Received: 22 April 2025 | Revised: 28 May 2025 | Accepted: 2 June 2025

DOI: 10.1111/dom.16527

ORIGINAL ARTICLE

WILEY

Type 2 diabetes and depression via microvascular dysfunction, neurodegeneration, inflammation, advanced glycation end products (AGEs), and arterial stiffness

Indra L. M. Steens MSc[1,2] | Miranda T. Schram MD[1,2,3,4,5] | Alfons J. H. M. Houben PhD[1,2] | Tos T. J. M. Berendschot PhD[6] | Jacobus F. A. Jansen PhD[4,7,8] | Walter H. Backes PhD[4,7] | Annemarie Koster PhD[9,10] | Hans Bosma PhD[9,10] | Simone J. P. M. Eussen PhD[1,9,11] | Bastiaan E. de Galan MD[1,2,12] | Thomas T. van Sloten MD[13]

[1]CARIM Cardiovascular Research Institute Maastricht, Maastricht University (UM), Maastricht, The Netherlands

[2]Department of Internal Medicine, Maastricht University Medical Center+ (MUMC+), Maastricht, The Netherlands

[3]Heart and Vascular Center, MUMC+, Maastricht, The Netherlands

[4]School of Mental Health and Neuroscience, MUMC+, Maastricht, The Netherlands

[5]Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands

[6]Department of Ophthalmology, MUMC+, Maastricht, The Netherlands

[7]Department of Radiology and Nuclear Medicine, Maastricht University Medical Centre+ (MUMC+), Maastricht, The Netherlands

[8]Department of Electrical Engineering Eindhoven, University of Technology Eindhoven, The Netherlands

[9]CAPHRI Care and Public Health Research Institute, Maastricht, UM, The Netherlands

[10]Department of Social Medicine, Maastricht University (UM), Maastricht, The Netherlands

[11]Department of Epidemiology, Maastricht University (UM), Maastricht, The Netherlands

[12]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

[13]Department of Vascular Medicine, Diabetology and Endocrinology, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence
Thomas T. van Sloten, Department of Vascular Medicine, Diabetology and Endocrinology, University Medical Center Utrecht, Utrecht, The Netherlands.
Email: t.t.vansloten@umcutrecht.nl

Funding information
Dutch Diabetes Research Foundation; European Regional Development Fund; Dutch Ministry of Economic Affairs, Grant/Award Number: 31O.041; Stichting De Weijerhorst; Pearl String Initiative Diabetes; Cardiovascular Center; CARIM School for Cardiovascular Diseases; CAPHRI School for Public Health and Primary Care; NUTRIM School for Nutrition and Translational Research in Metabolism; Stichting Annadal; Health Foundation Limburg; Janssen-Cilag B.V; Novo

Abstract

Aims: Type 2 diabetes increases the risk of depression, but the mechanisms underlying this association are incompletely understood. We investigated whether microvascular dysfunction, neurodegeneration, low-grade inflammation, advanced glycation end products (AGEs) and arterial stiffness, pathologies that are more common in diabetes, explain, or mediate the association between type 2 diabetes and incident clinically relevant depressive symptoms.

Materials and Methods: We used prospective data from The Maastricht Study, a population-based cohort study. Diabetes status and potential mediators were assessed at baseline. Clinically relevant depressive symptoms (PHQ-9 score ≥10) were assessed at baseline and each year during a median of 8.1 (IQR 4.2, 10.1) years of follow-up. Mediation analysis was employed to investigate the mediating effect of microvascular dysfunction (retinal, blood and MRI biomarkers), neurodegeneration

Nordisk Farma B.V; Sanofi-Aventis Netherlands B.V; Imedos Health GmbH

[Correction added on 8 July 2025, after first online publication: Authors Jacobus F. A. Jansen and Walter H. Backes, along with their respective affiliations, have been added.]

(retina and MRI biomarkers), low-grade inflammation (blood biomarkers), AGEs (skin and blood biomarkers) and arterial stiffness (tonometry and ultrasound biomarkers).

Results: Data of 6091 participants (age, 59.4 years [SD 8.6]; 51.3% women; 23.6% type 2 diabetes) were available. Type 2 diabetes was associated with a higher incidence of clinically relevant depressive symptoms (HR:1.37; 95% CI 1.13, 1.65). This association was partly mediated by microvascular dysfunction (proportion mediated:10.4% [95% CI:3.6%, 17.2%]); neurodegeneration (proportion mediated:12.1% [95% CI: 3.9%, 20.3%]); AGEs (proportion mediated:5.4% [95% CI: 3.0%, 8.8%]); and arterial stiffness (proportion mediated:8.4% [95% CI: 3.3%, 13.5%]); but not by low-grade inflammation.

Conclusions: The association between type 2 diabetes and a higher risk of clinically relevant depressive symptoms is partly mediated by microvascular dysfunction, neurodegeneration, AGEs and arterial stiffness.

KEYWORDS

cardiovascular disease, diabetes complications, population study, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes increases the risk of several comorbidities, one of which is late-life depression. Adults with type 2 diabetes have a doubled risk for depression compared to individuals without diabetes.[1] The mechanisms underlying type 2 diabetes-related depression are likely multifactorial but have been incompletely understood. There are several non-biological pathways that may contribute to type 2 diabetes-related depression, among others, diabetes-related distress or compromised coping with disease, reduced quality of life, sleep disturbances and anxiety.[2] However, biological mechanisms likely also play a role. Understanding these biological mechanisms is important, as this may identify targets that can help to prevent type 2 diabetes-related depression.

Several pathologies that are all more common in type 2 diabetes have been linked to cerebral damage and a higher risk of depression. These include microvascular dysfunction,[3–9] neurodegeneration,[10,11] low-grade inflammation,[12,13] advanced glycation end products (AGEs)[14,15] and arterial stiffening.[16,17] However, the extent to which these pathologies explain, or mediate, the association between type 2 diabetes and a higher risk of depression remains unclear. To date, one study has investigated the mediation effect of one of these pathologies on the association between type 2 diabetes and incident depression.[9] This study found that baseline cerebral small vessel disease and changes in cerebral small vessel disease mediated the association between baseline diabetes and a greater increase in depressive symptoms. However, cerebral small vessel disease may be an indirect measure of microvascular dysfunction. Furthermore, the potential mediating effect of other pathologies, i.e., neurodegeneration, low-grade inflammation, AGEs and arterial stiffening, has not been studied. In this study, we aim to address this gap by investigating a broader range of pathologies.

We investigated whether measures of microvascular dysfunction, neurodegeneration, low-grade inflammation, AGEs and arterial stiffness mediate the association between type 2 diabetes and a higher risk of incident clinically relevant depressive symptoms. To this end, we used longitudinal data from The Maastricht Study, a large population-based cohort study.

2 | MATERIALS AND METHODS

2.1 | Study population

The rationale and methodology of The Maastricht Study have been described previously.[18] In brief, the study focuses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes 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, as well as from municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes status, with an oversampling of individuals with type 2 diabetes, for reasons of efficiency. The present report includes data from $n = 9188$ participants who completed the baseline survey between November 2010 and October 2020. The baseline 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 Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105 234-PG). All participants gave written informed consent.

2.2 | Glucose metabolism status

Glucose metabolism status was determined with use of an oral glucose tolerance test and a medication review of glucose-lowering medication. Normal glucose metabolism, prediabetes (i.e. impaired fasting

glucose, impaired glucose tolerance, or both) and type 2 diabetes were defined in accordance with the World Health Organization 2006 criteria, as described previously.[18]

2.3 | Microvascular dysfunction

We quantified microvascular dysfunction by retinal flicker light-induced arteriolar and venular dilation response, blood biomarkers of microvascular dysfunction and urinary albumin excretion.

Retinal arteriolar and venular dilation response to flicker light exposure was determined by the dynamic vessel analyser (Imedos, Jena, Germany), as previously described.[19] The left or right eye was randomly chosen for this measurement. Briefly, vessel diameter was automatically and continuously measured for 150s. A baseline recording of 50s was followed by 40s flicker light exposure, followed by a 60s recovery period. Baseline retinal vessel diameters and flicker light-induced retinal vessel dilation were automatically calculated with the integrated Dynamic Vessel Analyser (DVA) software. Baseline diameter (expressed in measurement units (MU)) was calculated as the average diameter size of the 20–50s recording. Percentage dilation over baseline was based on the average dilation achieved at time points 10s and 40s during the flicker stimulation period.

Blood biomarkers of microvascular dysfunction were measured as described previously.[18] These included soluble intracellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble endothelial selectin (sE-selectin) and von Willebrand factor (vWf). We standardized and averaged these biomarkers into an average blood biomarker microvascular dysfunction score.

Urinary albumin excretion was measured as described previously.[18] Two 24-h urine collections were used to assess urinary albumin excretion. Urinary albumin concentration was measured with a standard immunoturbidimetric assay by an automatic analyser and multiplied by collection volume to obtain the 24-h urinary albumin excretion.

2.4 | Neurodegeneration

We assessed retinal thickness, a measure of neurodegeneration, in both eyes with optical coherence tomography (OCT; Spectralis unit and Eye Explorer version 5.7.5.0 software; Heidelberg Engineering, Heidelberg, Germany).[18] We assessed the central macular area (Early Treatment Diabetic Retinopathy Study [ETDRS] sectors 1–5) using a fovea-centred macular volume scan (73 sections, 60 μm).

We assessed cerebral neurodegeneration with an MRI performed on a 3T MRI scanner (Siemens Magnetom Prisma-fit Syngo MR D13D, Erlangen, Germany).[18] T1-weighted images were segmented into grey matter, white matter and cerebrospinal fluid volumes. Total brain parenchyma volume was calculated as the sum of grey and white matter volumes.

2.5 | Low-grade inflammation

Low-grade inflammation was quantified by measurement of six blood biomarkers.[18] These included sICAM-1, C-reactive protein (CRP), serum amyloid A (SAA), tumour necrosis factor alpha (TNFα), interleukin-8 (IL-8) and interleukin-6 (IL-6). We standardised and averaged the standardised low-grade inflammation blood biomarkers into an average low-grade inflammation score.

2.6 | AGEs

Plasma AGEs were measured in EDTA obtained from fasting venous blood, which were stored at −80°C until analysis, as described previously.[20] Protein-bound pentosidine was quantified using HPLC with fluorescence detection. Protein-bound N-carboxymethyllysine (CML), N-carboxyethyllysine (CEL) and lysine were quantified using UPLC MS/MS (ultraperformance) liquid chromatography-tandem MS. Concentrations of protein-bound pentosidine, CML and CEL were adjusted for levels of lysine and expressed as nanomoles per millimole lysine. We standardized and averaged the standardized AGEs blood biomarkers into an average plasma AGEs score.

AGE accumulation in the skin was quantified as skin autofluorescence, measured using the AGE Reader CU (DiagnOptics Technologies BV), as previously described.[20]

2.7 | Arterial stiffness

Distensibility coefficient was measured at the level of the carotid artery with use of high-resolution ultrasound as described previously.[21] Measurements of local carotid arterial properties were done at the left common carotid artery (10-mm proximal to the carotid bulb), with the use of an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab 70, Esaote Europe B.V., Maastricht, the Netherlands). We quantified carotid stiffness by calculating the carotid distensibility coefficient.

Carotid-to-femoral pulse wave velocity (cfPWV) was measured with the use of applanation tonometry (SphygmoCor; Atcor Medical, Sydney, Australia) as described previously.[21] Pressure waveforms were determined at the right common carotid and right common femoral arteries. The difference in the time of pulse arrival from the R-wave of the ECG between the two sites (transit time) was determined with the intersecting tangents algorithm. The pulse wave travel distance was calculated as 80% of the direct straight distance (measured with an infantometer) between the two arterial sites.

2.8 | Clinically relevant depressive symptoms

Depressive symptoms were assessed at baseline and annually during follow-up using the 9-item Patient Health Questionnaire (PHQ-9).[22] The PHQ-9 is a self-administered questionnaire based on the

Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria for a major depressive disorder. We defined the presence of clinically relevant depressive symptoms as a PHQ-9 score of ≥10. Incident clinically relevant depressive symptoms were defined as a PHQ-9 score of ≥10 at any annual follow-up.

2.9 | Statistical analyses

For each potential mediating pathology (i.e. microvascular dysfunction, neurodegeneration, low-grade inflammation, AGEs and arterial stiffness), we constructed a composite score based on the individual measures of each pathology that were available for each participant.[23] We calculated a microvascular dysfunction composite score by standardizing and averaging venular and arteriolar flicker-light induced dilatation, the blood biomarker microvascular dysfunction score and urinary albumin secretion. We inverted flicker-light induced dilatation as the direction of the associations with this measure was opposite to other measures included in the composite score. We also calculated a neurodegeneration composite score by standardizing and averaging total retinal thickness and total parenchyma volume. We inverted both total retinal thickness and total parenchyma volume so that a higher score would reflect more neurodegeneration. We made an AGEs composite score by standardizing and averaging the blood biomarkers of AGEs score and skin autofluorescence. We also made an arterial stiffness composite score by standardizing and averaging the carotid distensibility coefficient and pulse wave velocity. We inverted the carotid distensibility coefficient as the direction of the associations with this measure was opposite to other measures included in the composite score. Participants were assigned a value for the composite scores if they had data available for at least one of the individual components contributing to the respective composite score.

Characteristics of the study population with complete data on incident clinically relevant depressive symptoms were described using means and standard deviations for normally distributed continuous variables, medians with interquartile ranges (25th–75th percentiles) for skewed continuous variables, and counts with percentages for categorical variables. Differences between individuals with and without incident clinically relevant depressive symptoms were assessed using Pearson's Chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

We checked the proportional hazards assumption and used causal mediation analysis with a Cox proportional hazards model to investigate the association between type 2 diabetes and incident clinically relevant depressive symptoms, and whether any of this association was mediated, or explained, by any of the following potential mediators: microvascular dysfunction composite score (neurodegeneration composite score, low-grade inflammation score, AGEs composite score and arterial stiffness composite score). In the main analysis, we excluded participants with type 1 diabetes, prediabetes and participants with the presence of clinically relevant depressive symptoms (PHQ-9 score ≥10) at baseline. First, we examined the association between type 2 diabetes and each of the potential mediators with the use of linear regression, and expressed the results in standardized beta's with corresponding 95% confidence intervals (CIs). Second, we assessed the association between type 2 diabetes and incident clinically relevant depressive symptoms, and between each of the potential mediators and incident clinically relevant depressive symptoms. For these analyses, we used Cox proportional hazards regression models and expressed the results in hazard ratios (HRs) with corresponding 95% CIs. Finally, we calculated the potential mediating effect by using a combination of the regression coefficients obtained from the linear regression and Cox proportional hazards models. We estimated the total effect of type 2 diabetes on incident clinically relevant depressive symptoms that encompasses both the direct and indirect effects. The direct effect was calculated as the regression coefficient from the linear regression model adjusted for the potential mediator, and the indirect effect was obtained by multiplying the regression coefficient from the linear regression model by the HR from the Cox model. We performed the causal mediation analysis using counterfactual modelling and calculated corresponding CIs by employing bootstrapping (with $n = 2000$ iterations) using the 'CMAverse' package in R.

Results were adjusted for the following potential confounders: age, sex and educational level (model 1); and additionally for office systolic blood pressure, history of cardiovascular disease, use of antihypertensive medication, waist circumference, total cholesterol-to-high density lipid cholesterol ratio, use of lipid-modifying medication, smoking status and alcohol consumption (model 2). These confounders were selected based on prior literature demonstrating associations with type 2 diabetes, depression and the proposed mediators[24–30] Directed acyclic graphs (DAGs) showing the assumed relationships between variables in each mediation model are presented in the Figure S1.

We performed all analyses in R (4.2.2 (2022-10-31), R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a two-sided p-value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Characteristics

Figure 1 shows the flowchart of the study population selection. The sample size differed per analysis according to the availability of data on the individual mediation variables. A total of 6091 participants had data available for any of the main analyses. Table 1 shows the baseline characteristics of the study population. The mean age was 59.4 years (SD 8.6) and 51.3% were women. Overall, participants who had incident clinically relevant depressive symptoms more often had type 2 diabetes, had lower educational status, were more often smokers, more often used anti-hypertensive or lipid-modifying medication, and more often had a history of cardiovascular disease than participants who did not have incident clinically relevant depressive symptoms (Table 1). Baseline characteristics of participants included in the analysis were comparable to those of participants with missing data (Table S1).

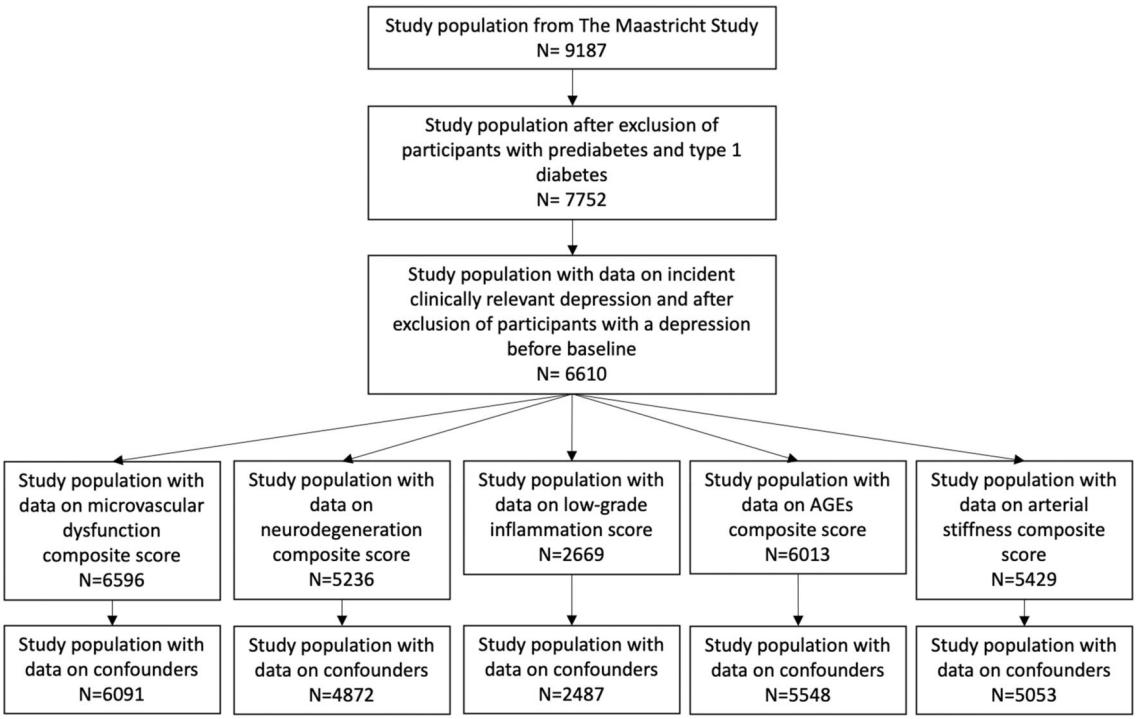

FIGURE 1 Flow chart of the selection of the study populations. AGEs, advanced glycation end products; MVD, microvascular dysfunction.

3.2 | Type 2 diabetes and incidence of clinically relevant depressive symptoms

After full adjustments, type 2 diabetes was associated with a *higher* incidence of clinically relevant depressive symptoms (Figure 2 and Table 2).

3.3 | Microvascular dysfunction

After full adjustments, type 2 diabetes was associated with a higher microvascular dysfunction composite score (Figure 2 and Table 2). A higher microvascular dysfunction composite score was associated with a higher incidence of clinically relevant depressive symptoms. Furthermore, the microvascular dysfunction composite score mediated the association between type 2 diabetes and incident clinically relevant depressive symptoms (Figure 2 and Table 2) explaining 10.4% (95% CI: 3.6%, 17.2%) of the total effect.

3.4 | Neurodegeneration

After full adjustments, type 2 diabetes was associated with a higher neurodegeneration composite score (Figure 2 and Table 2). A higher neurodegeneration composite score was associated with a higher incidence of clinically relevant depressive symptoms. Furthermore, the neurodegeneration composite score mediated the association between type 2 diabetes and incident clinically relevant depressive symptoms (Figure 2 and Table 2) explaining 12.1% (95% CI: 3.9%, 20.3%) of the total effect.

3.5 | Low-grade inflammation

The low-grade inflammation score was not associated with incident clinically relevant depressive symptoms and did not mediate the association between type 2 diabetes and incident clinically relevant depressive symptoms (Figure 2 and Table 2).

3.6 | AGEs

After full adjustments, type 2 diabetes was associated with a higher AGEs composite score (Figure 2 and Table 2). A higher AGEs composite score was associated with a higher incidence of clinically relevant depressive symptoms. Furthermore, the AGEs composite score mediated the association between type 2 diabetes and incident clinically relevant depressive symptoms (Figure 2 and Table 2) explaining 5.4% (95% CI: 3.0%, 8.8%) of the total effect.

3.7 | Arterial stiffness

After full adjustments, type 2 diabetes was associated with a higher arterial stiffness composite score (Figure 2 and Table 2). A higher arterial stiffness composite score was associated with a higher incidence

TABLE 1 Study population characteristics according to incidence of clinically relevant depressive symptoms in the microvascular dysfunction composite score study population.

Characteristic	Incident clinically relevant depressive symptoms[a]			
	Overall, *N* = 6091	No, *N* = 5200	Yes, *N* = 891	*p*-value*
Diabetes status				<0.001
No diabetes	4654 (76.4%)	4069 (78.3%)	585 (65.7%)	
Type 2 diabetes	1437 (23.6%)	1131 (21.8%)	306 (34.3%)	
Microvascular dysfunction				
Venular flicker-light induced dilatation	3.5 (2.2, 5.0)	3.5 (2.2, 5.1)	3.3 (2.3, 4.8)	0.2
Arteriolar flicker-light induced dilatation	2.7 (0.9, 5.0)	2.8 (0.9, 5.1)	2.2 (0.7, 4.5)	<0.001
Soluble intercellular adhesion molecule-1 (sICAM1, ng/mL)l	332.5 (286.1, 389.7)	329.7 (284.3, 385.7)	348.5 (300.9, 414.5)	<0.001
Soluble vascular cell adhesion molecule-1 (sVCAM1, ng/mL)	414.3 (363.4, 472.9)	412.5 (360.9, 469.5)	426.4 (378.2, 495.6)	<0.001
E-Selectin (ng/mL)	105.9 (73.4, 140.5)	104.6 (73.3, 139.3)	110.7 (75.1, 147.6)	0.055
Von Willebrand factor (%)	123.2 (97.9, 156.0)	122.2 (97.4, 154.0)	130.8 (100.9, 170.0)	<0.001
Albumin excretion (mg/24 h)	5.4 (3.5, 10.0)	5.4 (3.5, 9.8)	5.8 (3.7, 11.8)	<0.001
Neurodegeneration				
Total retinal thickness (µm)	332.5 (322.6, 342.3)	333.0 (323.0, 342.7)	330.8 (320.6, 340.7)	0.002
Total parenchyma volume (cm^3)	1133.5 (1065.7, 1212.0)	1136.2 (1069.3, 1215.6)	1114.8 (1048.6, 1196.1)	<0.001
Low-grade inflammation				
C-reactive protein (CRP, µg/mL)	1.1 (0.6, 2.5)	1.1 (0.6, 2.3)	1.4 (0.7, 3.3)	<0.001
Human interleukin-6 (IL6, pg/mL)	0.6 (0.4, 0.9)	0.6 (0.4, 0.8)	0.7 (0.4, 1.1)	<0.001
Human interleukin-8 (IL8, pg/mL)	4.1 (3.2, 5.3)	4.0 (3.2, 5.2)	4.5 (3.4, 5.8)	<0.001
Human tumour necrosis factor alpha (TNFa, pg/mL)	2.2 (1.9, 2.5)	2.2 (1.9, 2.5)	2.2 (1.9, 2.7)	0.001
Serum amyloid A (SAA, µg/mL)	3.2 (2.0, 5.2)	3.1 (1.9, 5.1)	3.4 (2.2, 5.6)	0.042
AGEs				
N-carboxymethyllysine (CML) in plasma (nmol/nmol LYS)	75.1 (65.0, 83.5)	75.3 (66.0, 83.8)	72.1 (60.6, 80.4)	0.052
N-carboxyethyllysine (CEL) in plasma (nmol/nmol LYS)	32.6 (26.9, 39.9)	32.7 (27.2, 39.8)	32.2 (24.6, 40.7)	0.6
Pentosidine in plasma (nmol/nmol LYS)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.7
Arterial stiffness				
Carotid distensibility coefficient carotid artery (10-3/kPa)	14.1 (10.9, 17.8)	14.2 (11.0, 17.8)	13.2 (10.4, 17.4)	0.013
Pulse wave velocity (m/s)	8.4 (7.4, 9.8)	8.4 (7.4, 9.8)	8.6 (7.6, 10.0)	0.012
Confounders				
Sex (Female)	3125 (51.3%)	2643 (50.8%)	482 (54.1%)	0.071
Age (years)	59.4 ± 8.6	59.4 ± 8.5	59.3 ± 8.9	>0.9
Educational status				<0.001
Low	1853 (30.4%)	1506 (29.0%)	347 (38.9%)	
Medium	1696 (27.8%)	1444 (27.8%)	252 (28.3%)	
High	2542 (41.7%)	2250 (43.3%)	292 (32.8%)	
Waist (cm)	93.7 ± 13.4	93.1 ± 13.0	97.2 ± 15.1	<0.001
Smoking status				<0.001
Never	2450 (40.2%)	2149 (41.3%)	301 (33.8%)	
Former	2953 (48.5%)	2506 (48.2%)	447 (50.2%)	
Current	688 (11.3%)	545 (10.5%)	143 (16.0%)	
Alcohol intake (g/day)	8.1 (1.7, 17.7)	8.4 (1.9, 18.0)	5.6 (1.0, 15.1)	<0.001
Total to-HDL cholesterol ratio	3.3 (2.7, 4.1)	3.3 (2.7, 4.1)	3.4 (2.8, 4.2)	0.009
Systolic blood pressure (mm/Hg)	132.2 ± 17.7	132.2 ± 17.7	132.4 ± 17.8	0.5

TABLE 1 (Continued)

Characteristic	Incident clinically relevant depressive symptoms[a]			
	Overall, $N = 6091$	No, $N = 5200$	Yes, $N = 891$	*p*-value*
Diastolic blood pressure (mm/Hg)	75.1 ± 9.8	75.0 ± 9.8	75.2 ± 10.0	>0.9
Use of anti-hypertensive medication (Yes/No)	2010 (33.0%)	1643 (31.6%)	367 (41.2%)	<0.001
History of cardiovascular disease (Yes/No)	942 (15.5%)	749 (14.4%)	193 (21.7%)	<0.001
Use of lipid-modifying medication (Yes/No)	1680 (27.6%)	1360 (26.2%)	320 (35.9%)	<0.001
Follow-up time (years)	8.1 (4.2, 10.1)	8.4 (5.2, 10.1)	3.3 (2.1, 6.2)	<0.001

Note: Characteristics in the study population with full data on incident clinically relevant depressive symptoms.
Abbreviations: AGEs, advanced glycation end products; HDL, high density lipoprotein; LYS, lysine; MVD, microvascular dysfunction.
*p-values are obtained with Pearson's Chi-squared test or Wilcoxon rank sum test, as appropriate.
[a]Data are shown as mean (standard deviation), median (25th and 75th percentile) or *n* (%), as appropriate.

of clinically relevant depressive symptoms. Furthermore, the arterial stiffness composite score mediated the association between type 2 diabetes and incident clinically relevant depressive symptoms (Figure 2 and Table 2) explaining 8.4% (95% CI: 3.3%, 13.5%) of the total effect.

3.8 | Additional analyses

Figures S2–S5 show the individual components of the microvascular dysfunction composite score, neurodegeneration composite score, AGEs composite score and arterial stiffness composite score, respectively. A lower arteriolar dilatation, higher blood biomarkers of microvascular dysfunction and a higher urinary albumin excretion, but not venular dilatation, mediated the association between type 2 diabetes and incident clinically relevant depressive symptoms; the total effects explained were 8.0 (95% CI: 2.6%, 13.3%), 9.4 (95% CI: 3.7%, 15.1%) and 3.2 (95% CI: 0.2%, 6.1%), respectively (Figure S2). A lower total retinal thickness and a lower total parenchyma volume significantly mediated the association between type 2 diabetes and incident clinically relevant depressive symptoms; the total effects explained were 3.0% (95% CI: 0.0%, 7.4%) and 11.3% (95% CI: 2.3%, 20.3%), respectively (Figure S3). A higher skin autofluorescence, but not the plasma AGEs score, mediated the association between type 2 diabetes and incident clinically relevant depressive symptoms; the total effect explained by a higher skin autofluorescence was 10.5% (95% CI: 4.3%, 16.7%) (Figure S4). A higher pulse wave velocity, but not carotid distensibility coefficient, mediated the association between type 2 diabetes and incident clinically relevant depressive symptoms; the total effect explained by a higher pulse wave velocity was 5.4% (95% CI: 2.1%, 8.7%) (Figure S5).

4 | DISCUSSION

The present study found that the association between type 2 diabetes and higher incidence of clinically relevant depressive symptoms was partially mediated by microvascular dysfunction, neurodegeneration, AGEs and arterial stiffness, but not by low-grade inflammation.

This study confirms previously reported associations between measures of microvascular dysfunction (i.e. retinal microvascular parameters,[5,7] higher levels of the blood biomarkers ICAM-1, VCAM-1, E-selectin and vWf[5,31] and higher urinary albumin excretion[4,32]), neurodegeneration (i.e. lower brain volume[33–35]), AGEs accumulation (i.e. higher skin autofluorescence)[15] and arterial stiffness (i.e. lower carotid distensibility coefficient[36] and higher pulse wave velocity[37]) with an increased risk of incident depression. In addition, these different pathologies have all been linked with type 2 diabetes.[3,6,8,9,11,13,14,17] One other study showed that MRI measures of cerebral small vessel disease, an indirect measure of microvascular dysfunction, mediated the increase of higher depressive symptoms over time in people with type 2 diabetes.[9] The current study extends these previous studies by showing that the association between type 2 diabetes and a higher risk of incident clinically relevant depressive symptoms is partially explained by higher levels of various biomarkers of microvascular dysfunction, neurodegeneration, AGEs and arterial stiffness, but not by low-grade inflammation. This is the first study to employ mediation analysis with these biomarkers, providing novel insights into the underlying pathways linking type 2 diabetes with depression.

Biologically, type 2 diabetes may lead to microvascular dysfunction, neurodegeneration, AGEs accumulation and arterial stiffness through various mechanisms, including hyperglycaemia, insulin resistance and inflammation.[38] The cerebral microvasculature plays a critical role in the regulation of many cerebral processes, including cerebral perfusion, neurovascular coupling, blood–brain barrier permeability and neurogenesis.[39] AGEs accumulation due to prolonged hyperglycaemia promotes cross-linking of extracellular matrix proteins, leading to arterial stiffness,[40] and directly contributes to neurodegeneration through mechanisms such as oxidative stress, inflammation, neuronal toxicity and disruption of the blood–brain barrier.[41] Arterial stiffness may impair cerebral perfusion regulation via increased pulsatile pressure and flow load, and neural damage through mechanisms including hypoperfusion, endothelial damage, oxidative stress and blood–brain barrier disruption.[40,42] These changes may all lead to ischemia and cell death, and neuronal dysfunction, which has been suggested to ultimately contribute to depressive symptoms via

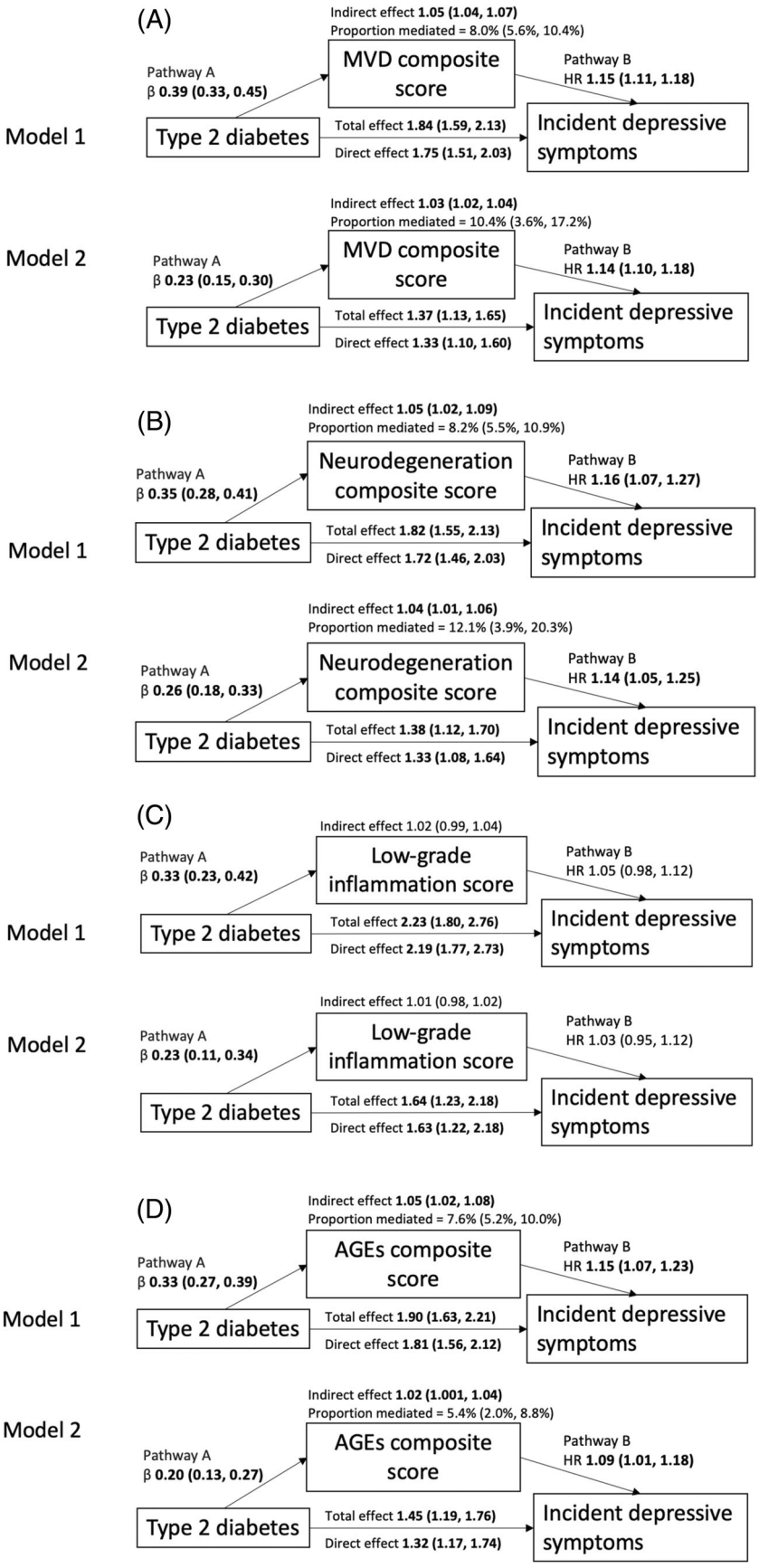

FIGURE 2 Legend on next page.

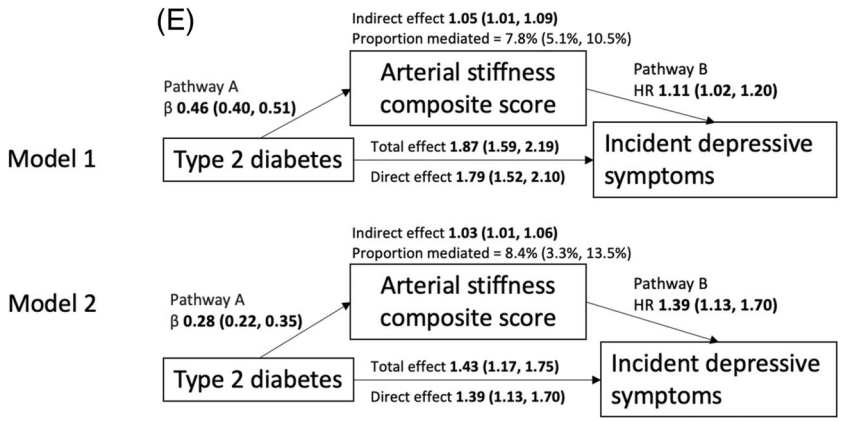

FIGURE 2 (Continued)

damage in deep and frontal brain structures involved in mood regulation.[9]

We found that microvascular dysfunction, neurodegeneration, AGEs and arterial stiffness explained a portion of the association between type 2 diabetes and the higher incidence of clinically relevant depressive symptoms. The remaining association may be due to (micro)vascular dysfunction or neurodegeneration that are not directly captured by the measures used in the current study (e.g. blood–brain barrier permeability and impaired autoregulation). Additionally, it is possible that only a subset of individuals with type 2 diabetes develops depressive symptoms related to these factors. Furthermore, non-biological factors might be able to partly explain the remaining association, such as diabetes-related distress or compromised coping with disease, reduced quality of life, sleep disturbances and anxiety — factors that were not considered in the current study.[2] Biological and non-biological pathways to depression likely interact. For example, psychological stressors may amplify biological responses, contributing to vascular and neural damage.[43,44] Conversely, neurodegeneration may exacerbate psychological factors such as anxiety or distress by impairing coping abilities.[45] Understanding these interactions is crucial for developing comprehensive interventions for depression in individuals with type 2 diabetes.

In contrast to some previous studies,[31,46] we did not find an association between low-grade inflammation and the risk of depressive symptoms. In the present study, blood biomarkers of low-grade inflammation score were available in a subsample only, and we may have had insufficient statistical power to detect mediating effects by these factors. This issue therefore, requires further study.

Strengths of this study are the large sample size and long follow-up duration, the comprehensive assessment of various markers of a large set of potential mediators, and the extensive adjustment for a series of potential confounders. In addition, the large set of additional analyses showed consistent findings with the main analysis, which strengthens the validity and robustness of our findings. The study also has several limitations. First, we did not measure changes in our mediators over time, which may have led to an underestimation of the mediating effects. Second, the associations between type 2 diabetes, the mediators and depression may be bidirectional, with

FIGURE 2 Mediation diagram showing the total and direct effects of type 2 diabetes on incident clinically relevant depressive symptoms, and the indirect effect by the microvascular dysfunction score (composite score of venular and arteriolar dilatation, blood biomarkers of microvascular dysfunction and urinary albumin excretion) (A), the neurodegeneration composite score (total retinal thickness and brain parenchyma volume) (B), the low-grade inflammation score (C), the AGEs composite score (plasma AGEs and skin autofluorescence) (D), the arterial stiffness composite score (carotid distensibility coefficient and pulse wave velocity) (E). Explanation: *The total effect* indicates the association between type 2 diabetes and the hazard of incident clinically relevant depressive symptoms after adjusting for MVD composite score, neurodegeneration composite score, low-grade inflammation score, AGEs composite score or arterial stiffness composite score; *pathway A* the difference per higher SD of MVD composite score, neurodegeneration composite score, low-grade inflammation score, AGEs composite score or arterial stiffness composite score between individuals with and without type 2 diabetes; *pathway B* the association between a higher SD of MVD composite score, neurodegeneration composite score, low-grade inflammation score, AGEs composite score or arterial stiffness composite score and the hazard of incident clinically relevant depressive symptoms; *the direct effect* the association between type 2 diabetes and the hazard of incident clinically relevant depressive symptoms without adjusting for MVD composite score, neurodegeneration composite score, low-grade inflammation score, AGEs composite score or arterial stiffness composite score; and *the indirect effect* the mediation effect by MVD composite score, neurodegeneration composite score, low-grade inflammation score, AGEs composite score or arterial stiffness composite score in the association between type 2 diabetes and incident clinically relevant depressive symptoms. *Pathway A* is expressed as standardized regression coefficient (β) with corresponding 95% confidence interval and all other effects are expressed as hazard ratio (HR) and corresponding 95% confidence interval. $N = 6091$ for the microvascular dysfunction composite score, $N = 5236$ for the neurodegeneration composite score, $N = 2487$ for the low-grade inflammation score, $N = 5548$ for the AGEs composite score, $N = 5053$ for the arterial stiffness composite score. HR, Hazard ratio; MVD, microvascular dysfunction.

TABLE 2 Total and direct effects of type 2 diabetes (exposure) on incident clinically relevant depressive symptoms (outcome), and the indirect effect by the microvascular dysfunction score (composite score of venular and arteriolar dilatation, blood biomarkers of microvascular dysfunction and urinary albumin excretion), the neurodegeneration composite score (total retinal thickness and brain parenchyma volume), the low-grade inflammation score, the AGEs composite score (plasma AGEs and skin autofluorescence), the arterial stiffness composite score (carotid distensibility coefficient and pulse wave velocity).

Mediator	Exposure-mediator β (95% CI)	Mediator-outcome HR (95% CI)	Total effect HR (95% CI)	Direct effect HR (95% CI)	Indirect effect HR (95% CI)
MVD composite score	**0.23 (0.15, 0.30)**	**1.14 (1.10, 1.18)**	**1.37 (1.13, 1.65)**	**1.33 (1.10, 1.60)**	**1.03 (1.02, 1.04)**
Neurodegeneration composite score	**0.26 (0.18, 0.33)**	**1.14 (1.05, 1.25)**	**1.38 (1.12, 1.70)**	**1.33 (1.08, 1.64)**	**1.04 (1.01, 1.06)**
Low-grade inflammation score	**0.23 (0.11, 0.34)**	1.03 (0.95, 1.12)	**1.64 (1.23, 2.18)**	**1.63 (1.22, 2.18)**	1.01 (0.98, 1.02)
AGEs composite score	**0.20 (0.13, 0.27)**	**1.09 (1.01, 1.18)**	**1.45 (1.19, 1.76)**	**1.32 (1.17, 1.74)**	**1.02 (1.001, 1.04)**
Arterial stiffness composite score	**0.28 (0.22, 0.35)**	**1.39 (1.13, 1.70)**	**1.43 (1.17, 1.75)**	**1.39 (1.13, 1.70)**	**1.03 (1.01, 1.06)**

Note: Explanation: *the total effect* indicates the incidence of clinically relevant depressive symptoms between individuals with and without type 2 diabetes after adjusting for the mediator; *the direct effect* the incidence of clinically relevant depressive symptoms between individuals with and without type 2 diabetes without adjusting for the mediator; and *the indirect effect* the mediation effect by the mediator in the association between type 2 diabetes and incident clinically relevant depressive symptoms. $N = 6091$ for the microvascular dysfunction composite score, $N = 5236$ for the neurodegeneration composite score, $N = 2487$ for the low-grade inflammation score, $N = 5548$ for the AGEs composite score, $N = 5053$ for the arterial stiffness composite score. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: HR, Hazard ratio; MVD, microvascular dysfunction.

complex interactions among the different mediators that our models do not fully account for.[31,46,47] Also, while we adjusted for a broad set of confounders, residual confounding due to unmeasured factors cannot be entirely excluded. These limitations are important to consider, as causal mediation analysis relies on several key assumptions, including the absence of unmeasured confounding between the exposure, mediator and outcome, as well as a correctly specified causal direction. Third, depressive symptoms were assessed using annual self-reported questionnaires, in which participants are asked to report symptoms in the last 2 weeks. Consequently, depression is only determined if symptoms were present during this specific period, and depressive episodes occurring earlier or later in the year may not have been captured. Fourth, although the potential mediators assessed in this study are likely interrelated, we did not examine their combined or interactive effects in a single model. Including all mediators simultaneously could lead to overadjustment, potentially underestimating the contribution of individual pathways. Clarifying these complex relationships may require mechanistic or experimental approaches that are better suited to capturing dynamic biological processes than observational data.

Clinically, efforts to favourably influence microvascular function, neurodegeneration, AGEs and arterial stiffness might help to prevent or treat type 2 diabetes-related depression.[38] Drugs such as renin-angiotensin-aldosterone (RAS) system inhibitors (e.g. angiotensin converting enzyme (ACE) inhibitors) may reduce arterial stiffness and improve microvascular function,[48] and antihyperglycemic agents (e.g. metformin and GLP-1 receptor agonists) help control glycaemic levels, reduce AGEs accumulation, improve microvascular function and support neural health.[38] Together, these treatments address complementary mechanisms that may contribute to type 2 diabetes-related depression.

In conclusion, the present study demonstrates that microvascular dysfunction, neurodegeneration, AGEs and arterial stiffness partly mediate the association between type 2 diabetes and a higher risk of incident clinically relevant depressive symptoms.

ACKNOWLEDGEMENTS

We thank all participants of the Maastricht Study, their community pharmacists, the Apothekers Vereniging Maastricht, and the Verenigde Apotheken Limburg for their cooperation.

FUNDING INFORMATION

Steens and van Sloten are supported by a junior fellowship grant from the Dutch Diabetes Research Foundation (Diabetes fonds Junior Fellowship). The Maastricht Study was supported by the European Regional Development Fund via OP-Zuid, the Province of Limburg, the Dutch Ministry of Economic Affairs (grant 31O.041), Stichting De Weijerhorst (Maastricht, the Netherlands), the Pearl String Initiative Diabetes (Amsterdam, the Netherlands), the Cardiovascular Center (CVC, Maastricht, the Netherlands), CARIM School for Cardiovascular Diseases (Maastricht, the Netherlands), CAPHRI School for Public Health and Primary Care (Maastricht, the Netherlands), NUTRIM School for Nutrition and Translational Research in Metabolism (Maastricht, the Netherlands), Stichting Annadal (Maastricht, the Netherlands), Health Foundation Limburg (Maastricht, the Netherlands), and by unrestricted grants from Janssen-Cilag B.V. (Tilburg, the Netherlands), Novo Nordisk Farma B.V. (Alphen aan den Rijn, the Netherlands), Sanofi-Aventis Netherlands B.V. (Gouda, the Netherlands), and Imedos Health GmbH (Jena, Germany).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16527.

DATA AVAILABILITY STATEMENT

The data are not publicly available.

ORCID

Indra L. M. Steens https://orcid.org/0000-0002-9025-2011

REFERENCES

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24(6):1069-1078.
2. Hackett RA, Steptoe A. Psychosocial factors in diabetes and cardiovascular risk. *Curr Cardiol Rep*. 2016;18(10):95.
3. Nguyen TT, Wang JJ, Sharrett AR, et al. Relationship of retinal vascular caliber with diabetes and retinopathy: the multi-ethnic study of atherosclerosis (MESA). *Diabetes Care*. 2008;31(3):544-549.
4. Martens RJH, Kooman JP, Stehouwer CDA, et al. Albuminuria is associated with a higher prevalence of depression in a population-based cohort study: the Maastricht study. *Nephrol Dial Transplant*. 2018;33(1):128-138.
5. Geraets AFJ, van Agtmaal MJM, Stehouwer CDA, et al. Association of Markers of microvascular dysfunction with prevalent and incident depressive symptoms. *Hypertension*. 2020;76(2):342-349.
6. Nikolaidou B, Gkaliagkousi E, Anyfanti P, et al. The impact of hyperglycemia on urinary albumin excretion in recent onset diabetes mellitus type II. *BMC Nephrol*. 2020;21(1):119.
7. van Gennip ACE, Sedaghat S, Carnethon MR, et al. Retinal microvascular caliber and incident depressive symptoms: the multi-ethnic study of atherosclerosis. *Am J Epidemiol*. 2022;191(5):843-855.
8. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CDA. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *Lancet Diabetes Endocrinol*. 2020;8(4):325-336.
9. Rensma SP, van Sloten TT, Ding J, et al. Type 2 diabetes, change in depressive symptoms over time, and cerebral small vessel disease: longitudinal data of the AGES-Reykjavik study. *Diabetes Care*. 2020;43(8):1781-1787.
10. Sexton CE, Mackay CE, Ebmeier KP. A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. *Am J Geriatr Psychiatry*. 2013;21(2):184-195.
11. Sachdeva MM. Retinal neurodegeneration in diabetes: an emerging concept in diabetic retinopathy. *Curr Diab Rep*. 2021;21(12):65.
12. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016;16(1):22-34.
13. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol*. 2011;11(2):98-107.
14. Chen G, Wu Y, Wang T, et al. Association between serum endogenous secretory receptor for advanced glycation end products and risk of type 2 diabetes mellitus with combined depression in the Chinese population. *Diabetes Technol Ther*. 2012;14(10):936-942.
15. van Dooren FEP, Pouwer F, Schalkwijk CG, et al. Advanced glycation end product (AGE) accumulation in the skin is associated with depression: the Maastricht study. *Depress Anxiety*. 2017;34(1):59-67.
16. Seldenrijk A, van Hout HPJ, van Marwijk HWJ, et al. Depression, anxiety, and arterial stiffness. *Biol Psychiatry*. 2011;69(8):795-803.
17. Prenner SB, Chirinos JA. Arterial stiffness in diabetes mellitus. *Atherosclerosis*. 2015;238(2):370-379.
18. Schram MT, Sep SJS, van der Kallen CJ, et al. The Maastricht study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *Eur J Epidemiol*. 2014;29(6):439-451.
19. Li W, Schram MT, Sörensen BM, et al. Microvascular phenotyping in the Maastricht study: design and Main findings, 2010–2018. *Am J Epidemiol*. 2020;189(9):873-884.
20. Spauwen PJJ, van Eupen MGA, Köhler S, et al. Associations of advanced glycation end-products with cognitive functions in individuals with and without type 2 diabetes: the maastricht study. *J Clin Endocrinol Metab*. 2015;100(3):951-960.
21. van der Heide FCT, Zhou TL, Henry RMA, et al. Carotid stiffness is associated with retinal microvascular dysfunction-the Maastricht study. *Microcirculation*. 2021;28(6):e12702.
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
23. Rensma SP, Stehouwer CDA, Van Boxtel MPJ, et al. Associations of arterial stiffness with cognitive performance, and the role of microvascular dysfunction. *Hypertension*. 2020;75(6):1607-1614.
24. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness. *JACC*. 2010;55(13):1318-1327.
25. Ismail L, Materwala H, Al Kaabi J. Association of risk factors with type 2 diabetes: a systematic review. *Comput Struct Biotechnol J*. 2021;19:1759-1785.
26. Maier A, Riedel-Heller SG, Pabst A, Luppa M. Risk factors and protective factors of depression in older people 65+. A systematic review. *PLoS One*. 2021;16(5):e0251326.
27. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684-696.
28. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. *Lancet*. 2020;396(10248):413-446.
29. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med*. 2019;25(12):1822-1832.
30. Botros N, Sluik D, van Waateringe RP, de Vries JHM, Geelen A, Feskens EJM. Advanced glycation end-products (AGEs) and associations with cardio-metabolic, lifestyle, and dietary factors in a general population: the NQplus study. *Diabetes Metab Res Rev*. 2017;33(5):e2892.
31. Janssen EPCJ, Köhler S, Geraets AFJ, et al. Low-grade inflammation and endothelial dysfunction predict four-year risk and course of depressive symptoms: the Maastricht study. *Brain Behav Immun*. 2021;97(1):61-67.
32. Poongothai S, Anjana RM, Pradeepa R, et al. Association of depression with complications of type 2 diabetes--the Chennai urban rural epidemiology study (CURES- 102). *J Assoc Physicians India*. 2011;59:644-648.
33. Geerlings MI, Gerritsen L. Late-life depression, hippocampal volumes, and hypothalamic-pituitary-adrenal Axis regulation: a systematic review and meta-analysis. *Biol Psychiatry*. 2017;82(5):339-350.
34. Kalenderoglu A, Çelik M, Sevgi-Karadag A, Egilmez OB. Optic coherence tomography shows inflammation and degeneration in major depressive disorder patients correlated with disease severity. *J Affect Disord*. 2016;204:159-165.
35. van der Heide FCT, Steens ILM, Geraets AFJ, et al. Association of Retinal Nerve Fiber Layer Thickness, an index of neurodegeneration, with depressive symptoms over time. *JAMA Netw Open*. 2021;4(11):e2134753.
36. van Sloten TT, Boutouyrie P, Tafflet M, et al. Carotid artery stiffness and incident depressive symptoms: the Paris prospective study III. *Biol Psychiatry*. 2019;85(6):498-505.

37. Onete V, Henry RM, Sep SJS, et al. Arterial stiffness is associated with depression in middle-aged men - the Maastricht study. *J Psychiatry Neurosci*. 2018;43(2):111-119.
38. Stehouwer CDA. Microvascular dysfunction and hyperglycemia: a vicious cycle with widespread consequences. *Diabetes*. 2018;67(9):1729-1741.
39. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci*. 2011;12(12):723-738.
40. Birukov A, Cuadrat R, Polemiti E, Eichelmann F, Schulze MB. Advanced glycation end-products, measured as skin autofluorescence, associate with vascular stiffness in diabetic, pre-diabetic and normoglycemic individuals: a cross-sectional study. *Cardiovasc Diabetol*. 2021;20(1):110.
41. Raghavan CT. Advanced glycation end products in neurodegenerative diseases. *J Mol Neurosci*. 2024;74(4):114.
42. van Sloten TT, Protogerou AD, Henry RMA, Schram MT, Launer LJ, Stehouwer CDA. Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2015;53:121-130.
43. Palamarchuk IS, Slavich GM, Vaillancourt T, Rajji TK. Stress-related cellular pathophysiology as a crosstalk risk factor for neurocognitive and psychiatric disorders. *BMC Neurosci*. 2023;24:65.
44. Sara JDS, Toya T, Ahmad A, et al. Mental stress and its effects on vascular health. *Mayo Clin Proc*. 2022;97(5):951-990.
45. Ma L. Depression, anxiety, and apathy in mild cognitive impairment: current perspectives. *Front Aging Neurosci*. 2020;12:9.
46. Herder C, Hermanns N. Subclinical inflammation and depressive symptoms in patients with type 1 and type 2 diabetes. *Semin Immunopathol*. 2019;41(4):477-489.
47. Chaudhuri J, Bains Y, Guha S, et al. The role of advanced glycation end products in aging and metabolic diseases: bridging association and causality. *Cell Metab*. 2018;28(3):337-352.
48. Neves MF, Cunha AR, Cunha MR, Gismondi RA, Oigman W. The role of renin–angiotensin–aldosterone system and its new components in arterial stiffness and vascular aging. *High Blood Press Cardiovasc Prev*. 2018;25(2):137-145.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Steens ILM, Schram MT, Houben AJHM, et al. Type 2 diabetes and depression via microvascular dysfunction, neurodegeneration, inflammation, advanced glycation end products (AGEs), and arterial stiffness. *Diabetes Obes Metab*. 2025;27(9):4847-4858. doi:10.1111/dom.16527