (DM1) on diabetes medication were classified as having DM2 (Schram et al. 2014). For this study, individuals with DM1, individuals with latent autoimmune diabetes of adults, steroid-induced diabetes and individuals who underwent a pancreas transplantation were excluded.

### Assessment of macular cysts

All participants were examined with the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany, Heidelberg Eye Explorer software version 5.7.5.0) with the eye tracking function enabled. A macular volume scan (17 ART, 73 sections, 60 μm) was performed in both eyes by experienced examiners masked to the conditions of the participants. Regional numeric data of the macular thickness were derived from the Macular Thickness Map (Massin et al. 2002). With use of the Macular Thickness Map, macular thickness was measured at the centre and the fovea. All the cross-sections of the macular volume scans were reviewed and scored for the presence of one or more macular cysts (Girach & Lund-Andersen 2007; Klein et al. 2009) by two experienced graders (EDC, IL) in a masked fashion based on a prespecified protocol (Liesenborghs et al. 2018). All the observed disorders were confirmed by a vitreoretinal surgeon (FG), and a random sample of normal OCTs was also confirmed. The inter-rater agreement was 100%. In individuals with macular cysts, macular thickness of the eye with the macular cysts was used. In individuals with macular cysts in both eyes and in individuals without macular cysts, macular thickness of the right eye was used (De Clerck et al. 2018). Individuals with an incomplete volume scan were excluded.

### Assessment of risk factors

Once the pupils were dilated with tropicamide 0.5% and phenylephrine 2.5%, fundus photography of both eyes was performed. All fundus photographs were made with an auto fundus camera (Model AFC-230, Nidek, Gamagori, Japan) in 45 degrees of at least three fields: one field centred on the optic disc, one field centred on the macula and one temporal field positioned one disc-diameter from the centre of the macula. These fundus photographs were evaluated by a trained and experienced grader (EDC) in a masked fashion, and in case of any doubt or an abnormal finding, the fundus photograph was discussed with a medical retina specialist (JS). Based on these fundus photographs, the minimum criterion for diagnosis of micro-aneurysms was the presence of at least one micro-aneurysm in any field of the retina. The presence of previous surgery was assessed by questionnaire. In addition, the presence of an intraocular lens was assessed on the Scheimpflug image of the anterior segment (Oculus

Pentacam HR, Wetzlar, Germany). Individuals with macular cysts who underwent intraocular surgery were excluded in order to avoid surgically induced cystoid macular oedema.

Ambulatory blood pressure was measured with ambulatory 24-hr BP monitoring (WatchBP O3; Microlife AG, Widnau, Switzerland) as described elsewhere (Schram et al. 2014). Pulse pressure (PP) was defined as systolic blood pressure minus diastolic blood pressure and mean arterial pressure (MAP) as diastolic blood pressure plus 0.412 times pulse pressure (Meaney et al. 2000). Hypertension was defined as a 24 hr blood pressure ≥140/90 mmHg or use of antihypertensive medication.

During the vascular assessment, brachial systolic, diastolic and mean arterial pressure were determined repeatedly with a 5-min interval, using an oscillometric device (Accutorr Plus, Datascope Inc., Montvale, NJ, USA), and the average of these measurements was calculated. Carotid-femoral pulse wave velocity was determined according to recent guidelines (Van Bortel et al. 2012) with applanation tonometry (SphygmoCor, Atcor Medical, Naperville, IL, USA). The pulse wave travel distance was calculated as 80% of the direct straight distance (measured with an infantometer) between the right common carotid and right common femoral arteries, as described previously (van Sloten et al. 2015). Elastic properties of the left common carotid artery (at least 10 mm proximal to the carotid bulb) were obtained by using an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab70, Esaote Europe B.V., Maastricht, The Netherlands). This setup enabled the measurement of diameter, distension, and intima-media thickness as described elsewhere (Willekes et al. 1999; Hermeling et al. 2009). Combined with brachial pulse pressure, these measures were used to calculate the carotid distensibility coefficient, which represents carotid arterial stiffness. Please note that higher values of carotid-femoral pulse wave velocity, and lower values of carotid distensibility reflect greater arterial stiffness. Reproducibility was assessed in 12 individuals (six men; 60.8 ± 6.8 years; 6 with type 2 diabetes), who were examined twice by two observers. The intra-and inter-observer intra-class correlation coefficients were 0.87 and 0.69 for the carotid-femoral pulse wave velocity and 0.85 and 0.73 for the carotid distensibility coefficient.

Body mass index (BMI), total and HDL cholesterol and triglycerides were determined as described elsewhere (Schram et al. 2014). Smoking status (never, former, or current) was assessed by questionnaire (Schram et al. 2014).

### Statistical analysis

Statistical analyses were performed in SPSS Statistics 23 for Windows (SPSS, Inc., IBM, Armonk, NY, USA). Differences between group characteristics were tested by one-way analysis of variance (ANOVA) for continuous variables and $\chi^2$ tests for categorical variables. The presence of macular cysts in one or both eyes was defined as one categorical variable. First, we defined which risk factors were associated with macular cystoid oedema using logistic regression analyses. The independent vascular variables were 24-hr systolic and diastolic blood pressure, pulse pressure, mean arterial pressure, carotid-femoral pulse wave velocity and carotid distensibility. Potential confounders were the presence of prediabetes or DM2, smoking, body mass index, total cholesterol-to-HDL cholesterol ratio and triglycerides. The outcome variable was the presence of macular cysts (binary categorical outcome variable). The association between the cardiovascular risk factor (exposure) and the presence of macular cysts (outcome) was presented as an odds ratio (OR) with its 95% confidence interval (95% CI) (Szumilas 2010). Adjustments were made for age and sex, as well as for diabetic status, in order to adjust for oversampling of individuals with DM2 in the total study population (model 1); additionally for mean arterial pressure and heart rate, which are well-known confounders of arterial stiffness (model 2); and cardiovascular risk factors: smoking habits (current, ever and never smoker), body mass index and total/high-density lipoprotein cholesterol ratio (model 3). Interaction terms (eg, cfPWV * type 2 diabetes) were incorporated in the regression model to test interaction effects between type 2 diabetes and arterial stiffness on the presence of macular cysts. Changes in regression coefficients of type 2 diabetes after inclusion of arterial stiffness in the model were calculated.

## Results

### General characteristics

Figure 1 shows the flow diagram of the study. From the 3451 participants included, forty-one participants with DM1 or other types of diabetes and thirteen individuals with surgically induced cystoid macular oedema were excluded from the present analysis. A valid OCT measurement was available in 2647 participants. The main reason for missing data ($n = 691$) was the later implementation of OCT measurements (from 8 December 2011 onwards). In addition, participants with an incomplete volume scan ($n = 66$) were excluded. Finally, exclusion of individuals with micro-aneurysms as assessed by fundus photography ($n = 32$) and individuals who did not underwent fundus photography ($n = 288$) resulted in a subpopulation of 2327 participants. Individuals with missing data on the risk factors were not excluded.

Table 1 shows general characteristics of the 2647 included participants stratified by the presence of macular cysts. In individuals with macular cysts, age, male sex, 24 hr systolic blood pressure, 24 hr pulse pressure, carotid-femoral pulse wave velocity, the presence of micro-aneurysms and body mass index were significantly higher compared with individuals without cysts ($p < 0.05$). However, carotid artery distensibility was not statistically significantly different between these groups ($p = 0.06$). In individuals with macular cysts, the centre thickness and the foveal thickness were significantly higher compared with individuals without macular cysts (mean centre thickness: 291.2 ± 92.9 μm versus 233.5 ± 33.6 μm, $p < 0.001$; mean foveal thickness: 326.8 ± 72.8 μm versus 285.7 ± 25.5 μm, $p < 0.001$). Of the 51 participants with macular cysts, 14 participants presented with clinically significant cystoid macular oedema (27.5%), as defined by the presence of macular cysts and a centre macular thickness above 300 μm. The prevalence of macular cysts according to glucose metabolism status was 0.8% in

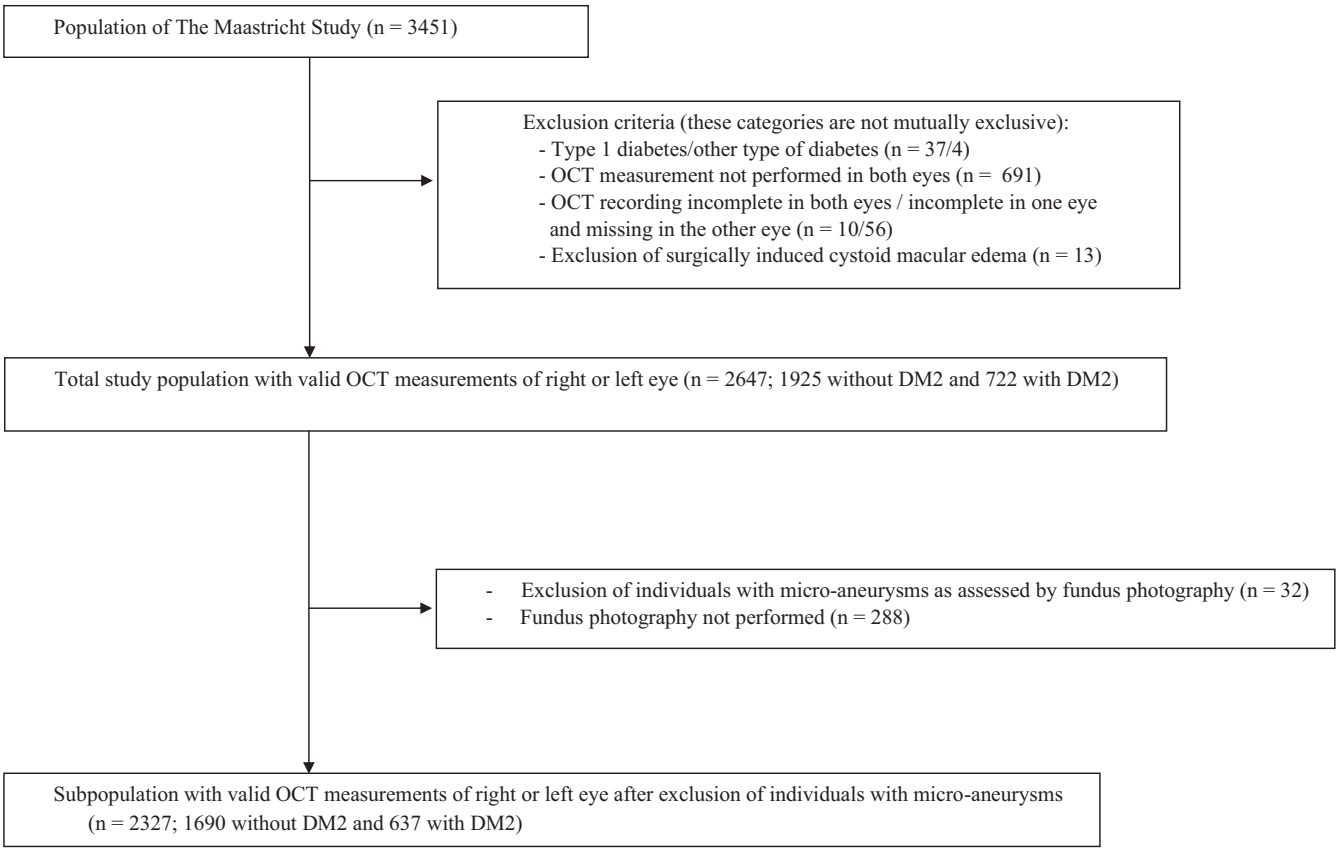


**Fig. 1.** Flow diagram of the study. DM2 = type 2 diabetes, NGM = normal glucose metabolism.

**Table 1.** Baseline characteristics of the study population stratified by the presence of macular cysts.

| | Characteristics in total group without macular cysts (*n* = 2596) | Characteristics in total group with macular cysts (*n* = 51) | p-Value |
|---|---|---|---|
| Age (years), mean (SD) | 60 (8) | 65 (7) | **<0.001*** |
| Male sex, *n* (%) | 1295 (50) | 33 (65) | **0.04*** |
| 24 hr systolic blood pressure (mmHg), mean (SD)[1] | 119 (11) | 125 (14) | **<0.001*** |
| 24 hr diastolic blood pressure (mmHg), mean (SD)[1] | 73 (7) | 73 (7) | 0.43 |
| 24 hr pulse pressure (mmHg), mean (SD)[1] | 45 (5) | 52 (6) | **<0.001*** |
| 24 hr mean arterial pressure (mmHg), mean (SD)[1] | 89 (8) | 90 (8) | 0.19 |
| Carotid-femoral pulse wave velocity (m/s), mean (SD)[2] | 9 (4) | 11 (5) | **<0.001*** |
| Distensibility coefficient carotid artery ($10^{-3}$/kPa), mean (SD)[3] | 14 (5) | 13 (5) | 0.06 |
| Presence of micro-aneurysms, *n* (%)[4] | 22 (1.0) | 10 (19.6) | **<0.001*** |
| Glucose metabolism status, NGM/prediabetes/DM2, *n* (%) | 1515/393/688 (58.4/15.1/26.5) | 12/5/34 (23.5/9.8/66.7) | **<0.001*** |
| Smoking status, never/former/current, *n* (%)[5] | 911/1323/320 (35.7/51.8/12.5) | 13/33/4 (26.0/66.0/8.0) | 0.14 |
| BMI (kg/m$^2$), mean (SD)[6] | 27.0 (4.5) | 28.8 (4.7) | **<0.01*** |
| Total cholesterol-to-HDL cholesterol ratio, mean (SD)[6] | 3.59 (1.15) | 3.32 (1.09) | 0.10 |
| Triglycerides (mmol/l), median (IQR)[6] | 1.42 (0.85) | 1.40 (0.71) | 0.91 |
| Centre thickness (μm), mean (SD) | 233.5 (33.6) | 291.2 (92.9) | **<0.001*** |
| Foveal thickness (μm), mean (SD) | 285.7 (25.5) | 326.8 (72.8) | **<0.001*** |

BMI = body mass index, DM2 = type 2 diabetes, HDL = high-density lipoprotein, NGM = normal glucose metabolism.
1 = available for 2294 participants without cysts and 49 with cysts. 2 = available for 2136 participants without cysts and 42 with cysts. 3 = available for 2163 participants without cysts and 44 with cysts. 4 = available in 2315 participants without cysts and 44 with cysts. 5 = available in 2554 participants without cysts and 50 with cysts. 6 = available in 2595 participants without cysts and 51 with cysts.
* $p < 0.05$ compared with individuals without macular cysts.

individuals with NGM and 4.7% in individuals with DM2. Seven participants out of 51 (13.7%) presented with hypertension and macular cysts in non-diabetic participants. In this group, three participants presented evidence of retinopathy, arguing for hypertensive macular oedema.

**Risk factors**

Table 2 shows the association between several risk factors and the presence of macular cysts, adjusted for age and sex.

**Table 2.** Association between vascular risk factors and potential confounders with the presence of macular cysts, adjusted for age, sex, and (pre)diabetes.

| | Macular cysts assessed by OCT | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total population ($n$ = 2647) | | | | | | After exclusion of individuals with micro-aneurysms ($n$ = 2327) | | | | | |
| | Crude analysis | | Analysis adjusted for age and sex | | Analysis adjusted for age, sex, and (pre)diabetes | | Crude analysis | | Analysis adjusted for age and sex | | Analysis adjusted for age, sex, and (pre)diabetes | |
| | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p |
| Age (years) | 1.10 (1.05–1.14) | **<0.001*** | – | – | – | – | 1.11 (1.05–1.17) | **<0.001*** | – | – | – | – |
| Sex | 0.54 (0.30–0.97) | **0.04*** | – | – | – | – | 0.87 (0.44–1.72) | 0.69 | – | – | – | – |
| 24 hr systolic blood pressure (mmHg) | 1.04 (1.02–1.06) | **<0.001*** | 1.03 (1.01–1.06) | **<0.01*** | 1.03 (1.00–1.05) | **0.03*** | 1.03 (1.00–1.06) | 0.05 | 1.02 (0.99–1.06) | 0.13 | 1.02 (0.99–1.05) | 0.19 |
| 24 hr diastolic blood pressure (mmHg) | 0.98 (0.94–1.03) | 0.43 | 0.99 (0.95–1.04) | 0.71 | 1.00 (0.96–1.05) | 0.90 | 0.98 (0.93–1.03) | 0.43 | 1.00 (0.95–1.05) | 0.99 | 1.01 (0.96–1.06) | 0.78 |
| 24 hr pulse pressure (10 mmHg) | 2.12 (1.62–2.77) | **<0.001*** | 1.81 (1.33–2.46) | **<0.001*** | 1.55 (1.13–2.12) | **<0.01*** | 1.80 (1.27–2.56) | **<0.01*** | 1.53 (1.02–2.29) | **0.04*** | 1.37 (0.91–2.07) | 0.13 |
| 24 hr mean arterial pressure (mmHg) | 1.02 (0.99–1.06) | 0.19 | 1.02 (0.98–1.06) | 0.30 | 1.02 (0.98–1.06) | 0.25 | 1.01 (0.97–1.06) | 0.65 | 1.02 (0.97–1.07) | 0.47 | 1.02 (0.97–1.07) | 0.42 |
| Carotid-femoral pulse wave velocity (m/s) | 1.28 (1.16–1.42) | **<0.001*** | 1.20 (1.07–1.34) | **<0.01*** | 1.14 (1.01–1.28) | **0.03*** | 1.27 (1.13–1.43) | **<0.001*** | 1.18 (1.03–1.36) | **0.02*** | 1.14 (0.99–1.32) | 0.07 |
| Distensibility coefficient carotid artery ($10^{-3}$/kPa) | 0.94 (0.88–1.00) | 0.06 | 0.99 (0.92–1.06) | 0.77 | 1.01 (0.94–1.08) | 0.88 | 0.91 (0.83–0.99) | **0.02*** | 0.96 (0.88–1.05) | 0.40 | 1.29 (0.64–2.62) | 0.48 |
| Presence of micro-aneurysms | 30.7 (13.5–69.6) | **<0.001*** | 28.2 (11.9–66.4) | **<0.001*** | 17.3 (7.1–42.3) | **<0.001*** | – | – | – | – | – | – |
| Presence of prediabetes | 0.61 (0.24–1.54) | 0.30 | 0.54 (0.21–1.36) | 0.19 | – | – | 0.96 (0.37–2.51) | 0.94 | 0.86 (0.33–2.25) | 0.76 | – | – |
| Presence of type 2 diabetes | 5.55 (3.08–9.99) | **<0.001*** | 4.22 (2.28–7.79) | **<0.001*** | – | – | 3.43 (1.73–6.80) | **<0.001*** | 2.72 (1.33–5.58) | **<0.01*** | – | – |
| Smoking status, former | 1.76 (0.99–3.15) | 0.06 | 1.42 (0.79–2.56) | 0.24 | 1.45 (0.80–2.62) | 0.22 | 1.57 (0.78–3.16) | 0.20 | 1.30 (0.64–2.62) | 0.47 | 1.29 (0.64–2.62) | 0.48 |
| Smoking status, current | 0.61 (0.22–1.69) | 0.34 | 0.75 (0.27–2.11) | 0.59 | 0.62 (0.22–1.75) | 0.36 | 0.97 (0.34–2.76) | 0.95 | 1.27 (0.44–3.69) | 0.66 | 1.10 (0.38–3.20) | 0.87 |
| BMI (kg/m$^2$) | 1.08 (1.03–1.14) | **<0.01*** | 1.08 (1.02–1.14) | **0.01*** | 1.02 (0.96–1.08) | 0.60 | 1.07 (1.00–1.14) | **0.04*** | 1.07 (0.99–1.15) | 0.05 | 1.03 (0.96–1.11) | 0.44 |
| Total cholesterol-to-HDL cholesterol ratio | 0.79 (0.59–1.04) | 0.10 | 0.79 (0.58–1.06) | 0.11 | 0.78 (0.58–1.05) | 0.11 | 0.85 (0.61–1.20) | 0.36 | 0.91 (0.64–1.30) | 0.60 | 0.90 (0.63–1.28) | 0.56 |
| Triglycerides (mmol/l) | 0.98 (0.70–1.37) | 0.91 | 0.94 (0.65–1.35) | 0.74 | 0.72 (0.47–1.09) | 0.12 | 1.04 (0.71–1.53) | 0.83 | 1.05 (0.69–1.59) | 0.83 | 0.87 (0.54–1.41) | 0.57 |

BMI = body mass index, CI = confidence interval, HDL = high-density lipoprotein, OCT = optical coherence tomography, OR = odds ratio.
* $p < 0.05$.

**Table 3.** Association between measures of arterial stiffness and the presence of macular cysts.

| | 24 hr pulse pressure (per 10 mmHg) | | Carotid-femoral pulse wave velocity (per 1.0 m/s) | | Carotid distensibility (per $1.0*10^{-3}$/kPa) | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p |
| Total population ($n$ = 2647) | | | | | | |
| Model 1 | 1.55 (1.13–2.12) | **<0.01*** | 1.14 (1.01–1.28) | **0.03*** | 1.01 (0.94–1.08) | 0.88 |
| Model 2 | 1.65 (1.14–2.37) | **<0.01*** | 1.16 (1.02–1.32) | **0.02*** | 1.03 (0.96–1.11) | 0.45 |
| Model 3 | 1.61 (1.11–2.34) | **0.01*** | 1.16 (1.02–1.32) | **0.02*** | 1.03 (0.96–1.11) | 0.45 |
| Individuals without DM2 ($n$ = 1925) | | | | | | |
| Model 1 | 1.42 (0.72–2.77) | 0.31 | 0.91 (0.70–1.18) | 0.46 | 0.90 (0.78–1.04) | 0.15 |
| Model 2 | 1.51 (0.70–3.27) | 0.30 | 0.99 (0.75–1.32) | 0.96 | 0.94 (0.81–1.10) | 0.46 |
| Model 3 | 1.49 (0.69–3.26) | 0.31 | 1.01 (0.76–1.34) | 0.97 | 0.94 (0.80–1.10) | 0.46 |
| Individuals with DM2 ($n$ = 722) | | | | | | |
| Model 1 | 1.54 (1.07–2.21) | **0.02*** | 1.20 (1.04–1.37) | **0.01*** | 1.05 (0.97–1.14) | 0.23 |
| Model 2 | 1.63 (1.07–2.48) | **0.02*** | 1.21 (1.05–1.40) | **0.01*** | 1.06 (0.98–1.16) | 0.15 |
| Model 3 | 1.57 (1.02–2.42) | **0.04*** | 1.22 (1.05–1.42) | **<0.01*** | 1.07 (0.98–1.17) | 0.13 |

CI = confidence interval, DM2 = type 2 diabetes, OR = odds ratio.
Model 1: adjusted for age, sex (and presence of prediabetes and type 2 diabetes in the total population); Model 2: additional adjustments for 24 hr mean arterial pressure and 24 hr mean heart rate; Model 3: additional adjustments for smoking, body mass index, and total/high-density lipoprotein cholesterol ratio.
* $p < 0.05$.

A significant association with the presence of macular cysts assessed by OCT was found for systolic blood pressure [OR = 1.03 (95% CI 1.00–1.05) per 1 mmHg, p = 0.03], 24 hr pulse pressure [OR = 1.55 (95% CI 1.13–2.12) per 10 mmHg, p < 0.01], carotid-femoral pulse wave velocity [OR = 1.14 (95% CI 1.01–1.28) per 1 m/s, p = 0.03] and the presence of micro-aneurysms [OR = 17.3 (95% CI 7.1–42.3), p < 0.001]. 24 hr diastolic blood pressure, 24 hr mean arterial pressure and carotid distensibility were not associated with the presence of macular cysts. After exclusion of individuals with micro-aneurysms, carotid-femoral pulse wave velocity [OR = 1.14 (95% CI 0.99–1.32) per 1 m/s, p = 0.07] showed a non-significant association with the presence of macular cysts, after additional adjustment for (pre)diabetes.

Table 3 shows the associations between 24 hr pulse pressure, carotid-femoral pulse wave velocity and carotid distensibility and the presence of macular cysts. After full adjustment, the presence of macular cysts was associated with 24 hr pulse pressure [OR = 1.61 (95% CI 1.11–2.34) per 10 mmHg, p = 0.01] and carotid-femoral pulse wave velocity [OR = 1.16 (95% CI 1.02–1.32) per 1 m/s, p = 0.02] in the total population. However, carotid artery distensibility was not significantly associated with the presence of macular cysts [OR = 1.03 (95% CI 0.96–1.11) per $1.0*10^{-3}$/kPa, p = 0.45].

Table 4 shows the associations between 24 hr pulse pressure, carotid-femoral pulse wave velocity, and carotid distensibility and the presence of macular cysts after exclusion of

**Table 4.** Association between measures of arterial stiffness and the presence of macular cysts after exclusion of individuals with micro-aneurysms.

| | 24 hr pulse pressure (per 10 mmHg) | | Carotid-femoral pulse wave velocity (per 1.0 m/s) | | Carotid distensibility (per $1.0*10^{-3}$/kPa) | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p |
| Total population ($n$ = 2327) | | | | | | |
| Model 1 | 1.37 (0.91–2.07) | 0.13 | 1.14 (0.99–1.32) | 0.07 | 0.97 (0.89–1.06) | 0.54 |
| Model 2 | 1.49 (0.94–2.37) | 0.09 | 1.16 (1.00–1.35) | 0.05 | 1.00 (0.91–1.10) | 0.95 |
| Model 3 | 1.48 (0.93–2.36) | 0.10 | 1.18 (1.01–1.38) | **0.03*** | 0.99 (0.91–1.10) | 0.96 |
| Individuals without DM2 ($n$ = 1690) | | | | | | |
| Model 1 | 1.87 (0.93–3.73) | 0.08 | 0.96 (0.70–1.32) | 0.79 | 0.83 (0.71–0.98) | **0.03*** |
| Model 2 | 1.84 (0.80–4.21) | 0.15 | 0.96 (0.67–1.38) | 0.82 | 0.88 (0.73–1.05) | 0.15 |
| Model 3 | 1.81 (0.79–4.13) | 0.16 | 0.97 (0.68–1.40) | 0.89 | 0.88 (0.73–1.06) | 0.18 |
| Individuals with DM2 ($n$ = 637) | | | | | | |
| Model 1 | 1.14 (0.68–1.91) | 0.62 | 1.23 (1.04–1.45) | **0.02*** | 1.05 (0.95–1.17) | 0.34 |
| Model 2 | 1.34 (0.76–2.36) | 0.32 | 1.25 (1.04–1.49) | **0.02*** | 1.07 (0.96–1.19) | 0.25 |
| Model 3 | 1.31 (0.74–2.33) | 0.36 | 1.31 (1.08–1.59) | **<0.01*** | 1.07 (0.95–1.20) | 0.29 |

CI = confidence interval, DM2 = type 2 diabetes; OR = odds ratio.
Model 1: adjusted for age, sex (and presence of prediabetes and type 2 diabetes in the total population); Model 2: additional adjustments for 24 hr mean arterial pressure and 24 hr mean heart rate; Model 3: additional adjustments for smoking, body mass index, and total/high-density lipoprotein cholesterol ratio.
* $p < 0.05$.

individuals with micro-aneurysms. After full adjustment, the presence of macular cysts showed an association with 24 hr pulse pressure [OR = 1.48 (95% CI 0.93–2.36) per 10 mmHg, p = 0.10] and carotid-femoral pulse wave velocity [OR = 1.18 (95% CI 1.01–1.38) per 1 m/s, p = 0.03] in the total population. The associations between measures of arterial stiffness and the presence of macular cysts did not differ statistically between individuals without and with type 2 diabetes in fully adjusted models (p-values for interaction ≥0.13). The association of type 2 diabetes with the presence of macular cysts was not substantially altered after additional adjustment for arterial stiffness (data not shown).

# Discussion

In this population-based cohort study, we assessed the associations between 24 hr pulse pressure, aortic stiffness, carotid stiffness and the presence of macular cysts. The presence of macular cysts was assessed by spectral domain optical coherence tomography (SD-OCT) with a highly detailed volume scan consisting of 73 sections. We found a significant association between 24 hr systolic blood pressure, 24 hr pulse pressure, carotid-femoral pulse wave velocity and the presence of macular cysts, after adjustment for age, sex, 24 hr mean arterial pressure, 24 hr mean heart rate, smoking, body mass index, total cholesterol-to-HDL cholesterol ratio, prediabetes and DM2. Also, in individuals without micro-aneurysms, we observed a positive association between 24 hr pulse pressure and carotid-femoral pulse wave velocity with the presence of macular cysts.

We observed a prevalence of macular cysts on OCT of 4.7% in individuals with DM2, which was higher than compared with individuals with NGM. This is in line with previous reported prevalences (Klein et al. 1984; Raheja et al. 1987; Klein et al. 1992; Delcourt et al. 1995; Schranz 1997). About one-third of the individuals with macular cysts presented with clinically significant cystoid macular oedema, which indicates that macular cysts commonly were subclinical. Hypertensive and diabetic macular oedema are not always two distinct entities but instead present significant overlap. The risk of diabetic macular oedema increases about four times in the presence of arterial hypertension (Fenwick et al. 2017). In individuals with DM2, the beneficial effect of better blood pressure control on the prevalence of diabetic macular oedema has been demonstrated previously (UKPDS 1998). Matthews et al. showed that a 10 mmHg decrease in systolic blood pressure decreases the risk of diabetic macular oedema development, the need for laser therapy for macular oedema and visual loss by 15% (Matthews et al. 2004). Tight blood pressure control must be continued in order to maintain these beneficial effects (Holman et al. 2008).

Similar to previous studies, we found a significant association of the presence of macular cysts with 24 hr systolic blood pressure (Klein et al. 1984; Lopes de Faria et al. 1999). Greater aortic stiffness (when it affects total arterial compliance) could lead to increased pulse pressure (Laurent et al. 2006; Kaess et al. 2012; Weisbrod et al. 2013). Importantly, in small retinal vessels the propagated pulsatile load could contribute to basement membrane thickening (de la Rubia et al. 1992), capillary occlusion, dilatation of neighbouring vessels, secretion of growth factors (Resnick et al. 1993) and new vessel formation (Kohner et al. 1995). Starling's law can be used to understand the formation of vasogenic macular cysts (Stefansson 2009). According to this law, the flow of fluid through the blood–retinal barrier is favoured by the difference in hydrostatic pressure between capillaries and retinal tissue. This is a function of the blood pressure, which must be counterbalanced by the osmotic pressure to avoid development of macular cysts. Increased pulse pressure could result in increased wall stress variations, which may finally contribute to breakdown of the tight junctions between endothelial cells (Wallow & Engerman 1977). This could force proteins into the tissue interstitium resulting in a decrease of the osmotic pressure (Cunha-Vaz 2017) and development of macular cysts (Ross 1990; O'Rourke & Safar 2005; Mitchell 2008; Cunha-Vaz 2017). Moreover, individuals with macular cysts have microvascular fragility, leading to earlier and greater damage and direct leakage of fluid caused by an increased pulsatile load (Schram et al. 2002; Schram et al. 2003; O'Rourke & Safar 2005). The association between greater pulse pressure and the presence of macular cysts was similar in individuals without and with type 2 diabetes in our population. Also the carotid-femoral pulse wave velocity, which reflects aortic stiffness, was significantly associated with the presence of macular cysts. In contrast with our findings in the aorta, our study did not show an association between carotid stiffness and the presence of macular cysts. The presence of an association with aortic stiffness but not with carotid stiffness was not expected and requires further investigation.

In our study, the presence of micro-aneurysms was strongly associated with the presence of macular cysts. Loss of endothelial cells in retinal vessel walls causes significant inflammation and breakdown of the inner blood–retina barrier (Augustin et al. 2010). The loss of pericytes and capillary endothelial cells are often the initial microvascular damage causing capillary closure and hypoxia, leading to micro-aneurysms. Subsequent expression of vascular endothelial growth factor and the increased capillary permeability modify the extra cellular matrix (Cunha-Vaz et al. 1975), contributing to the occurrence of macular cysts. A previous study has shown an association between diabetic retinopathy and arterial stiffness (Rema et al. 2004).

There are several limitations of the present study. First, this study has a cross-sectional design and does not allow conclusions on cause-and-effect relations. Second, we did not apply complete-case analyses, since the number of individuals with cystoid macular oedema was rather low. However, including individuals with missing data on risk factors allowed us to assess the association between macular cysts and vascular risk factors in a larger population, resulting in more accurate and, probably, more valid results.

In conclusion, 24 hr systolic blood pressure, 24 hr pulse pressure and carotid-femoral pulse wave velocity are associated with the presence of OCT-detected macular cysts. These associations are present in individuals with and without type 2 diabetes, even in the absence of micro-aneurysms. Therefore, blood pressure and aortic stiffness are potential factors contributing to macular cysts.

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