# Biological determinants of depression, the role of cerebral damage, microvascular dysfunction, and hyperglycaemia

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# Biological determinants of depression, the role of cerebral damage, microvascular dysfunction, and hyperglycaemia: a population-based approach

PROEFSCHRIFT

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# Chapter 1

## General Introduction

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## Depression

Depression is a common mental health problem that is characterized by a persistent depressed mood and/or loss of interest or pleasure. It can substantially impair an individual's ability to function at work or school, or cope with daily life, and it has been identified as the leading cause of disability worldwide [1]. Globally, up to 350 million individuals suffer from a major depressive disorder (MDD) or dysthymia, with prevalence rates peaking in older adulthood (above 7.5% among women aged 55-74 years, and above 5.5% among men) [1]. The number of individuals with depression is rising, particularly in lower-income countries, which reflects the overall growth of the global population, as well as a proportionate increase in the age groups at which depression is more prevalent [1]. The aetiology underlying depression is still unknown, possibly due to the heterogeneous nature of depression, including differences across age groups [2].

Late-life depression (LLD; mostly defined as a depression above the age of 60 years but in this dissertation often defined as a depression above the age of 40 years) is a common complex mood disorder with high comorbidity of other psychiatric and physical diseases, cognitive decline, and increased mortality [3-6]. The prevalence of MDD varies largely and ranges from 0.9% to 42% among older adults and clinically relevant depressive symptom are present in 7.2% to 49% [7]. Over half of the individuals with LLD fail to remit with first line antidepressant medication [8,9]. In addition, older age has been shown to be a consistent and important risk factor for a poorer, more persistent course of depression [10,11]. A study among individuals aged above the 60 years with MDD, dysthymia, or minor depressive disorder reported that 61% of them had a persistent, chronic course of depressive symptoms [12]. The mechanisms involved in LLD might differ from the mechanisms involved in depression in early life, and may include vascular dysfunction, neurodegeneration, and hyperglycaemia.

## Biological mechanisms involved in late-life depression

### *Vascular dysfunction*

The 'vascular depression' hypothesis, introduced by Alexopoulos et al. in 1997, proposes that cerebrovascular disease may predispose, precipitate, or perpetuate depression [13]. This hypothesis was based on the presence of cerebrovascular risk factors in individuals with depression, the comorbidity of depression with cerebrovascular lesions, and the frequent development of depression after stroke.

Presence of cerebrovascular disease or cerebrovascular risk factors are core features of vascular depression [14]. Increasing evidence suggests that cerebral microvascular dysfunction (MVD) may contribute to the onset of LLD by inducing chronic ischemia in brain tissue [15]. Chronic ischemia results from structural or functional occlusion that may result in cognitive and behavioural problems [15]. Disruptions of frontal-limbic systems involved in mood regulation or their modulating pathways by brain lesions in crucial white matter tracts may lead to depression [16]. Cerebral MVD may also play an important role in the persistence of LLD, as cerebral damage is likely to be irreversible and the plasticity of the brain is limited. In addition, this irreversible cerebral damage may prove a good explanation for the worse response to usual treatment of depression. Although, a recent meta-analysis has shown an association between MVD and LLD [17], longitudinal studies into this association remain scarce and have shown mixed results [17]. Furthermore, MRI markers of cerebral MVD may reflect structural consequences of long-term MVD, which are themselves preceded by more subtle changes in the microcirculation [18]. These changes can be measured noninvasively in various organs. No previous studies have assessed the association between early direct markers of MVD with LLD.

***Neurodegeneration***

Another biological mechanism involved in LLD is neurodegeneration. Depression is common in neurodegenerative diseases such as Alzheimer's Disease (AD), frontotemporal dementia, Huntington's disease, Lewy body disease, and Parkinson's disease [19]. It can be a response to cognitive decline, but it has been suggested that LLD itself may be an indication of latent neurodegeneration [20]. Indeed, LLD has been associated with brain atrophy, particular in the hippocampus and the orbitofrontal cortex [21]. These findings are in line with the 'glucocorticoid cascade' hypothesis, which proposes that increased secretion of glucocorticoids by prolonged hypothalamic-pituitary-adrenal (HPA) axis activation, can produce permanent brain damage [22]. Both glucocorticoid and mineralocorticoid steroid receptors are present in high concentrations in the hippocampus and frontal cortex, and chronically elevated glucocorticoid levels can produce neuronal dysfunction with decreased glucose uptake, reduced dendritic arborization, and, ultimately, neuronal death and cell loss in the hippocampus in animals [23]. However, longitudinal studies that provide insight into temporality of the association between neurodegeneration and LLD are limited and highly heterogeneous.

### *Cognition*

Both vascular dysfunction and neurodegeneration may contribute to impaired cognition and dementia [24,25]. Depression is strongly related to impaired cognition [26], including memory, executive functioning, and information processing speed in late-life [27]. Around two-thirds of individuals with depression experience impaired cognition [26], and studies in patients with LLD have shown that cognitive deficits persist despite remission of depressive symptoms [27].

Several prospective cohort studies suggest that individuals with depression show accelerated cognitive decline and have a two times higher risk for Alzheimer's Disease (AD) and a three times higher risk for vascular dementia [28]. Aside of a risk factor, LLD can also be a prodrome to dementia [29]. Small clinical studies have demonstrated that structural brain, including cerebral MVD and neurodegeneration, are related to impaired cognition in depression [29]. However, studies generally were small and confined to the more severely depressed spectrum such as inpatients, hence there is a lack of population-based cohort studies that generalize findings to the wider population with depression.

### *Hyperglycaemia and insulin resistance*

The prevalence of depression is nearly doubled in individuals with type 2 diabetes mellitus (T2DM) as compared with the general population, with prevalence rates of 6.5% to 33% [30]. Comorbid depression in T2DM is associated with impaired quality of life [31], worse self-care, suboptimal blood glucose levels and an increased risk for macro- and microvascular complications, mortality [32] and dementia [33]. In addition, depression appears to be highly persistent and/or recurrent in T2DM [34]. Although there is evidence for a bidirectional association between T2DM and depression, the exact nature and the aetiological direction of the relationship remain unknown [30].

Hyperglycaemia and insulin resistance are key features of T2DM, and have been proposed as underlying mechanisms involved in the aetiology of LLD [35]. Both fluctuations in plasma glucose and prolonged hyperglycaemia may be involved in the development of LLD. The brain is particularly vulnerable to fluctuations in plasma glucose levels because neurons do not possess an active glucose transporter. As a consequence, high extracellular glucose levels lead to high intracellular glucose levels. The resulting biochemical changes, for instance the formation of reactive oxygen species (ROS) or AGEs, and accumulation of the resulting damage over the years, may lead to neuronal damage and/or disturbances of the hypothalamic–pituitary–adrenal axis, which eventually may

lead to LLD [35]. However, current evidence on the temporality of these associations remains scarce.

**The Maastricht Study**

In this dissertation, data was used from The Maastricht Study, an ongoing population-based cohort study that focuses on the aetiology, pathophysiology, complications, and comorbidities of T2DM and other chronic diseases [36]. 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, the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency.

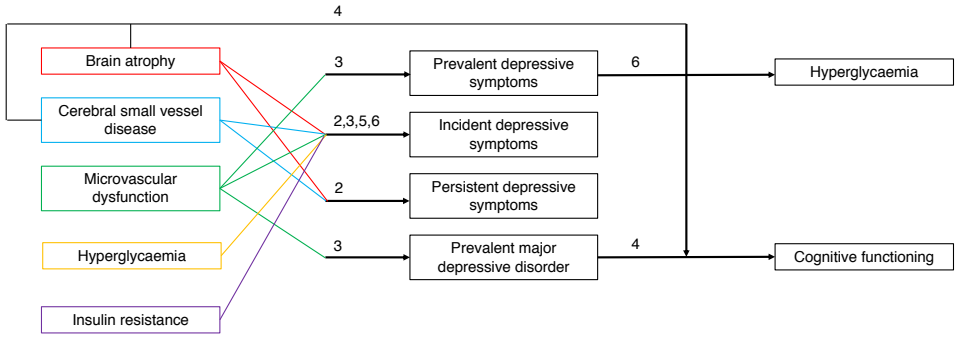
The Maastricht Study is characterised by an extensive phenotyping approach, including extensive assessment of depression, ultra-high field 3T MRI, state-of-the-art microcirculatory measurements, and an oral glucose tolerance test. The annual follow-up assessment of depression provides unique insight in both incidence and course of depressive symptoms in the general population. MRI measurements are time consuming for the participants and expensive to perform. The use of semi-automated volumetry made it possible to assess continuous values of brain volumes and vascular damage. In addition, state-of-the-art microcirculatory measurements are technically challenging to perform. The analyses of the raw images obtained from both MRI and microcirculatory measurements are time consuming, especially when performed in large population samples. The oral glucose tolerance test made it possible to assess multiple markers of hyperglycaemia and define T2DM according to the World Health Organization 2006 criteria [37]. Lastly, its extensive phenotyping approach made it possible to extensively adjust for potential demographic, cardiovascular, and lifestyle confounders, and perform of a range of sensitivity analyses.

For this dissertation, different data sets were used because of the difference in data availability at the time of preparing the manuscript. Two studies in this dissertation (chapter 3 and 5) used data of the first 3451 individuals who had completed the baseline survey between November 2010 and September 2013. Two other studies (chapters 2 and 4) used data from the first 7689 individuals who had completed the baseline survey between November 2010 and December 2017. MRI measurements were available in a subpopulation and assessed from December 2013 until February 2017. Follow-up data was collected annually over a period of seven years.

## Aim and outline of this dissertation

Vascular dysfunction, neurodegeneration, and hyperglycaemia may have an important contribution to the pathophysiology of LLD. Although studies have shown an association between these biological mechanisms and LLD, current evidence for the temporality of these association is limited because of the low number of longitudinal studies and heterogeneity across studies. It is important to further understand the contribution of vascular dysfunction, neurodegeneration, and hyperglycaemia in the pathophysiology of LLD to highlight targets for the prevention and treatment of LLD. In view of the above, the general aim of this dissertation was to investigate, in a population-based setting, the associations of vascular dysfunction, neurodegeneration, and hyperglycaemia with the prevalence, incidence and course of LLD over time (Figure 1.1). In addition, we investigated whether the association between LLD and cognitive functioning could be explained by structural brain abnormalities.

**Figure 1.1 Schematic outline of the associations investigated in this dissertation**




The following research questions will be answered in this dissertation:

1. Are markers of cerebral small vessel disease and brain atrophy associated with incidence and course of depressive symptoms in late-life? (chapter 2)
2. Are markers of microvascular dysfunction measured in the retina, skin, and plasma associated with prevalent and incident depressive symptoms in late-life? (chapter 3)
3. Is MDD associated with structural brain abnormalities and cognitive function in late-life? And if so, do structural brain abnormalities mediate the association between MDD and cognitive functioning in late-life? (chapter 4)

4. Are markers of hyperglycaemia and insulin resistance associated with incident depressive symptoms in late-life? (chapter 5)
5. Is there a bidirectional longitudinal association between hyperglycaemia and depression in late-life? (chapter 6)

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# Chapter 2

## The association of markers of cerebral small vessel disease and brain atrophy with incidence and course of depressive symptoms - The Maastricht Study

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## Abstract

### Background

Cerebral small vessel disease (CSVD) and neurodegeneration may be involved in the development and persistence of late-life depressive symptoms, but longitudinal evidence is scarce. We investigated the longitudinal associations of markers of CSVD and brain atrophy with incident depressive symptoms and the course of depressive symptoms, above and below 60 years of age.

### Methods

White matter hyperintensity volumes (WMH), presence of lacunar infarcts and cerebral microbleeds, and white matter, grey matter, and cerebral spinal fluid volumes were assessed at baseline by 3T MRI in The Maastricht Study (mean age 59.5±8.5 years, 49.6% women, n=4,347; 16,535 person-years of follow-up). Clinically relevant depressive symptoms (9-item Patient Health Questionnaire ≥10) were assessed at baseline and annually over seven years. We used Cox regression and multinomial logistic regression analyses adjusted for demographic, cardiovascular, and lifestyle risk factors.

### Results

Above 60 years of age, larger WMH volumes were associated with an increased risk for incident depressive symptoms (HR[95%CI]:1.24[1.04;1.48] per SD) and a persistent course of depressive symptoms (OR:1.44[1.04;2.00] per SD). Total CSVD burden was associated with persistent depressive symptoms irrespective of age (adjusted OR:1.58[1.03;2.43]), while no associations were found for general markers of brain atrophy.

### Limitations

Our findings need replication in other large-scale population-based studies.

### Conclusions

Our findings may suggest a temporal association of larger WMH volume with the incidence and persistence of late-life depression in the general population, and thus, may provide a potential target for the prevention of chronic late-life depression.

## Introduction

Late-life depression (LLD) is a common mood disorder with high comorbidity of psychiatric and physical diseases, cognitive decline, and increased mortality [1-4]. Clinically significant depressive symptoms are present in approximately 15% of community-dwelling older adults [3]. Over half of elderly individuals with LLD fail to remit with first line antidepressant medication [5,6]. Furthermore, older age has shown to be a consistent and important risk factor for a poorer, more persistent course of depression [7]. Clinically depressed elderly individuals were reported to have a persistent, chronic course of depressive symptoms in 61% of the cases [8]. However, the pathophysiology of LLD is still poorly understood [9,10], but may involve irreversible cerebral damage, including cerebral small vessel disease (CSVD) [11 9] and brain atrophy [12].

A recent meta-analysis by van Agtmaal et al. has shown a longitudinal association between higher WMH volume and incident depression [13]. However, the individual studies included in the meta-analyses showed mixed results, which may be due to suboptimal assessment of WMH markers (rating scales vs semi-automated volumetry) or depression (self-reported vs clinical diagnosis), or to the variation in age of included populations (range from 18 up to 80+ years). The latter is particularly important when investigating late-life depression, as LLD is most commonly defined as depression occurring at age >60 years, although there is no universal cut-off age. As CSVD is more common among the elderly, its relevance for depression is expected to be larger in LLD.

Only few studies have investigated the association of other features of CSVD, like lacunar infarcts [14,15] and cerebral microbleeds [14], and results are inconclusive.

CSVD and brain atrophy may also play an important role in the persistence of depressive symptoms, as cerebral damage is likely to be irreversible and the plasticity of the brain is limited. In addition, this irreversible cerebral damage may prove a good explanation for the worse response to depression treatment among elderly. However, data on chronic depression at population level are scarce, as only few studies apply depression assessment at multiple time points during a prolonged follow-up and MRI measurements are costly. We found only two population-based studies that assessed CSVD and such follow-up on depression [15,16]. Both found evidence for an association between CSVD and persistent depressive symptoms [15,16]. However, one study had a small number of cases with persistent depressive symptoms (n=32) and therefore applied limited

adjustments for potential confounders [15]. The other study reported a remarkable 40% prevalence of persistent depression in their population-based setting, which might be due to their broad definition of persistent depression [16].

Longitudinal studies that investigate the association between brain atrophy and depression are scarce as well. Previous studies have shown that a lower total brain volume [14], temporal lobe atrophy [17], and a smaller corpus callosum [18] are related to the incidence of LLD. Furthermore, some evidence suggest that brain atrophy contributes to the persistence of depression [9]. One clinical study found that men with a recurrent depression had a smaller left and right hippocampal volume in comparison to controls [19], while another study only found an association between a smaller left hippocampal volume and persistence of depressive symptoms [20]. Because clinical studies mostly investigated specific brain areas involved in mood regulation [9], it remains unclear whether there is an association between general markers of brain atrophy and the incidence and persistence of depression.

In view of the above, we investigated the longitudinal associations of markers of CSVD; white matter hyperintensity volume (WMH), lacunar infarcts, and cerebral microbleeds, and brain atrophy; white matter, grey matter, and cerebral spinal fluid (CSF) volume, with 1) incident depressive symptoms and 2) the course of depressive symptoms over time, stratified for age. In addition, we assessed whether these associations were independent of demographic, cardiovascular, and lifestyle risk factors.

## Methods

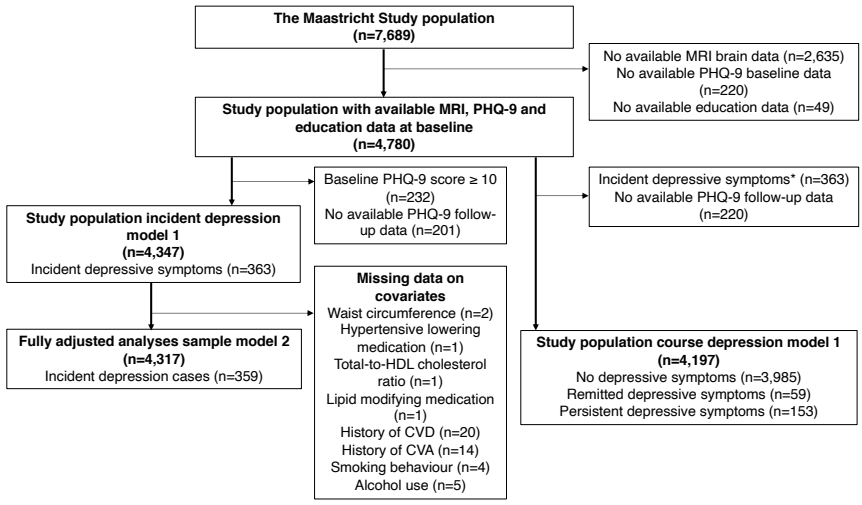
### *Population and Design*

We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously [21]. In brief, the study focuses on the etiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus (T2DM), heart disease, and other chronic conditions, and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years living in the southern part of the Netherlands. Further in- and exclusion criteria for this study populations are described in the paragraph below. 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, with an

oversampling of individuals with T2DM, for reasons of efficiency. Baseline data were collected between November 2010 and January 2018. Follow-up data was collected annually over a period of seven years, we used data currently available among 94.9% (year 1), 90.1% (year 2), 87.3% (year 3), 76.3% (year 4), 64.1% (year 5), 35.5% (year 6), and 14.0% (year 7) of the participants. It is important to note that the lower percentages after the fifth year are a result of the ongoing annual follow-up from year 6 onwards. 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.

Figure 2.1 shows the flowchart of the study population. From the initial 7,689 participants, baseline magnetic resonance imaging (MRI) data were available from n=5,054 participants. Of these, data on baseline Patient Health Questionnaire (PHQ-9) and education level were available in n=4,780. From these 4,780 participants two study population were composed; 1) for the analysis on incident depressive symptoms that included participants free of depressive symptoms at baseline, and 2) for the analysis on the course of depressive symptoms that included participants with prevalent depressive symptoms at baseline. 1) We excluded participants with clinically relevant depressive symptoms at baseline (PHQ-9 score ≥10, n=232) and those without PHQ-9 follow-up data (n=201), resulting in a study population of 4,347 participants with an average follow-up duration of 3.9 years (SD=1.0, median [IQR]=4.0[3.2;5.0]). 2) We excluded participants without PHQ-9 follow-up data (n=220), or incident depressive symptoms (n=363), and compared participants with and without clinically relevant depressive symptoms at baseline (PHQ-9 score ≥10). This resulted in a study population of 4,197 participants of whom 3,985 had no depressive symptoms, 153 persistent depressive symptoms, and 59 remitted depressive symptoms.

**Figure 2.1 Flowchart of study population**




PHQ-9 indicates 9 item Patient Health Questionnaire; MRI, magnetic resonance imaging; HDL, high-density lipoprotein; CVD, cardiovascular disease; CVA, cardiovascular accident. *Incident depressive symptoms are defined as baseline PHQ-9 score <10 and follow-up PHQ-9 score ≥10.

### *Brain magnetic resonance imaging*

Brain magnetic resonance imaging (MRI) was performed on a 3 Tesla MRI scanner (MAGNETOM Prismafit Syngo MR D13D; Siemens Healthcare, Erlangen, Germany) by use of a 64-element head coil for parallel imaging. The MRI protocol consists of a 3D T1-weighted sequence (TR/TE/TI2300/2.98/900ms, 1.00mm cubic voxel, 176 continuous slices, matrix size of 240x250 and reconstructed matrix size of 512x512), a T2-weighted fluid-attenuated inversion recovery (FLAIR; TR/TE/TI 5000/394/1800ms, 0.98x0.98x1.26mm acquisition voxel and 0.49x0.49x1.00 mm reconstructed voxel, 176 continuous slices, acquisition matrix size of 250x250 and reconstructed matrix size of 512x512), and a gradient recalled echo pulse sequence with susceptibility-weighted imaging. The protocols for MRI acquisition and analysis are in line with current STRIVE V2 imaging standards [22].

#### *White matter hyperintensities*

T1 images and T2-weighted FLAIR images were analyzed by use of an ISO-13485:2012–certified, automated method [23,24]. T1 images and T2-weighted FLAIR images were used to quantify total WMH volume [24]. WMH volumes were log-transformed and standardized. Additionally, WMH volumes were

dichotomized by use of an arbitrary cut-off of WMH volume >3.0 ml, which represents approximately the upper 7% of the WMH volumes in the study population.

*Lacunar infarcts and cerebral microbleeds*

The location and the number of lacunar infarcts and cerebral microbleeds are manually rated by three neuroradiologists. T2-weighted FLAIR images were used to define lacunar infarcts as focal lesions of ≥3 mm and <15 mm in size with a similar signal intensity as cerebrospinal fluid (CSF) on all sequences and a hyperintense rim [22]. Cerebral microbleeds were rated by use of the Microbleed Anatomical Rating Scale [25] and defined as focal lesions of ≥2 mm and ≤10 mm in size with a hypointense signal on T2-gradient recalled echo and susceptibility-weighted images. The intraclass correlation coefficient for the three raters based on 50 randomly selected scans was 0.84 (0.74; 0.91) and 0.83 (0.72; 0.90) for the presence of lacunar infarcts and cerebral microbleeds, respectively. Because of the small number of lacunar infarcts and cerebral microbleeds in our study population (Table 2.1 and Supplemental Table S2.1), we combined all MRI markers into a combined score. The combined CSVD score was defined as presence of any of the following: (1) WMH volume >3.0 ml, (2) presence of lacunar infarct, or (3) presence of cerebral microbleeds, resulting in a binary score of CSVD present (yes, no).

*Brain volumes*

To assess white matter, grey matter and cerebrospinal fluid (CSF) volumes, $T_1$-weighted images and FLAIR images were analyzed by use of an ISO-13485:2012 certified, automated method (which included visual inspection) [23,24]. Intracranial volume was calculated as the sum of white matter (including WMH volume), grey matter, and CSF. Volumes of white matter, grey matter, CSF, and intracranial volume were standardized.

### *Depression*

Depressive symptoms were assessed by a validated Dutch version of the 9-item Patient Health Questionnaire (PHQ-9) [26] both at baseline and during annual follow-up over seven years. The PHQ-9 is a self-administered questionnaire that assesses the presence of the nine symptoms for the DSM-IV criteria for a major depressive disorder on a 4-point Likert-scale ranging from 0 “not at all” to 4 ”nearly every day” [27]. When one or two items were missing, the total score was calculated as 9 × (total points/9−number of missing items) and rounded to the

nearest integer. When more items were missing, the total score was scored as missing. A cut-off score of ≥10 is most often used as a dichotomous scoring system for defining clinically relevant depressive symptoms, with a good sensitivity (88%) and specificity (78%) [28]. The internal consistency of the PHQ-9 in The Maastricht Study was good (Cronbach's alpha = 0.82 without T2DM, and 0.87 with T2DM) [29]. Because there was a time lag between the baseline data collection and the MRI scan, the PHQ-9 score obtained closest to the MRI scan was chosen as the baseline score for each individual.

Prevalent depressive symptoms were defined as clinically relevant depressive symptoms at baseline (PHQ-9 ≥10). Incident depressive symptoms were defined as no depressive symptoms at baseline (PHQ-9 <10) and presence of clinically relevant depressive symptoms on at least one follow-up moment (PHQ-9 ≥10). Course of depressive symptoms was defined as (1) persistent depressive symptoms, i.e. clinically relevant depressive symptoms at baseline and on at least one follow-up moment (PHQ-9 ≥10); (2) remitted depressive symptoms, i.e. clinically relevant depressive symptoms at baseline (PHQ-9 ≥10) and no clinically relevant depressive symptoms during follow-up (PHQ-9 <10); and (3) no depressive symptoms, i.e. no clinically relevant depressive symptoms at baseline and follow-up (no incident depressive symptoms; PHQ-9 <10).

***General characteristics and covariates***

General characteristics and covariates were measured at baseline. Educational level (low, intermediate, high), history of cardiovascular diseases (CVD) [30], smoking status (never, current, former), alcohol consumption (none, low, high), physical activity [31], and healthy diet score [32,33] were assessed by questionnaires [21]. Cerebrovascular accident (CVA) was assessed by a customized version of the Rose questionnaire [30] and MRI which we combined. Good validity of self-administered CVA in epidemiological research has been reported [34.] We measured, height, weight, waist circumference, office blood pressure, plasma lipid profile and 24h urinary albumin excretion (twice) as described elsewhere [21]. Urinary albumin excretion was defined as normal (<15 mg/24h), micro- (15-<30 mg/24h) and macroalbuminuria (≥30 mg/24h). Estimated glomerular filtration rate (eGFR; in mL/min/1.73 m2) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation based on both serum creatinine and serum cystatin C [35]. To determine T2DM status, all participants (except those who used insulin) underwent a standardized 7-point oral glucose tolerance test (OGTT) after an overnight fast. Glucose metabolism status was defined according to the World Health Organization 2006 criteria [36]. Participants were considered to have

T2DM if they had a fasting blood glucose ≥7.0 mmol/L or a 2-h postload blood glucose ≥11.1 mmol/L or used oral glucose-lowering medication or insulin. Medication use was assessed in a medication interview where generic name, dose, and frequency were registered.

***Statistical Analyses***

All statistical analyses were performed by use of the Statistical Package for Social Sciences (version 25.0; IBM, Chicago, Illinois, USA). General characteristics of the study population were evaluated using independent T-tests, Mann–Whitney U tests or $\chi^2$ tests. We used Cox proportional hazard regression analyses to assess the association of markers of CSVD and brain atrophy with incident depressive symptoms, with time-in-study as time axis.

Multinomial logistic regression analyses were used to investigated whether markers of CSVD and brain atrophy were associated with a persistent or remitted course of depressive symptoms, with no depressive symptoms as reference group. Associations were adjusted for potential confounders in two models: model 1, age, sex, educational level, T2DM and intracranial volume (volumes); model 2, additionally adjusted for cardiovascular risk factors (waist circumference, office systolic blood pressure, blood pressure lowering medication, total-to-high-density lipoprotein cholesterol ratio, lipid-modifying medication, and history of CVD and CVA), and modifiable lifestyle-related risk factors (smoking behavior and alcohol use). Due to the limited number of participants with persistent or remitted depression, we adjusted for model 1 in those analyses and for the potential confounders of model 2 in separate additional analyses. We also tested whether these associations differed according to age (> and ≤60 years), sex, and T2DM status, by use of interaction analyses. These interactions were tested in model 1 because model 2 may include variables that are in the causal pathway. Analyses were stratified for age (> and ≤60 years) to distinguish between LLD and depression earlier in life.

Several additional analyses were performed. To reduce potential misclassification of participants with subthreshold depression, we 1) additionally adjusted for use of antidepressant medication at baseline, 2) excluded participants who used antidepressant medication at baseline, and 3) excluded participants who had a MDD diagnosis at baseline. To restrict analyses to 'de novo' LLD we excluded participants who had a lifetime MDD diagnosis ≤60 years. We additionally adjusted for healthy diet and physical activity because this data was not complete, i.e., missing in respectively 202 and 348 participants. We also

applied stricter rules on the follow-up data, allowing a maximum of two missing follow-up measurements for individuals without incident depressive symptoms. To reduce the chance of attrition bias, we additional adjusted for follow-up duration in the course analyses, as participants with longer follow-up duration have a higher chance of being categorized into the persistent course group. A two-sided P-value < 0.05 was considered statistically significant. In interaction analyses we used a two-sided P-value < 0.10.

## Results

### *General characteristics of the study population*

During 16,535 person-years of follow-up, 363 (8.4%) participants developed clinically relevant depressive symptoms (PHQ-9≥10). Table 2.1 shows the general characteristics of the study population stratified for incident depressive symptoms. Participants had a mean age of 59.5±8.5 years and 49.6% were women. Participants with incident depressive symptoms were lower educated, less often had a partner, had a less healthy lifestyle, and a worse cardiometabolic risk profile compared to participants free of depressive symptoms. General characteristics of the study population stratified for persistent (n=153), remitted (n=59), and no depressive symptoms (n=3,985) are shown in Supplemental Table S2.1.

**Table 2.1 General characteristics of study population stratified for incident depressive symptoms**

| Characteristics at baseline | No depressive symptoms at baseline and follow-up (n=3,984) | Incident depressive symptoms (PHQ9≥10) (n=363) | *P*-value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 59.6±8.5 | 58.9±8.7 | 0.147 |
| Sex, n (% women) | 1,962(49.2) | 193(53.2) | 0.154 |
| Educational level, low/medium/high, n (%) | 1,192/1,129/1,663 (29.9/28.3/41.7) | 134/104/125 (36.9/28.7/34.4) | 0.002 |
| **Depression** | | | |
| Depressive symptoms at baseline (PHQ-9 score) | 1[0-3] | 4[2-7] | <0.001 |
| Major depressive disorder (MINI), n (%) | 44(1.1) | 28(7.9) | <0.001 |
| Anti-depressive medication, n (%) | 183(4.6) | 57(15.7) | <0.001 |
| Follow-up duration | 3.9±1.0 | 2.4±1.2 | <0.001 |
| **Cardiovascular risk factors** | | | |
| Body mass index (kg/m$^2$) | 26.2±3.9 | 27.5±4.6 | <0.001 |
| Waist circumference (cm) | 93.0±12.3 | 96.5±14.4 | <0.001 |
| Office systolic BP (mmHg) | 132.7±17.3 | 133.2±17.6 | 0.601 |
| Office diastolic BP (mmHg) | 75.3±9.6 | 76.2±9.7 | 0.070 |
| Antihypertensive medication, n (%) | 1,250(31.4) | 131(36.1) | 0.068 |
| Hypertension, n (%) | 1,930(48.5) | 200(55.1) | 0.018 |
| Total-to-HDL cholesterol ratio | 3.6±1.1 | 3.7±1.2 | 0.066 |
| Triglycerides (mmol/l) | 1.3±0.8 | 1.5±1.0 | <0.001 |
| Lipid-modifying medication, n (%) | 1,052(26.4) | 113(31.1) | 0.055 |
| eGFR (ml/min/1.73m$^2$) | 88.8±13.9 | 88.8±15.3 | 0.947 |
| Albuminuria, normal/micro/macro, n (%) | 3,704/250/15 (93.3/6.3/0.4) | 329/32/1 (90.9/8.8/0.3) | 0.081 |
| History of CVD, n (%) | 467(11.8) | 49(13.6) | 0.308 |
| History of CVA, n (%) | 146(3.7) | 13(3.6) | 1.000 |
| HbA1c (mmol/mol) | 38.3±8.1 | 40.3±10.3 | <0.001 |
| Type 2 diabetes mellitus, n (%) | 712(17.9) | 102(28.1) | <0.001 |
| **Lifestyle factors** | | | |
| Smoking, never/former/current, n (%) | 1,589/1,986/406 (39.9/49.9/10.2) | 132/173/57 (36.5/47.8/15.7) | 0.024 |
| Alcohol use, none/low/high, n (%) | 603/2,359/1,018 15.2/59.3/25.6 | 85/185/92 23.5/51.1/25.4 | 0.023 |
| Physical activity (hours/week) | 14.3±7.9 | 13.4±8.2 | 0.070 |
| Dutch healthy diet score | 84.8±14.8 | 82.0±15.8 | 0.001 |
| **Brain MRI** | | | |
| WMH volume (ml) | 0.21[0.07-0.70] | 0.20[0.07-0.61] | 0.920 |
| WMH volume >3ml, n (%) | 271(6.8) | 30(8.3) | 0.281 |
| Cerebral lacunar infarct, n (%) | 169(4.2) | 10(2.8) | 0.213 |
| Cerebral microbleeds, n (%) | 387(9.7) | 39(10.7) | 0.519 |
| Combined CSVD score, n (%) | 699(17.5) | 70(19.3) | 0.429 |
| White matter (ml) | 477.3±58.5 | 468.9±58.1 | 0.009 |
| Grey matter (ml) | 663.0±59.9 | 653.9±62.3 | 0.006 |
| Cerebrospinal fluid (ml) | 253.6±47.6 | 247.5±46.9 | 0.020 |
| Intracranial volume (ml) | 1394.9±132.9 | 1371.6±133.1 | 0.001 |

Data are presented as means ± standard deviation (SD), number (%) or median [interquartile range]. PHQ-9 indicates 9 item Patient Health Questionnaire; MINI, Mini-International Neuropsychiatric Interview; HbA1c, glycated hemoglobin A1c; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; CVA, cerebral vascular accident; WMH, white matter hyperintensities; CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging.

Participants not included in the analyses (n=3,129, 84% due to missing MRI data) were older, lower educated, more depressed, had a worse cardiometabolic risk profile, and a less healthy lifestyle than participants included in the analyses (Supplemental Table S2.2). In cross-sectional analyses a larger WMH volume was associated with prevalent depressive symptoms. No other cross-sectional associations between markers of CSVD or brain atrophy and prevalent depressive symptoms or MDD were found after full adjustment for demographic, cardiovascular, and lifestyle factors (Supplemental Table S2.3).

***Association of markers of CSVD with incident depressive symptoms***

Table 2.2 shows the association of WMH volume and the combined CSVD score with incident depressive symptoms. WMH volume and the combined CSVD score were not significantly associated with an increased risk for incident depressive symptoms in the total sample (HR [95%CI] 1.09 [0.96;1.22] and 1.18 [0.90;1.54] per SD, respectively). In analyses stratified for age we found an association between larger WMH volumes and incident depressive symptoms in individuals aged >60 years (1.24 [1.04;1.48] per SD), while no association was found in individuals aged ≤60 years or for the combined CSVD score, after full adjustment for demographic, cardiovascular, and lifestyle factors. Kaplan-Meijer curves are shown in Supplement Figures S2.1-2.2.

***Association of brain volumes with incident depressive symptoms***

The associations of brain volumes with incident depressive symptoms are shown in Table 2.2. No associations were found between white matter, grey matter, and CSF volume with incident depressive symptoms, neither in the whole study sample, nor in analyses stratified for age. Kaplan-Meijer curves are shown in Supplement Figures S2.3-2.5.

No interactions with sex or T2DM were found in the associations of WMH volume, the combined CSVD score, and brain volumes with incident depressive symptoms (data not shown).

**Table 2.2 Associations of markers of cerebral small vessel disease and brain atrophy with incident depressive symptoms stratified by age**

| | Total study population | | | Aged ≤ 60 years | | Aged > 60 years | |
|---|---|---|---|---|---|---|---|
| **Model** | **Incident depressive symptoms (PHQ-9≥10) n=363 cases** Hazard ratio (95% CI) | *P*-value | *P*-interaction for age ≤ or >60 years | **Incident depressive symptoms (PHQ-9≥10) n=204 cases** Hazard ratio (95% CI) | *P*-value | **Incident depressive symptoms (PHQ-9≥10) n=159 cases** Hazard ratio (95% CI) | *P*-value |
| **Markers of CSVD** | | | | | | | |
| **WMH volume (per 1 SD)** | | | | | | | |
| Model 1 | 1.09(0.96;1.22) | 0.185 | | 0.96(0.81;1.14) | 0.618 | **1.23(1.04;1.46)** | **0.018** |
| Model 2 | 1.08(0.96;1.22) | 0.195 | **0.018** | 0.95(0.80;1.13) | 0.554 | **1.24(1.04;1.48)** | **0.016** |
| **Combined CSVD score** | | | | | | | |
| Model 1 | 1.18(0.90;1.54) | 0.244 | | 1.18(0.76;1.85) | 0.464 | 1.15(0.82;1.62) | 0.425 |
| Model 2 | 1.18(0.90;1.55) | 0.236 | 0.819 | 1.19(0.76;1.87) | 0.451 | 1.14(0.80;1.61) | 0.479 |
| **Markers of brain atrophy** | | | | | | | |
| **WM volume (per 1 SD)** | | | | | | | |
| Model 1 | 0.95(0.75;1.19) | 0.648 | | 0.96(0.70;1.33) | 0.806 | 0.99(0.71;1.39) | 0.946 |
| Model 2 | 0.92(0.73;1.16) | 0.478 | 0.959 | 0.97(0.71;1.34) | 0.870 | 0.91(0.65;1.29) | 0.610 |
| **GM volume (per 1 SD)** | | | | | | | |
| Model 1 | 1.03(0.81;1.31) | 0.792 | | 1.17(0.83;1.65) | 0.378 | 0.93(0.66;1.31) | 0.696 |
| Model 2 | 1.10(0.87;1.40) | 0.421 | 0.504 | 1.17(0.83;1.64) | 0.372 | 1.10(0.77;1.56) | 0.609 |
| **CSF volume (per 1 SD)** | | | | | | | |
| Model 1 | 0.99(0.84;1.17) | 0.907 | | 0.93(0.73;1.18) | 0.544 | 1.01(0.79;1.29) | 0.946 |
| Model 2 | 0.97(0.81;1.15) | 0.689 | 0.285 | 0.92(0.72;1.17) | 0.484 | 0.95(0.74;1.22) | 0.694 |

Total study population n=4,347, study population ≤ 60 years n=2,159, and study population > 60 years n=2,188. PHQ-9 indicates 9 item Patient Health Questionnaire; CI, confidence interval; WMH, white matter hyperintensity; SD, standard deviation; CSVD, cerebral small vessel disease; WM, white matter; GM, grey matter; CSF, cerebrospinal fluid. Volumes of WMH are log10 transformed.

**Model 1:** adjusted for age, sex, educational level, type 2 diabetes mellitus, and intracranial volume (only for volumes).

**Model 2:** additionally adjusted for waist circumference, office systolic blood pressure, hypertensive medication, total/high density cholesterol ratio, lipid modifying medication, history of cardiovascular disease, history of cardiovascular accident, smoking behavior, and alcohol use.

### *Association of markers of CSVD with course of depressive symptoms*

Table 2.3 shows the association of WMH volume and the combined CSVD score with course of depressive symptoms. WMH volume was not associated with a persistent course of depressive symptoms in the total sample (OR [95%CI] 1.15 [0.95;1.39] per SD increase in WMH volume), while the combined CSVD score was associated (1.58 [1.03;2.43]), after adjustment for age, sex, educational level, and T2DM. In individuals aged >60 years, a larger WMH volume was associated with a persistent course of depressive symptoms while no association was found in individuals aged ≤60 years (1.44 [1.04;2.00] and 1.02 [0.80;1.31] per SD, respectively, $p\text{-}_{interaction}$=0.074), while this was not observed for the combined CSVD score (1.63 [0.87;3.02] for individuals aged >60 years and 1.59 [0.87;2.92] for individuals aged ≤60 years, $p\text{-}_{interaction}$=0.801).

No association was found of WMH volume or the combined CSVD score with a remitted course of depressive symptoms, neither in the whole study sample, nor in analyses stratified for age (Table 2.3).

### *Association of brain volumes with course of depressive symptoms*

The associations between brain volumes and course of depressive symptoms are shown in Table 2.3. No associations of white matter, grey matter, and CSF volume with a persistent course of depressive symptoms were found, neither in the whole study sample, nor in analyses stratified for age.

Furthermore, there was no association of white matter, grey matter, and CSF volume with a remitted course of depressive symptoms, neither in the whole study sample, nor in analyses stratified for age.

No interactions with sex or T2DM were found in the associations of WMH volume, the combined CSVD score, and brain volumes with a persistent course of depressive symptoms (data not shown). Due to the low number of individuals with a remitted course of depression (n=59), we could not test for interactions in this subgroup.

**Table 2.3 Associations of markers of cerebral small vessel disease and brain atrophy with course of depressive symptoms stratified by age**

| | Total study population | | | | | Aged ≤ 60 years | | | | Aged > 60 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model** | **Remitted (n=59)** Odds ratio (95% CI) | *P*-value | **Persistent (n=153)** Odds ratio (95% CI) | *P*-value | *P*-interaction for age ≤ or >60 years | **Remitted (n=42)** Odds ratio (95% CI) | *P*-value | **Persistent (n=106)** Odds ratio (95% CI) | *P*-value | **Remitted (n=17)** Odds ratio (95% CI) | *P*-value | **Persistent (n=47)** Odds ratio (95% CI) | *P*-value |
| **Markers of CSVD** | | | | | | | | | | | | | |
| **WMH volume (per SD)** | | | | | | | | | | | | | |
| Model 1 | 1.27(0.94;1.73) | 0.117 | 1.15(0.95;1.39) | 0.163 | **0.074** | 1.31(0.91;1.89) | 0.148 | 1.02(0.80;1.31) | 0.862 | 1.24(0.73;2.11) | 0.420 | **1.44(1.04;2.00)** | **0.029** |
| **Combined CSVD score** | | | | | | | | | | | | | |
| Model 1 | 1.14(0.56;2.33) | 0.718 | **1.58(1.03;2.43)** | **0.038** | 0.801 | 1.48(0.60;3.63) | 0.392 | 1.59(0.87;2.92) | 0.133 | 0.81(0.26;2.52) | 0.713 | 1.63(0.87;3.02) | 0.125 |
| **Markers of brain atrophy** | | | | | | | | | | | | | |
| **WM volume (per SD)** | | | | | | | | | | | | | |
| Model 1 | 0.86(0.49;1.52) | 0.609 | 1.07(0.73;1.55) | 0.742 | 0.943 | 1.11(0.55;2.25) | 0.774 | 0.98(0.61;1.57) | 0.925 | 0.48(0.18;1.30) | 0.149 | 1.22(0.64;2.33) | 0.540 |
| **GM volume (per SD)** | | | | | | | | | | | | | |
| Model 1 | 0.66(0.37;1.18) | 0.158 | 0.69(0.47;1.01) | 0.059 | 0.786 | 0.52(0.25;1.05) | 0.068 | 0.62(0.38;1.02) | 0.058 | 0.96(0.34;2.74) | 0.940 | 0.75(0.39;1.45) | 0.395 |
| **CSF volume (per SD)** | | | | | | | | | | | | | |
| Model 1 | 1.41(0.96;2.07) | 0.083 | 1.19(0.92;1.55) | 0.182 | 0.424 | 1.40(0.86;2.30) | 0.177 | 1.34(0.96;1.87) | 0.082 | 1.58(0.82;3.02) | 0.169 | 1.04(0.66;1.66) | 0.864 |

Reference category = no depressive symptoms (total study population n=3,985, study population ≤ 60 years n=1,956, and study population > 60 years n=2,029). CI indicates confidence interval; WMH, white matter hyperintensities; CSVD, cerebral small vessel disease; WM, white matter; GM, grey matter; CSF, cerebrospinal fluid. Volumes of WMH are log10 transformed. No depressive symptoms are defined as no depression at baseline and follow-up (PHQ-9 <10), persistent depression as depression at baseline and follow-up (PHQ-9 ≥10), and remitted depressive symptoms as depression at baseline (PHQ-9 ≥10) and no depression during follow-up (PHQ-9 <10).

**Model 1:** adjusted for age, sex, educational level, type 2 diabetes mellitus, and intracranial volume (only for volumes).

### *Additional analyses*

To assess robustness of our findings, a range of additional analyses were performed which are shown in Supplement Table S2.4-2.5. Adjustments to reduce potential misclassification of participants with subthreshold depression did not materially change our results with regard to incident depressive symptoms. Similar strengths of the association between WMH volume and incident depressive symptoms were found after additional adjustment for physical activity or healthy diet score. Furthermore, applying stricter rules on the follow-up data, allowing no or a maximum of one missing follow-up measurement for the control participants, did not materially change our results (Supplemental Table S2.4).

The associations of WMH volume and the combined CSVD score with a persistent course of depressive symptoms did not materially alter but became non-significant after additional adjustments for hypertension, prior CVD or CVA, smoking behavior, or alcohol use, and after adjustments to reduce potential misclassification of participants with subthreshold depression, although the attenuations in odds ratios were very small (< 8%; Supplemental Table S2.5).

## Discussion

Our finding that larger WMH volumes were associated with incident depressive symptoms in individuals above 60 years of age corroborates with and extends the results of a recent meta-analysis that found an association between WMH and incidence of depression [13]. Previous studies that consistently found an association between WMH volume and incident depression included study populations aged >60 years [13]. WMH become more apparent at later age [22], which may explain the absence of this association in younger individuals. Indeed, the variations in WMH volume in participants aged below the 61 years (0.10[0.04;0.29]) was much smaller compared to the variation in WMH volume in participants age >60 years (0.44[0.15;1.35]).

Intriguingly, we found an association for WMH volume but not the combined CSVD score with incident depressive symptoms. We included this combined CSVD score next to WMH because previous research showed an association between lacunar infarcts and incident depressive symptoms [14]. Several explanations can be found for the absence of this association. While van Sloten et al. [14] observed an association between lacunar infarcts and incident depressive symptoms, the only other population-based study into lacunar infarcts found no association [15]. Absence of a significant contribution of lacunar infarcts

and cerebral microbleeds might therefore have diluted the association. Furthermore, the combined CSVD score was assessed on a dichotomous scale based on presence of WMH, and manually counted lacunar infarcts and cerebral microbleeds, defined by a predefined size and/or shape [22], which may result in less power compared to the more precise continuous measures of semi-automatically generated WMH volume. Lastly, WMH are more common than the other components of the combined CSVD score, which may make WMH an earlier marker of CSVD and more accessible to assess in epidemiological studies [37]. Because the numbers of incident depression cases with a lacunar infarct (n=10) and cerebral microbleeds (n=39) were small in this relatively healthy study population, a relation between lacunar infarcts and cerebral microbleeds with incident depression cannot be excluded.

We found that larger WMH volume is associated with a persistent course of depressive symptoms in individuals >60 years. The p-interaction for LLD (age >60 years) for a persistent course of depressive symptoms (p=0.074) was higher compared to the p-interaction for LDD (age >60 years) for incident depressive symptoms (p=0.018), although this could be attributed to the smaller number of LLD in the persistent course analyses (n=49) as compared to the incident analyses (n=159). However, replication of these results in future studies is recommended. Additionally, we found an association between the combined CSVD score and a persistent course of depressive symptoms regardless of age. These results generalize findings reported in clinical studies of more severely depressed patient to the general population. WMH burden has been found to predict clinical outcome in LLD patients [9]. Severity of WMH has been associated with worse treatment outcome [9]. A recent meta-analysis that assessed the association between WMH burden and response to antidepressant treatment found that higher WHM burden predicted a poor response or no remission [38]. However, there are studies reporting no association between WMH and treatment outcome as well [9,38]. The two previous population-based studies that assessed the association of markers of CSVD with a persistent course of depression [15,16] yielded inconclusive results, but methodology differed. Beyond methodological variations, observed differences could be explained by the variability of pathophysiological subtypes within the LLD concept, which may have led to mixed results. Therefore, future studies to identify and characterize LLD subtypes are recommended to better understand its etiology.

No associations were found between markers of brain atrophy and incident or persistent depressive symptoms. Although some previous studies have related reductions in brain volume to incident depressive symptoms [14,18,39], participants

included in these studies were older. This difference in age may lead to various results, as it has been shown that the associations of frontal and temporal volume reductions on depression increases with age [40]. Furthermore, two studies investigated the associations of specific brain regions with incident LLD [18,39]. A smaller corpus callosum size was related to incident LLD over 10 years in elderly women, but not in men [18]. Another study only found an association between temporal lobe atrophy and incident LLD, while no associations were found between frontal, parietal, and occipital lobe atrophy and LLD [39]. Results from cross-sectional studies have shown that LLD is related to smaller volumes in brain regions involved in affective and cognitive processing [41,42], especially the orbitofrontal cortex, anterior cingulate cortex (ACC), amygdala, basal ganglia, hippocampus, and parahippocampus [9]. Thus, LLD may be related to focal volume loss rather than generalized volume loss.

Several mechanisms may explain the association of WMH with incidence and persistence of LLD. First, our results support the vascular depression hypothesis, which proposes that cerebrovascular diseases can predispose or perpetuate depression [11]. WMH may lead to LLD via disruption of frontal-limbic systems involved in mood regulation or their modulating pathways by brain lesions in crucial white matter tracts [43-45]. The interaction found with age may suggest that the aging brain has less capacity to compensate for the disruptions caused by WMH. Second, the association between WMH and LLD may exist because LLD represents an early manifestation of vascular dementia or a psychological response to subjective cognitive decline [46]. This explanation is supported by the association of WMH with both depression and vascular dementia [47]. Third, endothelial dysfunction and low-grade inflammation can be the mechanisms underlying WMH and LLD, as both are related to the development of CSVD [48] and depression [9,49]. Endothelial dysfunction in the cerebral microcirculation may lead to cerebral perfusion deficits, blood-brain-barrier impairment and chronic ischemia; and in case of strategic lesions affecting mood regulating regions, it may consequently lead to depressive symptoms [13]. Low grade inflammation may contribute to the biological mechanisms associated the onset and evolution of depression, including HPA-axis activity and cortisol release, serotonergic pathways, neurogenesis and neuroinflammation [50]. Furthermore, both endothelial dysfunction and low-grade inflammation appear to be more pronounced in treatment-resistant depression [50,51].

Strengths of our study include its large sample size and population-based longitudinal design; the inclusion of individuals aged between 40 and 75 years, which enabled stratification for age and thus LLD; the annual assessment of the

PHQ-9 to assess both incidence and course of depressive symptoms over a seven-year period; the use of continuous WMH values; the extensive adjustment for potential confounders; and the execution of a range of sensitivity analyses to assess robustness of our findings.

This study also has some limitations. First, selection and/or attrition bias could have occurred because participants with more severe depressive symptoms and greater comorbidity were less likely to undergo MRI and follow-up assessments. This may lead to an underestimation of our results [52]. Second, we measured depressive symptoms with the PHQ-9 questionnaire. High scores on this questionnaire are suggestive for depressive symptoms, but do not necessarily equate with MDD [29]. Although a number of participants in both the non-depressed and incident/persistent groups had MDD at baseline, exclusion of these participants did not materially change our results. Third, as acknowledged previously, the number of participants with lacunar infarcts and cerebral microbleeds were too small to assess associations with these specific markers individually and incident or course of depression. Fourth, we used an arbitrary volumetric cut-off score of WMH volume >3.0 ml in the combined CSVD score. Though volumetric measurements have shown to be more sensitive in differentiating clinical groups compared to visual rating scales [53], there is no available validated cut-off score for WMH volume. To test the robustness of this cut-off score we used several alternatives, e.g., 2ml, 4ml, upper quartile, and upper percentile, which provided similar results. Fifth, low numbers in course types probably rendered testing for interactions with age, sex and T2DM underpowered. Sixth, we did not study segmented brain areas to assess region-specific differences such as hippocampal or prefrontal lobar volumes [9].

Our findings have important clinical implications. WMH volume, as an early marker of CSVD, may provide a potential target for the prevention and treatment of LLD. Modifiable cerebrovascular disease risk factors are associated with WMH in healthy young adults [54]. Targeting these risk factors in young and middle age through lifestyle modification, such as weight loss and exercise, is a logical approach to improve vascular health and prevent LLD [55]. In addition, drugs, as renin-angiotensin-aldosterone system inhibitors and angiotensin receptor blockers may improve cerebral hemodynamics and endothelial function [56]. Use of angiotensin receptor blockers has been associated with improvement depression [57]. Some evidence also shows that calcium channel blockers may reduce depressive symptoms [57]. Two recent meta-analyses suggest that statins are effective in the prevention and improvement of depression [58,59]. The mechanisms underlying the effects of statins on depression are unclear but

reduction of oxidative stress and low-grade inflammation and improved blood flow may have a neuroprotective effect.

**Conclusion**

In conclusion, we observed an association of WMH volume with incidence of depressive symptoms in individuals above 60 years of age in a population-based setting, independent of major demographical, cardiovascular, and lifestyle risk factors. Furthermore, WMH volume was associated with persistence of depressive symptoms in individuals above 60 years, while the combined CSVD score was associated with persistence of depressive symptoms irrespective of age. No associations were found between markers of global brain atrophy and incidence or persistence of depressive symptoms. Replication of our results in large population-based studies is recommended. WMH volume, as an early marker of CSVD, may be involved in both the incidence and persistence of LLD, and thus may provide a potential target for the prevention of LLD.

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## Supplemental Material to Chapter 2

## Supplemental Tables

**Table S2.1 General characteristics of study population according to course of depressive symptoms**

| Characteristic at baseline | No depressive symptoms (n=3,985) | Remitted depressive symptoms (n=59) | Persistent depressive symptoms (n=153) |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 59.6±8.5 | 57.1±8.0* | 56.4±8.6*** |
| Sex, n (% women) | 1,962(49.2) | 31(52.5) | 98(64.1)*** |
| Educational level, low/medium/high, n (%) | 1,193/1,129/1,663 (29.9/28.3/41.7) | 20/22/17 (33.9/37.3/28.8) | 65/46/42 (42.5/30.1/27.5)*** |
| **Depression** | | | |
| Depressive symptoms at baseline (PHQ-9 score) | 1[0-3] | 11[10-12]*** | 13[11-17]*** |
| Major depressive disorder (MINI), n (%) | 44(1.1) | 10(17.5)*** | 46(31.5)*** |
| Anti-depressive medication, n (%) | 183(4.6) | 7(11.9)* | 50(32.7)*** |
| Follow-up duration | 3.9±1.0 | 3.5±1.3*** | 1.4±0.6*** |
| **Cardiovascular risk factors** | | | |
| Body mass index (kg/m$^2$) | 26.2±3.9 | 27.2±4.6 | 28.5±5.2*** |
| Waist circumference (cm) | 93.0±12.3 | 95.5±13.4 | 97.2±14.9*** |
| Office systolic BP (mmHg) | 132.7±17.3 | 132.1±17.1 | 133.1±17.9 |
| Office diastolic BP (mmHg) | 75.3±9.6 | 75.8±10.8 | 76.5±10.8 |
| Antihypertensive medication, n (%) | 1,250(31.4) | 21(35.6) | 74(48.4)*** |
| Hypertension, n (%) | 1,931(48.5) | 30(50.8) | 87(56.9)* |
| Total-to-HDL cholesterol ratio | 3.6±1.1 | 3.7±1.0 | 3.8±1.5* |
| Triglycerides (mmol/l) | 1.3±0.8 | 1.4±0.8 | 1.6±1.2*** |
| Lipid-modifying medication, n (%) | 1,052(26.4) | 11(18.6) | 53(34.6)* |
| eGFR (ml/min/1.73m$^2$) | 88.8±13.9 | 87.6±19.0 | 90.3±15.9 |
| Albuminuria, normal/micro/macro, n (%) | 3,705/250/15 (93.3/6.3/0.4) | 54/4/1 (91.5/6.8/1.7) | 137/13/1 (90.7/8.6/0.7) |
| History of CVD, n (%) | 467(11.8) | 6(10.5) | 30(19.9)** |
| History of CVA, n (%) | 146(3.7) | 2(3.5) | 13(8.6)** |
| HbA1c (mmol/mol) | 38.3±8.1 | 38.5±7.5 | 42.3±13.5*** |
| Type 2 diabetes mellitus, n (%) | 712(17.9) | 14(23.7) | 50(32.7)*** |
| **Lifestyle factors** | | | |
| Smoking, never/former/current, n (%) | 1,589/1,986/407 (39.9/49.9/10.2) | 23/29/7 (39.0/49.2/11.9) | 55/59/37 (36.4/39.1/24.5)** |
| Alcohol use, none/low/high, n (%) | 603/2,360/1,018 (15.1/59.3/25.6) | 9/43/6 (15.5/74.1/10.3)* | 51/70/31 (33.6/46.1/20.4)*** |
| Physical activity (hours/week) | 14.3±7.9 | 13.5±7.4 | 12.9±8.8 |
| Dutch healthy diet score | 84.8±14.8 | 81.3±15.5 | 82.6±14.5 |
| **Brain MRI** | | | |
| WMH volume (ml) | 0.21[0.07-0.70] | 0.30[0.11-0.50] | 0.18[0.05-0.61] |
| WMH volume >3ml, n (%) | 271(6.8) | 3(5.1) | 11(7.2) |
| Cerebral lacunar infarct, n (%) | 169(4.2) | 5(8.5) | 13(8.5)* |
| Cerebral microbleeds, n (%) | 387(9.7) | 5(8.5) | 18(11.8) |
| Combined CSVD score, n (%) | 699(17.5) | 10(16.9) | 31(20.3) |
| White matter (ml) | 477.3±58.5 | 471.3±66.5 | 459.2±57.9*** |
| Grey matter (ml) | 663.5±60.2 | 652.9±58.7 | 641.0±66.4*** |
| Cerebrospinal fluid (ml) | 253.6±47.6 | 252.1±47.4 | 239.4±43.7*** |
| Intracranial volume (ml) | 1,394.8±132.9 | 1,379.3±146.5 | 1,340.4±136.5*** |

Remitted and persistent are compared to no depressive symptoms. Data are presented as means ± standard deviation (SD), number (%) or median [interquartile range]. PHQ-9 indicates 9 item Patient Health Questionnaire; MINI, Mini-International Neuropsychiatric Interview; HbA1c, glycated hemoglobin A1c; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; CVA, cerebral vascular accident; WMH, white matter hyperintensities; CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging. No depressive symptoms are defined as no depression at baseline and follow-up (PHQ-9 <10), persistent depression as depression at baseline and follow-up (PHQ-9 ≥10), and remitted depressive symptoms as depression at baseline (PHQ-9 ≥10) and no depression during follow-up (PHQ-9 <10). *$p$-value <0.05, **$p$-value <0.01, ***$p$-value <0.001.

**Table S2.2 General characteristics of participants stratified for study inclusion**

| Characteristic at baseline | Included (n=4,560) | Excluded (n=3,129) |
|---|---|---|
| **Demographics** | | |
| Age (years) | 59.4±8.5 | 60.4±8.9*** |
| Sex, n (% women) | 2,284(50.1) | 1,531(48.9) |
| Educational level, | 1,412/1,301/1,847 | 1,218/791/1,005 |
| low/medium/high, n (%) | (31.0/28.5/40.5) | (40.4/26.2/33.3)*** |
| Depression | | |
| Depressive symptoms at baseline (PHQ-9 score) | 2[0-4] | 2[1-6]*** |
| Major depressive disorder (MINI), n (%) | 128(2.9) | 120(4.1)** |
| Anti-depressive medication, n (%) | 297(6.5) | 254(8.1)** |
| Follow-up duration | 3.7±1.1 | 3.5±1.3*** |
| **Cardiovascular risk factors** | | |
| Body mass index (kg/m$^2$) | 26.4±4.1 | 27.8±5.0*** |
| Waist circumference (cm) | 93.5±12.6 | 98.0±14.7*** |
| Office systolic BP (mmHg) | 132.8±17.4 | 135.2±18.6*** |
| Office diastolic BP (mmHg) | 75.4±9.7 | 75.7±10.0 |
| Antihypertensive medication, n (%) | 1,476(32.4) | 1,460(46.7)*** |
| Hypertension, n (%) | 2,248(49.3) | 1,889(60.5)*** |
| Total-to-HDL cholesterol ratio | 3.6±1.2 | 3.7±1.2** |
| Triglycerides (mmol/l) | 1.4±0.8 | 1.5±1.0*** |
| Lipid-modifying medication, n (%) | 1,229(27.0) | 1,275(40.8)*** |
| eGFR (ml/min/1.73m$^2$) | 88.9±14.2 | 87.1±15.9** |
| Albuminuria, | 4,225/299/18 | 2,735/292/37 |
| normal/micro/macro, n (%) | (93.0/6.6/0.4) | (89.3/9.5/1.2)*** |
| History of CVD, n (%) | 552(12.2) | 746(24.4)*** |
| History of CVA, n (%) | 174(3.8) | 35(5.9)* |
| HbA1c (mmol/mol) | 38.6±8.6 | 41.7±10.8*** |
| Type 2 diabetes mellitus, n (%) | 878(19.3) | 1,015(32.4)*** |
| **Lifestyle factors** | | |
| Smoking, | 1,799/2,247/508 | 1,036/1,517/518 |
| never/former/current, n (%) | (39.5/49.3/11.2) | (33.7/49.4/16.9)*** |
| Alcohol use, | 748/2,658/1,147 | 664/1,773/634 |
| none/low/high, n (%) | (16.4/58.4/25.2) | (21.6/57.7/20.6)*** |
| Physical activity (hours/week) | 14.1±8.0 | 13.7±8.5* |
| Dutch healthy diet score | 84.5±14.9 | 82.5±15.3*** |
| **Brain MRI** | | |
| WMH volume (ml) | 0.21[0.07-0.69] | 0.22[0.06-0.74] |
| WMH volume >3ml, n (%) | 315(6.9) | 47(1.5)*** |
| Cerebral lacunar infarct, n (%) | 197(4.3) | 27(4.1) |
| Cerebral microbleeds, n (%) | 449(9.8) | 62(11.0) |
| Combined CSVD score, n (%) | 810(17.8) | 98(17.5) |
| White matter (ml) | 475.9±58.6 | 473.3±61.1 |
| Grey matter (ml) | 661.4±60.5 | 658.3±64.0 |
| Cerebrospinal fluid (ml) | 252.6±47.5 | 254.3±53.7 |
| Intracranial volume (ml) | 1,391.0±133.7 | 1,387.1±137.2 |

Data are presented as means ± standard deviation (SD), number (%) or median [interquartile range]. Remitted and persistent are compared to no depressive symptoms. PHQ-9 indicates 9 item Patient Health Questionnaire; MINI, Mini-International Neuropsychiatric Interview; HbA1c, glycated hemoglobin A1c; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; CVA, cerebral vascular accident; WMH, white matter hyperintensities; CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging. *$p$-value <0.05, **$p$-value <0.01, ***$p$-value <0.001.

**Table S2.3 Cross-sectional associations of markers of cerebral small vessel disease and brain atrophy with prevalent depression**

| Model | **Prevalent depressive symptoms (PHQ-9 score)** Rate ratio (95% CI) | *P*-value | **Prevalent clinically relevant depressive symptoms (PHQ-9≥10) (n=232)** Odds ratio (95% CI) | *P*-value | **Major depressive disorder (MINI) (n=140)** Odds ratio (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| **WMH volume (per 1 SD)** | | | | | | |
| Model 1 | **1.06(1.02;1.10)** | **0.005** | **1.19(1.02;1.39)** | **0.030** | 1.22(1.00;1.48) | 0.050 |
| Model 2 | **1.04(1.00;1.09)** | **0.041** | 1.14(0.97;1.34) | 0.112 | 1.19(0.98;1.45) | 0.087 |
| **Combined CSVD score** | | | | | | |
| Model 1 | 1.09(1.00;1.20) | 0.056 | **1.46(1.03;2.08)** | **0.034** | 1.09(0.69;1.72) | 0.706 |
| Model 2 | 1.06(0.97;1.17) | 0.188 | 1.36(0.94;1.96) | 0.100 | 1.03(0.64;1.64) | 0.909 |
| **WM volume (per 1 SD)** | | | | | | |
| Model 1 | 0.96(0.89;1.03) | 0.219 | 0.90(0.67;1.21) | 0.484 | 1.04(0.72;1.51) | 0.840 |
| Model 2 | 0.95(0.89;1.03) | 0.200 | 0.87(0.64;1.18) | 0.363 | 1.03(0.71;1.50) | 0.875 |
| **GM volume (per 1 SD)** | | | | | | |
| Model 1 | 0.96(0.90;1.04) | 0.321 | 0.74(0.55;1.01) | 0.061 | 0.92(0.63;1.35) | 0.679 |
| Model 2 | 1.00(0.93;1.08) | 0.978 | 0.82(0.60;1.13) | 0.223 | 0.98(0.66;1.44) | 0.906 |
| **CSF volume (per 1 SD)** | | | | | | |
| Model 1 | 1.05(1.00;1.11) | 0.069 | **1.28(1.04;1.58)** | **0.022** | 1.03(0.79;1.35) | 0.828 |
| Model 2 | 1.03(0.97;1.08) | 0.318 | 1.24(1.00;1.54) | 0.050 | 1.00(0.76;1.32) | 0.997 |

Negative binomial and logistic regression analyses were used to investigate the cross-sectional associations of markers of CSVD with respectively depressive symptoms and clinically relevant depressive symptoms. PHQ-9 data n=4,780, MINI data n=4,623 in model 1. PHQ-9 indicates 9 item Patient Health Questionnaire; MINI, Mini-International Neuropsychiatric Interview; CI, confidence interval; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; SD, standard deviation; WM, white matter; GM, grey matter; CSF, cerebrospinal fluid. Volumes of WMH are log10 transformed.

**Model 1:** adjusted for age, sex, educational level, type 2 diabetes mellitus, and intracranial volume (only for volumes).

**Model 2:** additionally adjusted for waist circumference, office systolic blood pressure, hypertensive medication, total/high density cholesterol ratio, lipid modifying medication, history of cardiovascular disease, history of cardiovascular accident, smoking behavior, and alcohol use.

**Table S2.4 Additional analyses for the association white matter hyperintensity volume with incident depressive symptoms stratified by age**

| | **Total study population** | | **Aged ≤ 60 years** | | **Aged > 60 years** | |
|---|---|---|---|---|---|---|
| **Model** | **Incident depressive symptoms (PHQ-9≥10) n=359 cases** Hazard ratio (95% CI) | *P*-value | **Incident depressive symptoms (PHQ-9≥10) n=204 cases** Hazard ratio (95% CI) | *P*-value | **Incident depressive symptoms (PHQ-9≥10) n=155 cases** Hazard ratio (95% CI) | *P*-value |
| **WMH volume (per 1 SD)** | | | | | | |
| Model 2 | 1.08(0.96;1.22) | 0.195 | 0.95(0.80;1.13) | 0.554 | **1.24(1.04;1.48)** | **0.016** |
| Model 2 + antidepressant medication | 1.07(0.95;1.21) | 0.276 | 0.95(0.80;1.13) | 0.582 | **1.20(1.01;1.43)** | **0.042** |
| Model 2 excl. antidepressant users (excluded data n=238) | 1.08(0.94;1.23) | 0.268 | 0.94(0.78;1.14) | 0.539 | **1.24(1.02;1.49)** | **0.028** |
| Model 2 excl. baseline MDD (excluded data n=208) | 1.08(0.95;1.23) | 0.250 | 0.95(0.79;1.14) | 0.555 | **1.22(1.02;1.47)** | **0.034** |
| Model 2 excl. lifetime MDD ≤60 years (excluded data n=1,211) | N/A | N/A | N/A | N/A | 1.20(0.94;1.53) | 0.142 |
| Model 2 + healthy diet score (missing data n=170)* | 1.11(0.98;1.26) | 0.090 | 0.99(0.82;1.18) | 0.874 | **1.25(1.05;1.49)** | **0.014** |
| Model 2 + physical activity (missing data n=314) | 1.08(0.95;1.23) | 0.235 | 0.95(0.80;1.14) | 0.582 | **1.24(1.04;1.49)** | **0.019** |
| Model 2 excl. controls >2 missing follow-ups (excluded data n=1,557) | 1.08(0.96;1.22) | 0.219 | 0.92(0.77;1.09) | 0.325 | **1.27(1.06;1.51)** | **0.008** |

Total study population n=4,317, study population ≤ 60 years n=2,159, and study population > 60 years n=2,172. PHQ-9 indicates 9 item Patient Health Questionnaire; CI, confidence interval; WMH, white matter hyperintensity; SD, standard deviation; excl., excluding; MDD, major depressive disorder; N/A, not applicable. Volumes of WMH are log10 transformed.

**Model 2:** adjusted for age, sex, educational level, type 2 diabetes mellitus, and intracranial volume, waist circumference, office systolic blood pressure, hypertensive medication, total/high density cholesterol ratio, lipid modifying medication, history of cardiovascular disease, history of cardiovascular accident, smoking behavior, and alcohol use.

*Alcohol use was eliminated from the model as it is included in the healthy diet score.

**Table S2.5 Additional analyses for white matter hyperintensities volume and combined cerebral small vessel disease score with course of depressive symptoms stratified by age**

| | Total study population | | | | Aged ≤ 60 years | | | | Aged > 60 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model** | **Remitted (n=59)** Odds ratio (95% CI) | *P*-value | **Persistent (n=153)** Odds ratio (95% CI) | *P*-value | **Remitted (n=42)** Odds ratio (95% CI) | *P*-value | **Persistent (n=106)** Odds ratio (95% CI) | *P*-value | **Remitted (n=17)** Odds ratio (95% CI) | *P*-value | **Persistent (n=47)** Odds ratio (95% CI) | *P*-value |
| **WMH volume (per SD)** | | | | | | | | | | | | |
| Model 1 | 1.27(0.94;1.73) | 0.117 | 1.15(0.95;1.39) | 0.163 | 1.31(0.91;1.89) | 0.148 | 1.02(0.80;1.31) | 0.862 | 1.24(0.73;2.11) | 0.420 | **1.44(1.04;2.00)** | **0.029** |
| Model 1 + waist circumference | 1.27(0.94;1.72) | 0.122 | 1.14(0.94;1.39) | 0.173 | 1.30(0.91;1.88) | 0.154 | 1.01(0.79;1.29) | 0.917 | 1.26(0.75;2.14) | 0.387 | **1.46(1.05;2.02)** | **0.025** |
| Model 1 + OSBP and hypertensive med. | 1.26(0.93;1.71) | 0.132 | 1.11(0.92;1.35) | 0.275 | 1.29(0.89;1.86) | 0.177 | 0.99(0.78;1.27) | 0.954 | 1.25(0.74;2.12) | 0.406 | 1.39(1.00;1.93) | 0.050 |
| Model 1 + total-to-HDL cholesterol ratio and lipid modifying med. | 1.25(0.91;1.70) | 0.164 | 1.14(0.94;1.39) | 0.181 | 1.25(0.86;1.83) | 0.242 | 1.02(0.80;1.30) | 0.898 | 1.28(0.75;2.20) | 0.366 | **1.45(1.04;2.02)** | **0.029** |
| Model 1 + prior CVD | 1.33(0.97;1.81) | 0.073 | 1.14(0.94;1.39) | 0.177 | 1.32(0.91;1.90) | 0.139 | 1.04(0.81;1.33) | 0.776 | 1.41(0.80;2.48) | 0.233 | 1.38(0.99;1.92) | 0.055 |
| Model 1 + prior CVA | 1.33(0.97;1.81) | 0.075 | 1.11(0.91;1.35) | 0.295 | 1.32(0.91;1.91) | 0.139 | 1.00(0.78;1.28) | 0.983 | 1.41(0.80;2.49) | 0.236 | 1.35(0.97;1.87) | 0.074 |
| Model 1 + smoking behavior | 1.27(0.94;1.72) | 0.120 | 1.11(0.91;1.36) | 0.287 | 1.31(0.91;1.88) | 0.152 | 0.98(0.76;1.26) | 0.889 | 1.25(0.74;2.13) | 0.404 | 1.39(1.00;1.94) | 0.051 |
| Model 1 + alcohol use | 1.34(0.99;1.82) | 0.063 | 1.12(0.92;1.36) | 0.267 | 1.35(0.93;1.96) | 0.111 | 1.01(0.79;1.29) | 0.947 | 1.38(0.80;2.39) | 0.249 | 1.38(0.99;1.92) | 0.060 |
| Model 1 + antidepressant medication | 1.27(0.94;1.73) | 0.117 | 1.13(0.93;1.39) | 0.218 | 1.32(0.91;1.90) | 0.140 | 1.03(0.79;1.32) | 0.852 | -* | -* | 1.38(0.98;1.94) | 0.062 |
| Model 1 excl. antidepressant users (excluded data n=241) | 1.21(0.88;1.67) | 0.248 | 1.16(0.92;1.47) | 0.201 | 1.20(0.80;1.80) | 0.370 | 1.06(0.79;1.43) | 0.700 | 1.25(0.74;2.12) | 0.409 | 1.38(0.95;2.03) | 0.095 |
| Model 1 excl. baseline MDD from controls and missing MDD data (excluded data n=170) | 1.27(0.94;1.72) | 0.123 | 1.14(0.94;1.39) | 0.179 | 1.31(0.91;1.89) | 0.146 | 1.01(0.79;1.30) | 0.912 | 1.23(0.73;2.08) | 0.444 | **1.44(1.03;1.99)** | **0.031** |
| Model 1 + healthy diet score (missing data n=179) | 1.26(0.92;1.72) | 0.150 | 1.21(0.98;1.49) | 0.072 | 1.35(0.93;1.97) | 0.120 | 1.09(0.83;1.42) | 0.539 | 1.13(0.66;1.95) | 0.653 | **1.48(1.05;2.09)** | **0.027** |
| Model 1 + physical activity (missing data n=325) | 1.26(0.91;1.72) | 0.161 | 1.16(0.94;1.43) | 0.172 | 1.33(0.92;1.94) | 0.130 | 1.01(0.77;1.31) | 0.967 | 1.17(0.66;2.08) | 0.599 | **1.53(1.06;2.20)** | **0.023** |
| Model 1 + follow-up duration | 1.24(0.91);1.68) | 0.171 | 1.15(0.94);1.39) | 0.168 | 1.28(0.89;1.85) | 1.85 | 1.02(0.80;1.31) | 0.852 | 1.24(0.73;2.11) | 0.431 | **1.42(1.02;1.97)** | **0.037** |

**Table S2.5 (Continued)**

| | Total study population | | | | Aged ≤ 60 years | | | | Aged > 60 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model** | **Remitted (n=59)** Odds ratio (95% CI) | *P*-value | **Persistent (n=153)** Odds ratio (95% CI) | *P*-value | **Remitted (n=42)** Odds ratio (95% CI) | *P*-value | **Persistent (n=106)** Odds ratio (95% CI) | *P*-value | **Remitted (n=17)** Odds ratio (95% CI) | *P*-value | **Persistent (n=47)** Odds ratio (95% CI) | *P*-value |
| **Combined CSVD score** | | | | | | | | | | | | |
| Model 1 | 1.14(0.56;2.33) | 0.718 | **1.58(1.03;2.43)** | **0.038** | 1.48(0.60;3.63) | 0.392 | 1.59(0.87;2.92) | 0.133 | 0.81(0.26;2.52) | 0.713 | 1.63(0.87;3.02) | 0.125 |
| Model 1 + waist circumference | 1.14(0.56;2.33) | 0.724 | **1.58(1.03;2.43)** | **0.037** | 1.48(0.60;3.62) | 0.394 | 1.60(0.87;2.93) | 0.130 | 0.81(0.26;2.53) | 0.719 | 1.62(0.87;3.03) | 0.130 |
| Model 1 + OSBP and hypertensive med. | 1.12(0.55;2.30) | 0.755 | 1.51(0.98;2.32) | 0.062 | 1.46(0.59;3.59) | 0.409 | 1.53(0.83;2.82) | 0.171 | 0.81(0.26;2.53) | 0.715 | 1.56(0.83;2.90) | 0.165 |
| Model 1 + total-to-HDL cholesterol ratio and lipid modifying med. | 1.07(0.51;2.25) | 0.865 | **1.56(1.02;2.41)** | **0.043** | 1.28(0.49;3.35) | 0.632 | 1.54(0.84;2.84) | 0.163 | 0.84(0.27;2.65) | 0.769 | 1.65(0.89;3.08) | 0.115 |
| Model 1 + prior CVD | 1.25(0.61;2.57) | 0.548 | 1.46(0.94;2.26) | 0.095 | 1.49(0.61;3.66) | 0.384 | 1.53(0.83;2.83) | 0.171 | 0.96(0.30;3.10) | 0.947 | 1.48(0.78;2.79) | 0.226 |
| Model 1 + prior CVA | 1.24(0.60;2.56) | 0.559 | 1.44(0.93;2.24) | 0.102 | 1.51(0.61;3.73) | 0.370 | 1.48(0.79;2.74) | 0.219 | 0.97(0.30;3.11) | 0.956 | 1.47(0.78;2.78) | 0.235 |
| Model 1 + smoking behavior | 1.14(0.56;2.32) | 0.727 | 1.55(1.00;2.40) | 0.050 | 1.46(0.60;3.59) | 0.408 | 1.60(0.87;2.96) | 0.132 | 0.82(0.26;2.55) | 0.728 | 1.54(0.82;2.89) | 0.184 |
| Model 1 + alcohol use | 1.20(0.58;2.46) | 0.627 | 1.53(0.99;2.37) | 0.055 | 1.50(0.61;3.69) | 0.376 | 1.58(0.86;2.90) | 0.144 | 0.87(0.28;2.77) | 0.819 | 1.55(0.83;2.92) | 0.173 |
| Model 1 + antidepressant medication | 1.14(0.56;2.34) | 0.719 | **1.61(1.03;2.50)** | **0.036** | 1.52(0.62;3.74) | 0.361 | 1.71(0.91;3.21) | 0.095 | -* | -* | 1.57(0.84;2.96) | 0.160 |
| Model 1 excl. antidepressant users (excluded data n=241) | 1.12(0.53;2.38) | 0.773 | 1.59(0.96;2.64) | 0.073 | 1.48(0.55;3.95) | 0.435 | 1.70(0.83;3.46) | 0.144 | 0.81(0.26;2.53) | 0.713 | 1.54(0.74;3.19) | 0.244 |
| Model 1 excl. baseline MDD from control and missing MDD data (excluded data n=170) | 1.12(0.54;2.28) | 0.766 | **1.54(1.00;2.37)** | **0.049** | 1.44(0.59;3.55) | 0.423 | 1.55(0.85;2.86) | 0.155 | 0.78(0.25;2.44) | 0.667 | 1.58(0.85;2.94) | 0.152 |
| Model 1 + healthy diet score (missing data n=179) | 1.10(0.52;2.34) | 0.801 | **1.70(1.07;2.69)** | **0.024** | 1.69(0.68;4.19) | 0.259 | 1.77(0.91;3.42) | 0.091 | 0.58(0.16;2.09) | 0.408 | 1.70(0.89;3.26) | 0.108 |
| Model 1 + physical activity (missing data n=325) | 1.14(0.54;2.42) | 0.734 | **1.64(1.04;2.61)** | **0.035** | 1.54(0.63;3.80) | 0.348 | 1.72(0.91;3.23) | 0.094 | 0.73(0.20;2.66) | 0.630 | 1.60(0.81;3.19) | 0.179 |
| Model 1 + follow-up duration | 1.12(0.55;2.30) | 0.758 | **1.58(1.03;2.42)** | **0.038** | 1.47(0.60;3.63) | 0.403 | 1.60(0.87;2.93) | 0.132 | 0.80(0.26;2.51) | 0.706 | 1.60(0.86;2.99) | 0.137 |

Reference category = no depressive symptoms (total study population n=3,985, study population ≤ 60 years n=1,956, and study population > 60 years n=2,029). CI indicates confidence interval; WMH, white matter hyperintensities; OSBP, office systolic blood pressure; HDL, high-density lipoprotein; med., medication; CVD, cardiovascular disease; CVA, cardiovascular accident; MDD, major depressive disorder; CSVD, cerebral small vessel disease. Volumes of WMH are log10 transformed. No depressive symptoms are defined as no depression at baseline and follow-up (PHQ-9 <10), persistent depression as depression at baseline and follow-up (PHQ-9 ≥10), and remitted depressive symptoms as depression at baseline (PHQ-9 ≥10) and no depression during follow-up (PHQ-9 <10).

**Model 1:** adjusted for age, sex, educational level, type 2 diabetes mellitus, and intracranial volume (only for WMH volume).

*No anti-depressant users in the remitted group.

## Supplemental Figures

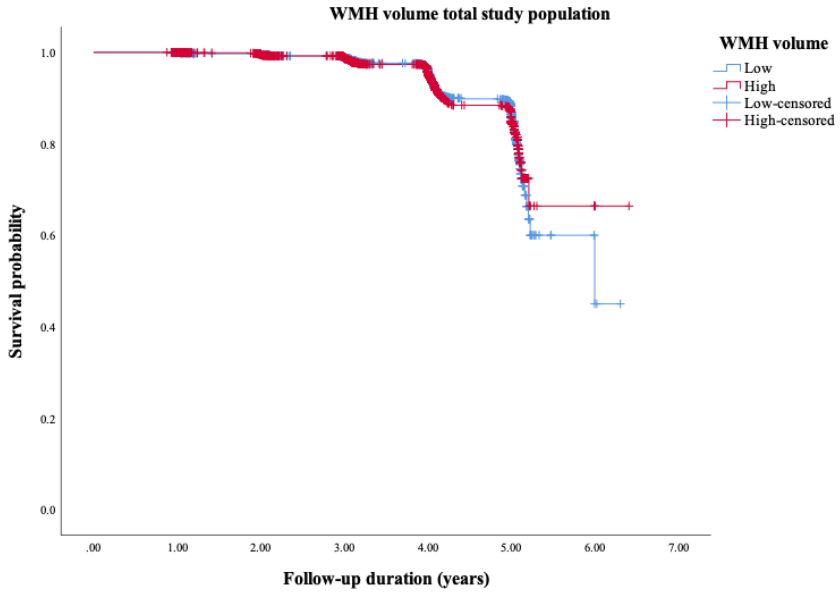


**Figure S2.1a Kaplan-Meier plot for survival probability of incident depressive symptoms by white matter hyperintensity volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a WMH volume below the median. Red line indicates survival probability of incident depressive symptoms for participants with a WMH volume above the median. Median [IQR] is 0.22 [0.07;0.69] ml.

n=4,347. Incident depressive symptoms (PHQ-9 ≥ 10) n=363. WMH indicates white matter hyperintensity; IQR, interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

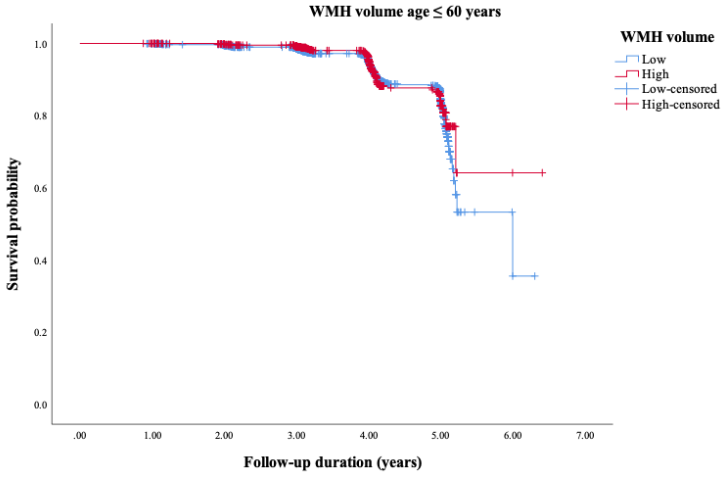


**Figure S2.1b Kaplan-Meier plot for survival probability of incident depressive symptoms by white matter hyperintensity volume**
Blue line indicates survival probability of incident depressive symptoms for participants with a WMH volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a WMH volume above the median for the total study population. Median [IQR] for the total study population is 0.22 [0.07;0.69] ml.
n=2,159. Incident depressive symptoms (PHQ-9 ≥ 10) n=204. WMH indicates white matter hyperintensity; IQR, interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

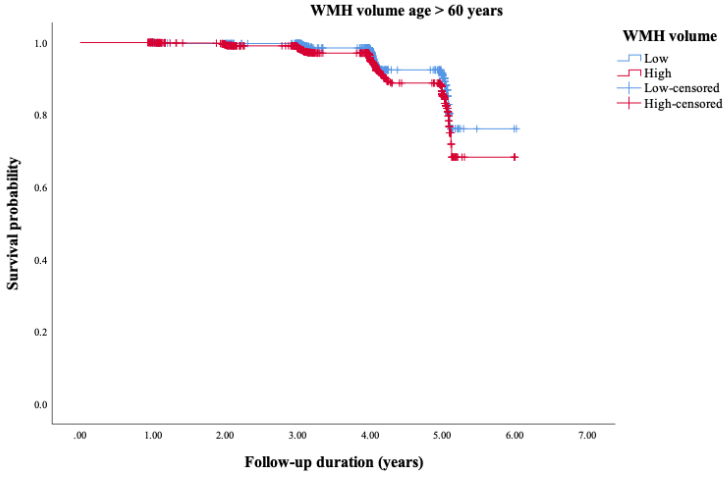


**Figure S2.1c Kaplan-Meier plot for survival probability of incident depressive symptoms by white matter hyperintensity volume**
Blue line indicates survival probability of incident depressive symptoms for participants with a WMH volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a WMH volume above the median for the total study population. Median [IQR] for the total study population is 0.22 [0.07;0.69] ml.
n=2,188. Incident depressive symptoms (PHQ-9 ≥ 10) n=159. WMH indicates white matter hyperintensity; IQR, interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

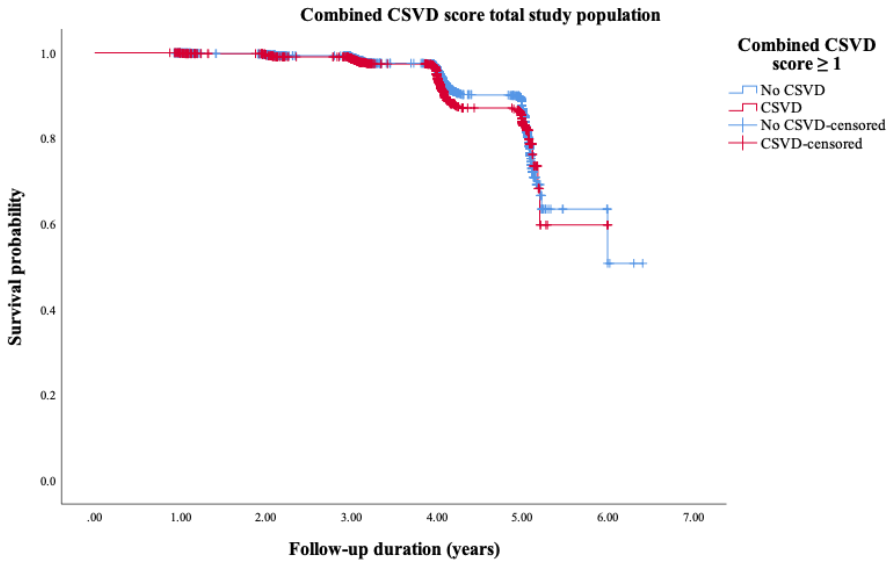


**Figure S2.2a Kaplan-Meier plot for survival probability of incident depressive symptoms by combined cerebral small vessel disease score**

Blue line indicates survival probability of incident depressive symptoms for participants with a combined CSVD score < 1. Red line indicates survival probability of incident depressive symptoms for participants with a combined CSVD score ≥ 1.

n=4,347. Incident depressive symptoms (PHQ-9 ≥ 10) n=363. CSVD indicates cerebral small vessel disease; IQR, interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

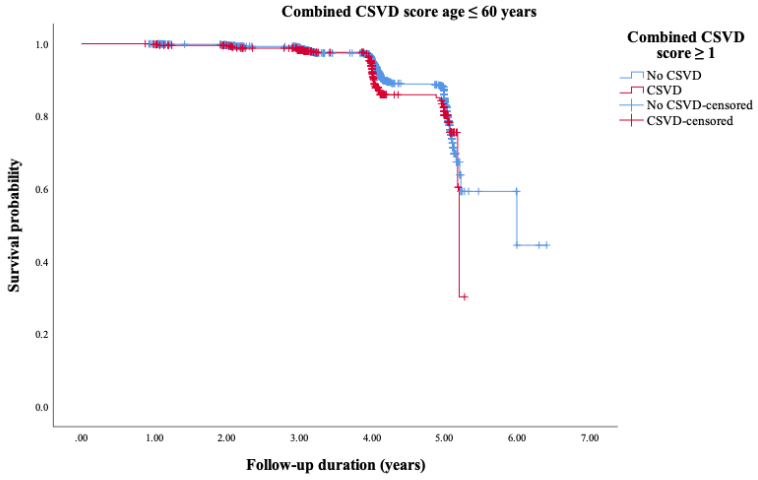


**Figure S2.2b Kaplan-Meier plot for survival probability of incident depressive symptoms by combined cerebral small vessel disease score**

Blue line indicates survival probability of incident depressive symptoms for participants with a combined CSVD score < 1. Red line indicates survival probability of incident depressive symptoms for participants with a combined CSVD score ≥ 1.

n=2,159. Incident depressive symptoms (PHQ-9 ≥ 10) n=204. CSVD indicates cerebral small vessel disease; IQR, interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

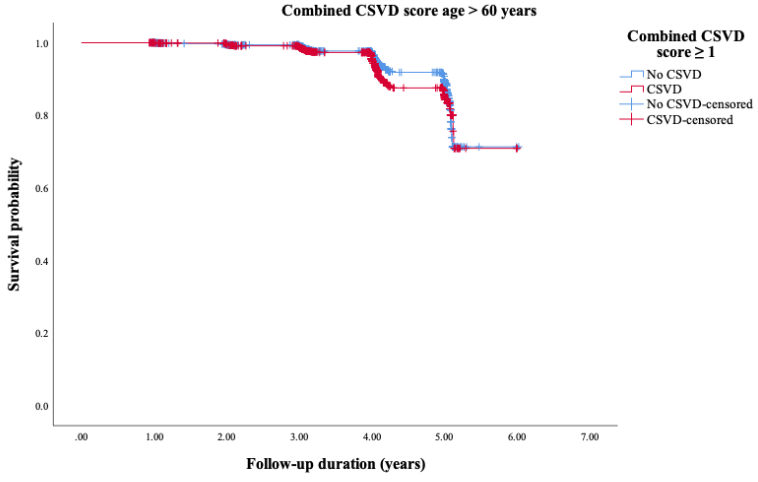


**Figure S2.2c Kaplan-Meier plot for survival probability of incident depressive symptoms by combined cerebral small vessel disease score**

Blue line indicates survival probability of incident depressive symptoms for participants with a combined CSVD score < 1. Red line indicates survival probability of incident depressive symptoms for participants with a combined CSVD score ≥ 1.

n=2,188. Incident depressive symptoms (PHQ-9 ≥ 10) n=159. CSVD indicates cerebral small vessel disease; IQR, interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

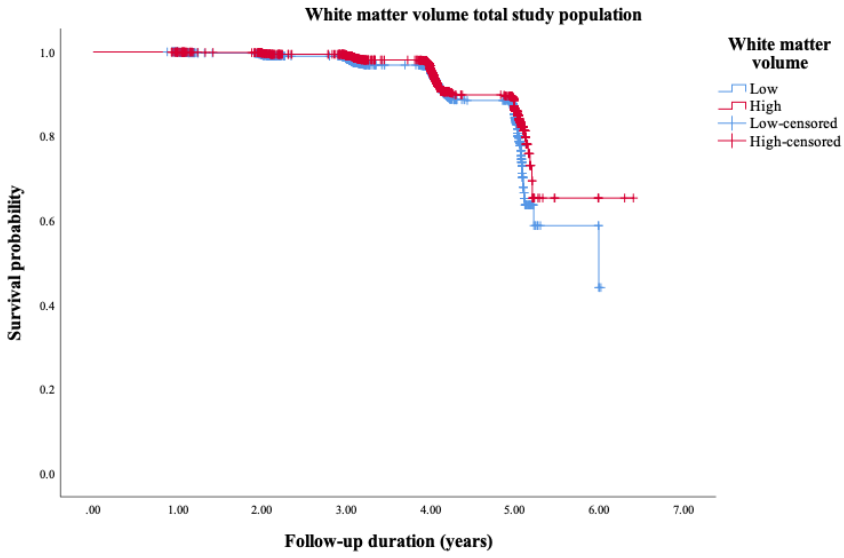


**Figure S2.3a Kaplan-Meier plot for survival probability of incident depressive symptoms by white matter volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a white matter volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a white matter volume above the median for the total study population. Median [IQR] for the total study population is 471.33 [433.85;514.48] ml.

n=4,347. Incident depressive symptoms (PHQ-9 ≥ 10) n=363. IQR indicates interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

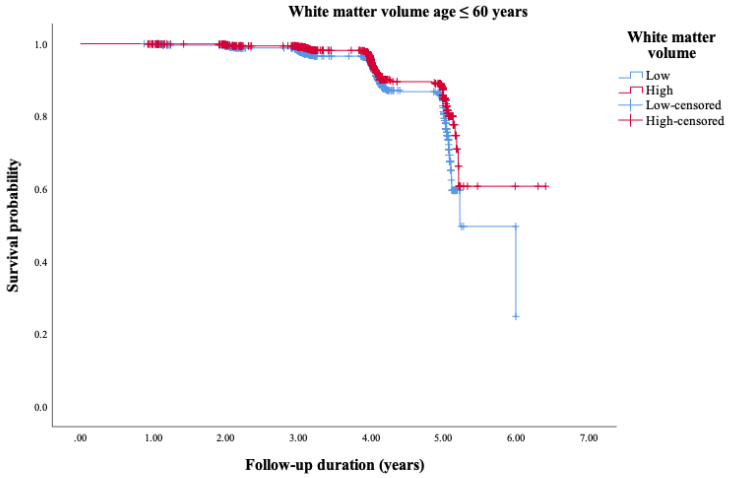


**Figure S2.3b Kaplan-Meier plot for survival probability of incident depressive symptoms by white matter volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a white matter volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a white matter volume above the median for the total study population. Median [IQR] for the total study population is 471.33 [433.85;514.48] ml.

n=2,159. Incident depressive symptoms (PHQ-9 ≥ 10) n=204. IQR indicates interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

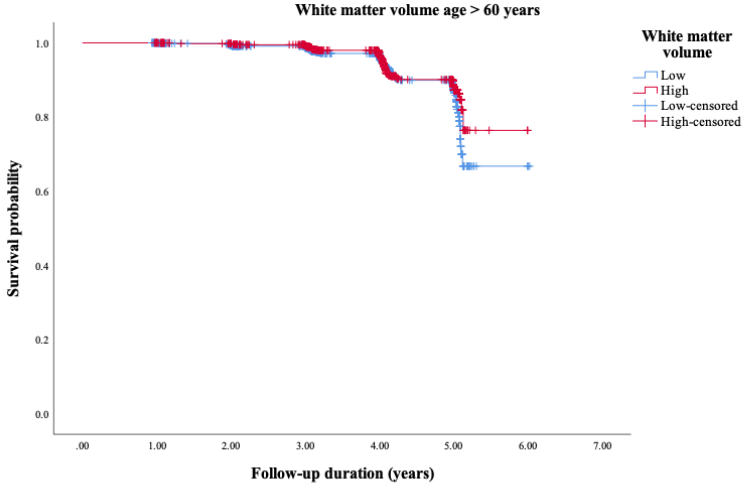


**Figure S2.3c Kaplan-Meier plot for survival probability of incident depressive symptoms by white matter volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a white matter volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a white matter volume above the median for the total study population. Median [IQR] for the total study population is 471.33 [433.85;514.48] ml.

n=2,188. Incident depressive symptoms (PHQ-9 ≥ 10) n=159. IQR indicates interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

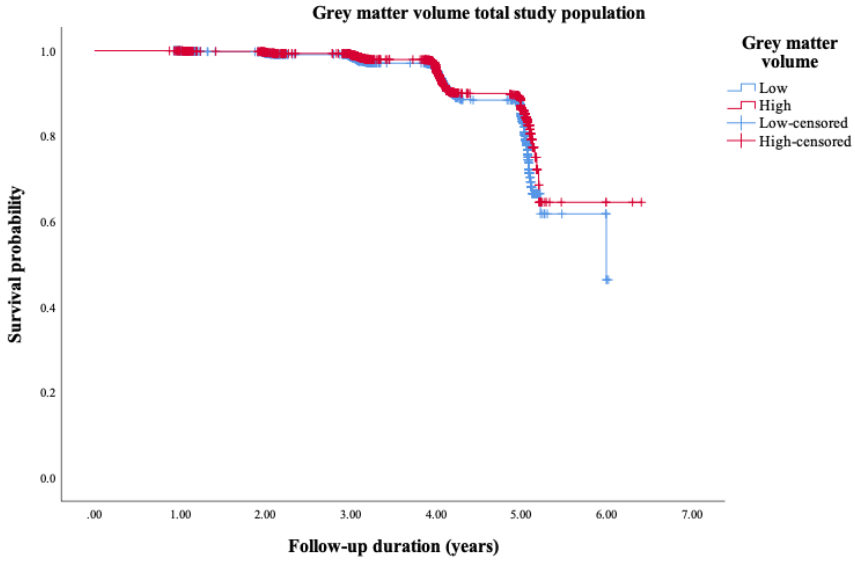


**Figure S2.4a Kaplan-Meier plot for survival probability of incident depressive symptoms by grey matter volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a grey matter volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a grey matter volume above the median for the total study population. Median [IQR] for the total study population is 657.80 [618.55;698.99] ml.

n=4,347. Incident depressive symptoms (PHQ-9 ≥ 10) n=363. IQR indicates interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

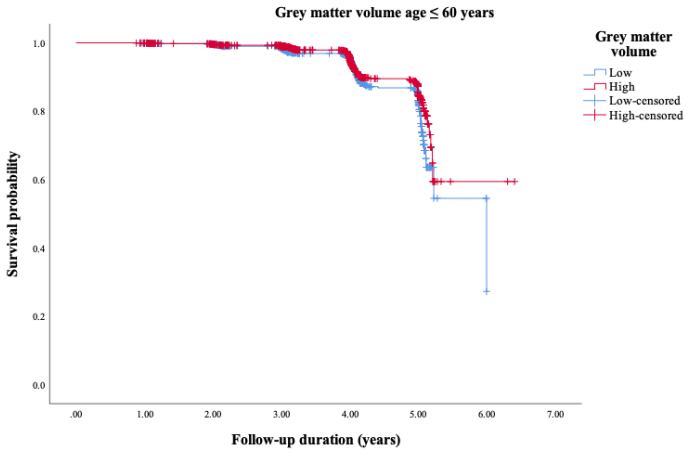


**Figure S2.4b Kaplan-Meier plot for survival probability of incident depressive symptoms by grey matter volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a grey matter volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a grey matter volume above the median for the total study population. Median [IQR] for the total study population is 657.80 [618.55;698.99] ml.

n=2,159. Incident depressive symptoms (PHQ-9 ≥ 10) n=204. IQR indicates interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

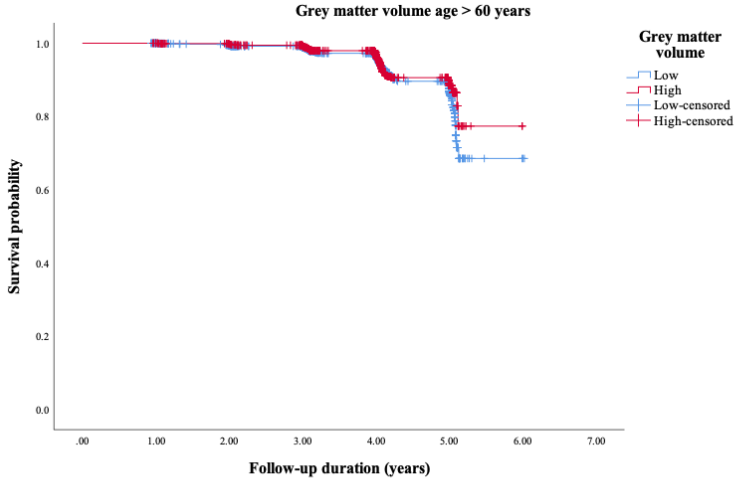


**Figure S2.4c Kaplan-Meier plot for survival probability of incident depressive symptoms by grey matter volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a grey matter volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a grey matter volume above the median for the total study population. Median [IQR] for the total study population is 657.80 [618.55;698.99] ml.

n=2,188. Incident depressive symptoms (PHQ-9 ≥ 10) n=159. IQR indicates interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

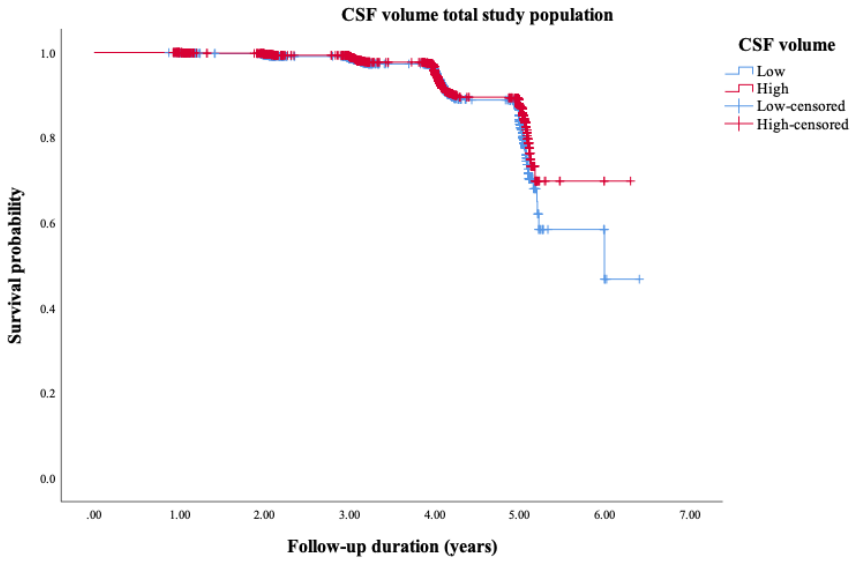


**Figure S2.5a Kaplan-Meier plot for survival probability of incident depressive symptoms by cerebrospinal fluid volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a cerebrospinal fluid volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a grey matter volume above the median for the total study population. Median [IQR] for the total study population is 248.74 [218.16;281.17] ml.

n=4,347. Incident depressive symptoms (PHQ-9 ≥ 10) n=363. CSF indicates cerebrospinal fluid; IQR, interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

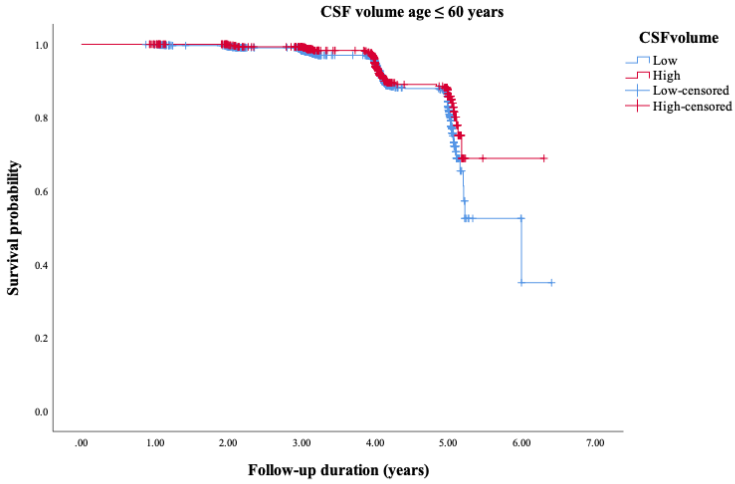


**Figure S2.5b Kaplan-Meier plot for survival probability of incident depressive symptoms by cerebrospinal fluid volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a cerebrospinal fluid volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a grey matter volume above the median for the total study population. Median [IQR] for the total study population is 248.74 [218.16;281.17] ml.

n=2,159. Incident depressive symptoms (PHQ-9 ≥ 10) n=204. CSF indicates cerebrospinal fluid; IQR, interquartile range; PHQ-9, 9 item Patient Health Questionnaire.

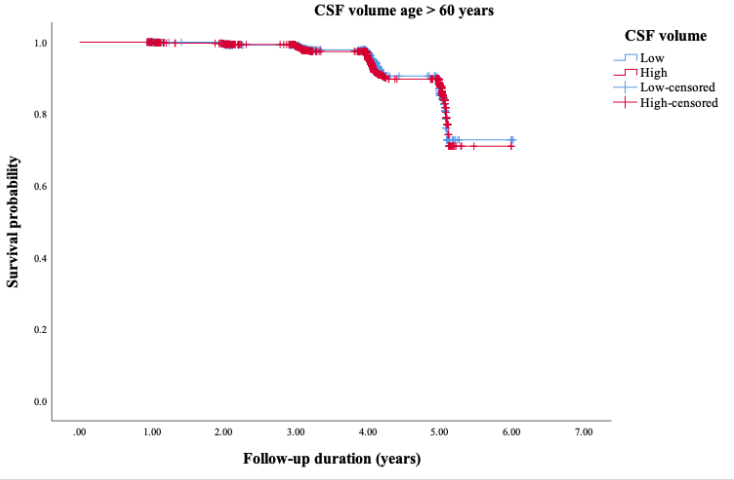


**Figure S2.5c Kaplan-Meier plot for survival probability of incident depressive symptoms by cerebrospinal fluid volume**

Blue line indicates survival probability of incident depressive symptoms for participants with a cerebrospinal fluid volume below the median for the total study population. Red line indicates survival probability of incident depressive symptoms for participants with a grey matter volume above the median for the total study population. Median [IQR] for the total study population is 248.74 [218.16;281.17] ml.

n=2,188. Incident depressive symptoms (PHQ-9 ≥ 10) n=159. CSF indicates cerebrospinal fluid; PHQ-9, 9 item Patient Health Questionnaire.

# Chapter 3

## Association of Markers of Microvascular Dysfunction With Prevalent and Incident Depressive Symptoms - The Maastricht Study

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*Hypertension, 2020*

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**Abstract**

The etiology of late-life depression (LLD) is still poorly understood. Microvascular dysfunction (MVD) has been suggested to play a role in the etiology of LLD, but direct evidence of this association is scarce. The aim of this study was to investigate whether direct and indirect markers of early microvascular dysfunction are associated with prevalent and incident LLD in the population-based Maastricht Study cohort. We measured microvascular dysfunction at baseline by use of flicker light-induced retinal vessel dilation response (Dynamic Vessel Analyzer), heat-induced skin hyperemic response (laser- Doppler flowmetry), and plasma markers of endothelial dysfunction (endothelial dysfunction; sICAM-1 [soluble intercellular adhesion molecule-1], sVCAM-1 [soluble vascular adhesion molecule-1], sE-selectin [soluble E-selectin], and vWF [Von Willebrand Factor]). Depressive symptoms were assessed with the 9-item Patient Health Questionnaire (PHQ-9) at baseline and annually over 4 years of follow-up (n=3029; mean age 59.6±8.2 years, 49.5% were women, n=132 and n=251 with prevalent and incident depressive symptoms [PHQ-9≥10]). We used logistic, negative binominal and Cox regression analyses, and adjusted for demographic, cardiovascular, and lifestyle factors. Retinal venular dilatation and plasma markers of endothelial dysfunction were associated with the more prevalent depressive symptoms after full adjustment (PHQ-9 score, RR, 1.05 [1.00–1.11] and RR 1.06 [1.01–1.11], respectively). Retinal venular dilatation was also associated with prevalent depressive symptoms (PHQ-9≥10; odds ratio, 1.42 [1.09–1.84]), after full adjustment. Retinal arteriolar dilatation and plasma markers of endothelial dysfunction were associated with incident depressive symptoms (PHQ-9≥10; HR, 1.23 [1.04–1.46] and HR, 1.19 [1.05–1.35]), after full adjustment. These findings support the concept that microvascular dysfunction in the retina, and plasma markers of endothelial dysfunction is involved in the etiology of LLD and might help in finding additional targets for the prevention and treatment of LLD.

## Introduction

Late-life depression (LLD) is a complex mood disorder with high comorbidity of psychiatric and physical diseases and cognitive decline.[1–3] Incidence rates of LLD vary from 0.2 to 14.1/100 person-years.[4] LLD has been associated with increased mortality,[5] and its pathophysiology is complex and still poorly understood.[6] Over half of older adults with LLD fail to remit with first line antidepressant medication.[7] It has been suggested that individuals with treatment-resistant LLD might suffer from a vascular subtype of depression and there- fore may not benefit from the current standard care.[8] In light of the increasing elderly population,[9] incidence of LLD will increase. Therefore, it is imperative to gain a better understanding of its etiology.

Increasing evidence suggests that cerebral microvascular dysfunction (MVD) may contribute to the onset of LLD by inducing chronic ischemia in brain tissue.[10] Chronic ischemia results from structural or functional occlusion that may result in cognitive and behavioral problems.[10] When regions of the brain that are involved in mood regulation are affected, this may contribute to the development of depression.[11] Indeed, our recent meta-analysis[12] showed associations of MRI markers of cerebral small vessel disease (CSVD) with incident depression.

Although it has been shown that structural damage in the brain may already start at middle age,[13] most studies related to LLD only included participants >65 years of age when widespread cerebrovascular changes exist. MRI markers of CSVD may reflect structural consequences of long-term MVD, which are themselves preceded by functional changes.[14] MVD can be measured noninvasively in various organs. Direct measures include flicker light–induced retinal arteriolar and venular dilation response and heat-induced skin hyperemia.[15] Indirect markers of MVD include plasma biomarkers of endothelial dysfunction (ED).[16] CSVD is closely linked to brain microvasculature structure, and evidence indicates that CSVD originate from cerebral MVD.[14,17] Retinal arteriolar and venular dilation response are also closely linked to the brain microvasculature.[18] In addition, to the extent that MVD is a generalized phenomenon, plasma biomarkers of ED and skin hyperemia may also reflect brain MVD.[19]

No previous studies have investigated the association between direct markers of MVD with prevalent and incident depressive symptoms. Therefore, the aim of this study was to determine, in a population-based setting of individuals aged

between the 40 and 75 years old, whether markers of MVD as measured in retina, skin, and plasma are associated with prevalent and incident depressive symptoms, independently of demographic, cardiovascular, and lifestyle risk factors.

## Methods

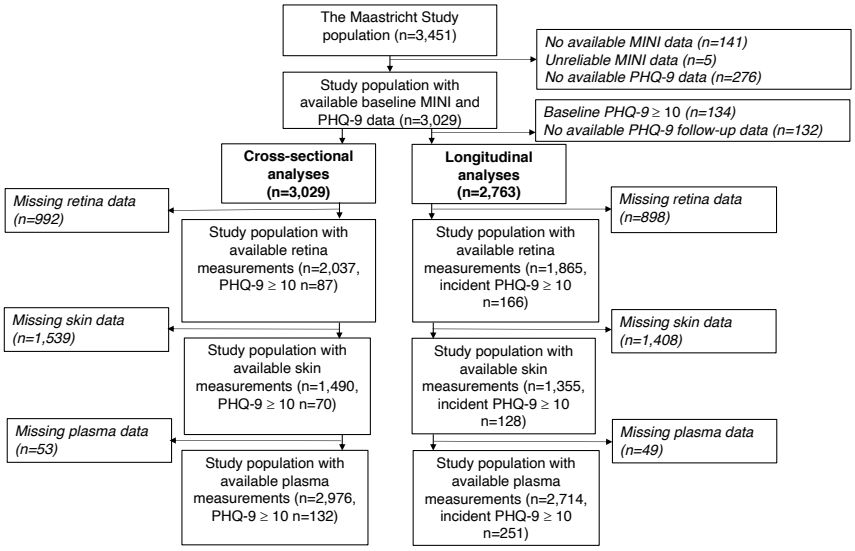
### *Data Availability*

The data of this study derive from The Maastricht Study, but restrictions apply to the availability of these data, which were used under license for the current study. Data are however available from the authors upon reasonable request and with permission of The Maastricht Study management team.

### *Study Population and Design*

We used data from The Maastricht Study, an observational population-based cohort study. The rationale and methodology have been described previously.[20] In brief, the study focuses on the etiology, 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, the municipal registries, and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status. The present report includes data from 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. This study complies with the Declaration of Helsinki and 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. Figure 3.1 shows the flowchart of the study population. The main reasons for missing retina, skin, and plasma data were logistical (no equipment available, no trained researcher available, and technical failure). For longitudinal analyses, participants with prevalent depressive symptoms at baseline (n=134) and without available follow-up data (n=132) were excluded. The averaged follow-up period in this study population (n=2763) was 3.85 years (SD=1.00).

**Figure 3.1 Flowchart of study population**




Missing data on retina and skin measurements were mainly due to logistic reasons (no equipment available, no trained researcher available, and technical failure). MINI indicates Mini-International Neuropsychiatric Interview; and PHQ-9, 9-item Patient Health Questionnaire.

## Materials and Methods

### *Assessment of MVD*

All participants were asked to refrain from smoking and drinking caffeine-containing beverages 3 hours before the measurement.[15] A light meal (breakfast or lunch), low in fat content, was allowed at least 90 minutes before the examination. For retinal measurements, pupils were dilated with 0.5% tropicamide and 2.5% phenylephrine at least 15 minutes before the start of the examination. Skin blood flow measurements were performed in a climate-controlled room at 24°C.[15]

#### *Retinal Arteriolar and Venular Dilation Responses*

Retinal arteriolar and venular dilation to flicker light exposure was measured by the Dynamic Vessel Analyzer (Imedos, Jena, Germany), as previously described.[15] Briefly, a baseline recording of 50 seconds was followed by 40-second flicker light exposure followed by a 60-second recovery period. Baseline retinal and venular diameters were calculated as the average diameter size of the 20 to 50 seconds recording and were expressed in measurement units. Percentage dilation over baseline was based on the average dilation achieved

at time points 10 and 40 seconds during the flicker stimulation period for both the arteriolar and venular response.

*Skin Hyperemic Response*

Heat-induced skin hyperemic response was measured by laser-Doppler flowmetry (Perimed, Järfälla, Sweden), as previously described.[15] Briefly, skin blood flow at the wrist, expressed in arbitrary perfusion units (PU), was recorded unheated for 2 minutes to serve as a baseline. After 2 minutes, the temperature of the laser-Doppler probe was rapidly and locally increased to 44°C and was kept constant until the end of the registration. The heat-induced skin hyperemic response was expressed as the percentage increase in average PU during the 23 minutes heating phase over the 2 minutes average baseline PU.

*Plasma Biomarkers of ED*

Since microvascular endothelium covers ≈98% of the total vascular surface area and synthetic capacity,[21] plasma biomarkers of ED can be regarded as reflecting mainly microvascular ED. sICAM-1 (soluble intercellular adhesion molecule-1), sVCAM-1 (soluble vascular adhesion molecule-1), and sE-selectin (soluble E-selectin) were measured at baseline in ethylenediaminetetraacetic acid (EDTA) plasma samples with commercially available 4-plex sandwich immunoassay kits with different standards and antibodies (Meso Scale Discovery [MSD], Rockville, MD). For this technique in this study, the intra- and inter-assay coefficients of variation were 10.3 and 8.4% for sICAM-1, 5.0 and 4.7% for sVCAM-1, and 2.9 and 7.4% for sE- selectin, respectively. vWF (Von Willebrand Factor) was quantified in citrate plasma using ELISA (Dako, Glostrup, Denmark). The intra- and inter-assay coefficients of variation were 3.0 and 4.3%, respectively. For reasons of statistical efficiency and to reduce the influence of the biological variability of each plasma marker, a standardized averaged sum score of ED was determined according to a predefined cluster of conceptually related biomarkers, as described elsewhere.[22]

### *Depression*

Severity and presence of clinically relevant depressive symptoms (9-item Patient Health Questionnaire [PHQ-9]≥10) were assessed at baseline and during annual follow-up by a validated Dutch version of the PHQ-9.[23] 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 as described previous. When 1 or 2 items were missing, the total-score was calculated as 9×(total points/9−number of missing items) and rounded to the nearest integer. A predefined cutoff score of ≥10 was used as a dichotomous scoring system for defining clinically relevant depressive symptoms.[24] PHQ-9 questionnaires were completed annually by participants during 4 years of follow-up. Incident depressive symptoms were defined as no depressive symptoms at baseline (PHQ-9 <10) and presence of clinically relevant depressive symptoms on at least one follow-up examination (PHQ-9≥10).

Major depressive disorder (MDD) was assessed at baseline by the Mini-International Neuropsychiatric Interview (MINI).[25] The MINI is a short diagnostic structured interview used to assess the presence of MDD in the preceding 2 weeks according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. We also used the MINI to assess lifetime history of MDD by asking about presence of symptoms during minimally 2 weeks in lifetime. The MINI was conducted at baseline only by trained staff members at the research center.

***General Characteristics and Covariates***

General characteristics and covariates were measured at baseline. Educational level (low, intermediate, high), partner status (partner/ no partner), history of cardiovascular diseases, smoking status (never, current, former), alcohol consumption (none, low, high), and physical activity were assessed by questionnaires.[20] We measured, height, weight, waist circumference, office blood pressure, plasma glucose levels, hemoglobin A1c (HbA1c), plasma lipid profile, 24-hour urinary albumin excretion (twice), and plasma biomarkers of low- grade inflammation (LGI; high-sensitivity CRP [C-reactive protein], SAA [serum amyloid A], sICAM-1 [soluble intercellular adhesion molecule-1], IL-6 [interleukin-6], IL-8 [interleukin-8], and TNF-α [tumor necrosis factor alpha]) as described elsewhere.[20,22] sICAM-1 was included in both ED and LGI sum scores, as it is expressed by both monocytes and the endothelium.[26] T2DM status was de- fined by a standardized 2-hour 75-g oral glucose tolerance test after an overnight fast and use of antidiabetic medication as previously described.[20] Urinary albumin excretion was defined as normal (<15 mg/24 hour), micro- (15 to <30 mg/24 hour), and macroalbuminuria (≥30 mg/24 hour). Estimated glomerular filtration rate (eGFR; in mL/ minute per 1.73 m2) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation based on both serum creatinine and serum cystatin C.[27] Medication

use was assessed in a medication interview where generic name, dose, and frequency were registered.

### *Statistical Analysis*

All statistical analyses were performed with Statistical Package for Social Sciences (version 25.0; IBM, Chicago, IL). General characteristics of the study population were presented as mean with SD or as percentages and were evaluated using ANOVA, Mann-Whitney U tests or $\chi 2$ tests, as appropriate. We inversed the flicker light-induced retinal arteriolar and venular dilation and heat-induced skin hyper- emic responses (i.e., multiplying it by –1) to reflect MVD.

PHQ-9 scores were right-skewed and contained many null values. To account for this, we used negative binomial regression analyses to assess the association of markers of MVD with prevalent depressive symptoms (PHQ-9 score). Logistic regression analyses were used to assess the associations of MVD with prevalent clinically relevant depressive symptoms (PHQ-9≥10) and MDD. Cox proportional regression analyses were used to assess the association of MVD with incident depressive symptoms (PHQ-9≥10), with time-in-study as time axis.

We adjusted for several covariates in the analyses. Model 1 was unadjusted. Model 2 was adjusted for age and sex, model 3 was additionally adjusted for T2DM because of the oversampling of T2DM in our study-population, and model 4 was additionally adjusted for systolic blood pressure, use of antihypertensive medication, body mass index, total-to-high-density lipoprotein cholesterol ratio, use of lipid-modifying medication, educational level, and smoking status. We also tested the interactions of the MVD markers with sex and T2DM on prevalent and incident depressive symptoms in the fully adjusted models. A 2-sided *P*-value <0.05 was considered statistically significant.

## Results

### *General Characteristics of the Study Population*

Table S3.1 in the Data Supplement shows the general characteristics of the study population at baseline with available retinal data, stratified for the prevalence and incidence of clinically relevant depressive symptoms. Participants had a mean age of 59.6±8.2 years and 49.4% were women. Participants with depressive symptoms had a worse cardiometabolic risk profile compared with participants without depressive symptoms (Table S3.1). The

study populations on skin and plasma data were mainly comparable with regard to demographics, cardiovascular risk profile, medication use, and lifestyle profile (Tables S3.2 and S3.3). Participants with missing baseline PHQ-9 and MINI data (n=422) were statistically significant older, had a higher BMI and waist circumference, lower GFR levels, and higher levels of HbA1c, triglycerides, ED, and LGI than participants included in the analyses (data not shown).

### *Cross-Sectional Associations of MVD With Prevalent Depression*

Results of the cross-sectional associations are shown in Table 3.1.

**Table 3.1 Cross-sectional associations of markers of microvascular dysfunction with prevalent depressive symptoms and major depressive disorder**

| Model | **Depressive symptoms (PHQ-9 score)** Rate ratio (95% CI) | *P*-value | **Clinically relevant depressive symptoms (PHQ-9≥10)** Odds ratio (95% CI) | *P*-value | **Major depressive disorder (MINI)** Odds ratio (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.05(1.00;1.11) | 0.063 | 1.21(0.97;1.52) | 0.097 | 0.93(0.73;1.18) | 0.556 |
| Model 2 | 1.07(1.02;1.13) | 0.011 | 1.28(1.01;1.63) | 0.039 | 0.94(0.73;1.19) | 0.590 |
| Model 3 | 1.05(0.99;1.10) | 0.089 | 1.22(0.96;1.55) | 0.105 | 0.89(0.70;1.14) | 0.360 |
| Model 4* | 1.04(0.99;1.09) | 0.168 | 1.13(0.89;1.44) | 0.327 | 0.87(0.68;1.12) | 0.270 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.08(1.02;1.14) | 0.005 | 1.51(1.18;1.93) | 0.001 | 1.12(0.87;1.45) | 0.370 |
| Model 2 | 1.08(1.03;1.14) | 0.002 | 1.57(1.22;2.02) | <0.001 | 1.13(0.87;1.46) | 0.349 |
| Model 3 | 1.07(1.02;1.13) | 0.006 | 1.51(1.17;1.94) | 0.001 | 1.10(0.85;1.43) | 0.454 |
| Model 4* | 1.05(1.00;1.11) | 0.049 | 1.42(1.09;1.84) | 0.009 | 1.10(0.84;1.45) | 0.482 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | | | | | |
| Model 1 | 1.02(0.96;1.09) | 0.523 | 1.18(0.90;1.54) | 0.233 | 1.22(0.89;1.66) | 0.224 |
| Model 2 | 1.10(1.03;1.17) | 0.004 | 1.37(1.02;1.83) | 0.034 | 1.28(0.92;1.78) | 0.137 |
| Model 3 | 1.07(1.01;1.14) | 0.035 | 1.27(0.95;1.71) | 0.103 | 1.23(0.89;1.71) | 0.216 |
| Model 4* | 1.05(0.99;1.12) | 0.129 | 1.27(0.93;1.75) | 0.138 | 1.24(0.87;1.76) | 0.242 |
| **Higher ED score (per 1 SD)** | | | | | | |
| Model 1 | 1.09(1.05;1.14) | <0.001 | 1.29(1.11;1.49) | 0.001 | 1.30(1.10;1.54) | 0.002 |
| Model 2 | 1.15(1.10;1.20) | <0.001 | 1.45(1.25;1.67) | <0.001 | 1.35(1.15;1.58) | <0.001 |
| Model 3 | 1.11(1.06;1.15) | <0.001 | 1.31 1.12;1.52) | 0.001 | 1.25(1.05;1.48) | 0.011 |
| Model 4* | 1.06(1.01;1.11) | 0.013 | 1.16(0.97;1.39) | 0.106 | 1.11(0.91;1.36) | 0.317 |

n=2037 (retinal data), n=1490 (skin data), n=1490(skin data), and n=2976(plasma data). PHQ-9 ≥10 in n=87 (retinal data), n=70 (skin data), and n=132 (plasma data). MDD is present in n=66 (retinal data), n=53 (skin data), and n=98 (plasma data).

**Model 1:** unadjusted.

**Model 2:** adjusted for age and sex.

**Model 3:** additionally adjusted for type 2 diabetes mellitus.

**Model 4:** additionally adjusted for office systolic blood pressure, antihypertensive medication, total- to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status, and educational level. ED indicates endothelial dysfunction; MDD, major depressive disorder; MINI, mini-international neuropsychiatric interview; and PHQ-9, 9-item patient health questionnaire.

*Additional data on variables in model 4 were missing in n=54 (retinal data), n=47 (skin data), and n=76 (plasma data).

*Retinal Arteriolar and Venular Dilation Response*

A lower retinal arteriolar dilation response was not associated with more depressive symptoms (rate ratio per SD 1.05 [1.00–1.11]), clinically relevant depressive symptoms (odds ratio [OR] per SD 1.21 [0.97–1.52]), or MDD (OR 0.93 per SD [0.73–1.18]). A lower retinal venular dilation response was associated with more depressive symptoms (rate ratio per SD 1.05 [1.00–1.11]) and with clinically relevant depressive symptoms (OR per SD 1.42 [1.09–1.84]), after full adjustment, but not with MDD (OR 1.12 per SD [0.87–1.45]; Table 3.1). However, there was an interaction of retinal venular dilatation with sex ($P_{interaction}$=0.041) on clinically relevant depressive symptoms only. In stratified analyses, a lower venular dilatation was associated with clinically relevant depressive symptoms in women (OR 1.65 per SD [1.16–2.35]) but not in men (OR 1.12 per SD [0.74–1.68]). No interactions were found for T2DM.

*Heat-Induced Skin Hyperemic Response*

A lower heat-induced skin hyperemic response was associated with more depressive symptoms after adjustment for sex, age and T2DM (rate ratio 1.07 per SD [1.01–1.14]). This association was attenuated after adjustment for cardiovascular risk factors and educational level (rate ratio 1.05 per SD [0.99–1.12]). A lower heat-induced skin hyperemic response was also associated with clinically relevant depressive symptoms (OR, 1.37 per SD [1.02–1.83]), after adjustment for age and sex. After adjustment for T2DM, this association was attenuated (OR, 1.27 per SD [0.95–1.71]). No association was found between heat-induced skin hyperemic response and presence of MDD (OR, 1.22 per SD [0.89–1.66], Table 3.1). No interactions were found for sex or T2DM.

*Plasma Biomarkers of Microvascular Endothelial Dysfunction*

A higher ED score was associated with more depressive symptoms (rate ratio, 1.06 per SD [1.01–1.11]), after full adjustment. In addition, a higher ED score was associated with clinically relevant depressive symptoms and MDD after adjustment for age, sex, and T2DM (OR, 1.31 per SD [1.12– 1.52], and OR, 1.25 per SD [1.05–1.48]). These associations were attenuated after adjustment for cardiovascular risk factors and educational level (OR, 1.16 per SD [0.97–1.39] and OR, 1.11 per SD [0.91–1.36], Table 3.1). Associations of the individual markers of ED were similar in direction and consistent with the associations of the ED score (data not shown). No interactions were found for sex or T2DM.

### *Longitudinal Associations of MVD With Incident Depressive Symptoms*

A lower flicker light–induced retinal arteriolar dilation at baseline was associated with an increased risk of incident depressive symptoms after full adjustment (hazard ratio [HR], 1.23 per SD [1.04–1.46]; Table 3.2). Flicker light–induced retinal venular dilatation at baseline was not associated with incident depressive symptoms (HR, 1.10 per SD [0.94–1.29]). A lower heat-induced skin hyperemic response at baseline was not associated with incident depressive symptoms after adjustment for age and sex (HR, 1.20 per SD [0.98–1.46]). A higher ED score at baseline was associated with an increased risk for incident depressive symptoms after full adjustment (HR, 1.19 per SD [1.05–1.35]; Table 3.2). Associations with the individual markers of ED were similar in direction and consistent with the associations of the ED score (data not shown). No interactions were found for sex or T2DM.

**Table 3.2 Longitudinal associations of markers of microvascular dysfunction with incident depressive symptoms**

| Model | Incident clinically relevant depressive symptoms (PHQ-9≥10) Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | |
| Model 1 | 1.28(1.09;1.51) | 0.003 |
| Model 2 | 1.29(1.09;1.52) | 0.003 |
| Model 3 | 1.23(1.05;1.46) | 0.013 |
| Model 4* | 1.23(1.04;1.46) | 0.018 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | |
| Model 1 | 1.10(0.94;1.29) | 0.238 |
| Model 2 | 1.10(0.94;1.28) | 0.251 |
| Model 3 | 1.07(0.91;1.25) | 0.414 |
| Model 4* | 1.05(0.89;1.23) | 0.567 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | |
| Model 1 | 1.22(1.00;1.48) | 0.046 |
| Model 2 | 1.20(0.98;1.46) | 0.076 |
| Model 3 | 1.16(0.95;1.42) | 0.146 |
| Model 4* | 1.17(0.96;1.43) | 0.130 |
| **Higher ED score (per 1 SD)** | | |
| Model 1 | 1.35(1.21;1.51) | <0.001 |
| Model 2 | 1.37(1.22;1.53) | <0.001 |
| Model 3 | 1.26(1.12;1.41) | <0.001 |
| Model 4* | 1.19(1.05;1.35) | 0.008 |

n=1865 (retina data), n=1355 (skin data), and n=2714 (plasma data).
Incident depressive symptoms in n=166 (retinal data), n=128 (skin data), and n=251 (plasma data).
**Model 1**: unadjusted.
**Model 2:** adjusted for age and sex.
**Model 3:** additionally adjusted for type 2 diabetes mellitus.
**Model 4:** additionally adjusted for office systolic blood pressure, antihypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level. ED indicates endothelial dysfunction; and PHQ-9, 9-item patient health questionnaire. *Additional data on variables in model 4 were missing in n=45(retinal data), n=41(skin data), and n=64 (plasma data).

### *Additional Analyses*

Results of additional analyses are shown in the Data Supplement. Qualitatively similar associations were found after (1) replacing office systolic blood pressure with 24-hour ambulatory systolic blood pressure, and BMI with waist circumference (Tables S3.4 and S3.8), (2) additional adjustment for use of antidepressant medication (prescribed for depression or neuropathy), antipsychotic and anxiolytic medication, antidiabetic and insulin medication, history of cardiovascular disease, LGI, physical activity, alcohol use, or cognitive functioning (Tables S3.5 and S3.9), (3) excluding participants with MDD at baseline for the longitudinal analyses (Table S3.11) using absolute values instead of percentages for the retina and skin analyses (Tables S3.6 and S3.10), and (5) using a control group with only one or no missing follow-up measurements for the incidence analyses (data not shown). The associations between markers of MVD and incident depressive symptoms became slightly stronger after excluding participants with an age of MDD onset of ≤40 years (Table S3.12), the cross-sectional association between a lower retinal venular dilatation and prevalent depressive symptoms attenuated although other cross-sectional analyses did not materially change the results (Table S3.7). Overall MVD, calculated as the standardized average of all MVD markers, resulted in a substantive smaller study population (≈35% of the original) but stronger associations (Table S3.13).

## Discussion

This population-based study demonstrates that functional markers of the microcirculation in the retina and plasma are associated with prevalent and incident depressive symptoms, independently of demographic, cardiovascular, and lifestyle risk factors. These markers of MVD may represent early deficits in the microcirculation because any functional impairments found in our study are likely to precede structural impairments, supporting the concept that early MVD plays a role in the pathophysiology of LLD. However, no association was found between the skin hyperemic response and prevalent or incident depressive symptoms after full adjustment, nor between any marker of MVD with prevalent MDD.

Our results are in line with previous studies on plasma markers of ED,[16,22] and retinal diameters in individuals with T2DM,[28] and provide additional evidence for the association of attenuated microvascular reactivity in the retina in individuals with depression in the general population. However, differences were found

between the retinal arteriolar and venular microvascular reactivity. A lower retinal arteriolar response at baseline was associated only with a higher incidence of depressive symptoms. A lower retinal venular response at baseline was associated only with a higher prevalence of depressive symptoms at baseline in women, not in men. These differences may have been a result of underlying pathophysiological differences. Central retinal arteriolar diameters and central retinal venular diameters have been associated with different risk factors. A smaller central retinal arteriolar diameter has been associated with current alcohol consumption, blood pressure, and body mass index, although a larger CRVE has additionally been associated with serum HDL cholesterol, smoking, diabetes mellitus, and inflammation markers,[29] suggesting different effects of these risk factors on arterioles and venules. Although we measured arteriolar and venular reactivity instead of diameters, similar differences in effects may have contributed to the observed differences in the associations between retinal arteriolar and venular reactivity and depression. The associations between the skin hyperemic response and depressive symptoms became nonsignificant after adjustment for cardiovascular risk factors. The absence of this association could be because of lack of power because the study population with skin data comprised only half the number of participants of the plasma marker study population. Alternatively, the association between the skin hyperemic response and depressive symptoms may be mediated by cardiovascular risk factors. Cardiovascular risk factors might be on the causal path and our final models may thus be overadjusted. For example, T2DM and hypertension are associated with both MVD and depression,[30,31] adjustment for these variables may lead to overadjustment since part of the variance between MVD and depression is explained by these variables. Furthermore, different mechanisms may be involved in skin hyperemic response as compared with dilatation in both the retinal arterioles and venules.

Several pathophysiological mechanisms may be involved in the association of MVD with LLD.[10] First, arterioles are responsible for distributing blood according to metabolic demand.[32] ED of vessels supplying the brain may contribute to disruption of the normal distribution of blood and induce chronic ischemia. Second, tight junctions of the cerebral endothelial cells constitute the blood-brain barrier.[32] Loss of normal endothelial function may contribute to blood-brain barrier disruption and to leakage of blood cells and/or fluid, which causes disruption of the normal architecture, including damaged arteriolar smooth muscle cells and fibrin depositions.[10] Third, venules collect capillary blood and play a role in determining capillary pressure.[30] ED and blood-brain barrier

disruption may lead to venular wall collagenosis and thickening, which may obstruct blood flow and impair the perivascular drainage through the brain, contributing to cerebral ischemia.[33] Fourth, ED impairs neurovascular coupling, the mechanism responsible for regulation of the blood flow to different parts of the brain in according to the metabolic demand.[34]

Strengths of our study include its large sample size and population-based longitudinal design; the annual assessment of the PHQ-9 to assess depressive symptoms over a 4-year period; the use of the MINI to assess MDD at baseline; the comparable incidence rate of depression to other population-based studies; the extensive assessment of potential confounders used in main and additional analyses; and the use of multiple direct measures of specific MVD. All markers of MVD included in the present study are likely to reflect MVD, probably in conjunction with vascular smooth muscle cell dysfunction and/or neuronal dysfunction.[35–37] Impairments in both flicker light–induced retinal dilation and heat-induced skin hyperemia have been shown to be partly nitric oxide-dependent.[38,39] Plasma biomarkers of ED also reflect microvascular endothelial function because ≈98% of the endothelium is located in the microcirculation.[21]

This study has some limitations. First, there could have been selection and/or attrition bias, which is inherent to prospective population-based studies; individuals with more severe depressive symptoms or with greater comorbidity may have been more likely not to participate or to withdraw. Although the dropout rate was relatively low, this may have led to an underestimation of the observed findings. Second, the study population was well treated with regard to cardiovascular risk factors, which may have led to less variations in MVD. As a result, the effects of MVD in this study may have been suppressed and associations may be stronger in individuals with more severe MVD. In addition, the population was mainly of white ethnicity; heterogeneous with respect to their histories of depression; and aged 40 to 75 years, which should be considered when extrapolating these findings to other populations. Finally, longitudinal data only included depressive symptoms as measured with the PHQ-9 questionnaire. The PHQ-9 questionnaire is a screening instrument to measure depressive symptoms that consists of the criteria upon which MDD is based.[23] High scores on the PHQ-9 are suggestive for depressive symptoms but do not necessarily equate with MDD.

In conclusion, we show that markers of early MVD in the retina and plasma are associated with prevalent and incident depressive symptoms in the general

population, independently of major demographic, cardiovascular, and lifestyle risk factors.

**Perspectives**

These findings support the concept that early generalized MVD is associated with the development of LLD and may play a role in its pathophysiology. MVD might, therefore, be a target for prevention strategies and treatment of LLD. Evidence suggests that lifestyle modifications, such as weight loss and exercise, may, at least in part, favorably influence MVD.[40] In addition, drugs, such as renin-angiotensin-aldosterone system inhibitors and antihyperglycemic agents (i.e., metformin and GLP-1R [glucagon-like peptide 1 receptor] agonists), may improve microvascular function, possibly beyond their blood pressure- or glucose-lowering effects.[41] Other longitudinal population-based studies are needed to replicate these findings.

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## Supplemental Material to Chapter 3

## Supplemental Tables

**Table S3.1 General characteristics and markers of microvascular dysfunction of the retinal study population at baseline according to depression status**

| Characteristic | No depressive symptoms at baseline or follow up (PHQ9<10) (n=1,699) | Prevalent depressive symptoms (PHQ9≥10) (n=87) | *P*-value* | Incident depressive symptoms (PHQ9≥10) (n=166) | *P*-value* |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (years) | 59.6±8.1 | 57.2±7.5 | 0.007 | 59.8±8.4 | 0.826 |
| Sex (% female) | 49.4 | 65.5 | 0.004 | 46.4 | 0.465 |
| Educational level, low/medium/high (%) | 28.0/29.3/42.6 | 36.1/34.9/28.9 | 0.017 | 44.8/30.9/24.2 | <0.001 |
| Partner status (% partner) | 86.6 | 72.6 | 0.001 | 81.3 | 0.077 |
| Depressive symptoms (PHQ-9 score) | 2.0±2.1 | 13.8±3.6 | <0.001 | 4.5±2.6 | <0.001 |
| Major depressive disorder (MINI) (%) | 1.1 | 39.1 | <0.001 | 6.0 | <0.001 |
| **Cardiovascular risk factors** | | | | | |
| Body mass index (kg/m$^2$) | 26.6±4.2 | 28.7±5.8 | <0.001 | 28.2±4.9 | <0.001 |
| Waist circumference (cm) | 94.4±13.1 | 99.6±16.6 | <0.001 | 99.2±14.9 | <0.001 |
| Office systolic BP (mmHg) | 134.8±17.8 | 134.6±19.1 | 0.909 | 135.1±17.0 | 0.825 |
| Office diastolic BP (mmHg) | 76.4±9.7 | 77.4±11.0 | 0.315 | 76.0±10.7 | 0.693 |
| Hypertension (%) | 54.1 | 61.1 | 0.153 | 61.4 | 0.073 |
| Type 2 diabetes mellitus (%)† | 23.1 | 39.8 | <0.001 | 39.8 | <0.001 |
| HbA1c (mmol/mol) | 39.9±9.1 | 44.9±16.8 | <0.001 | 43.4±10.4 | <0.001 |
| Total-to-HDL cholesterol | 3.6±1.1 | 3.8±1.3 | 0.073 | 3.7±1.2 | 0.077 |
| Triglycerides (mmol/l) | 1.4±0.8 | 1.8±0.9 | <0.001 | 1.7±1.2 | <0.001 |
| eGFR (ml/min/1.73m$^2$) | 88.7±14.0 | 89.5±14.5 | 0.617 | 86.8±17.4 | 0.118 |
| Albuminuria, normal/micro/macro (%) | 93.2/6.3/0.5 | 82.3/17.7/0.0 | <0.001 | 85.8/12.3/1.9 | 0.001 |
| History of CVD (%) | 13.9 | 21.7 | 0.054 | 25.2 | <0.001 |
| LGI score | -0.02±0.56 | 0.10±0.47 | 0.054 | 0.07±0.77 | 0.052 |
| **Medication use** | | | | | |
| Anti-depressive medication (%) | 4.9 | 25.3 | <0.001 | 18.1 | <0.001 |
| Anxiolytic medication (%) | 1.1 | 13.8 | <0.001 | 7.2 | <0.001 |
| Sleep medication (%) | 1.9 | 5.7 | 0.035 | 3.0 | 0.382 |
| Anti-psychotic medication (%) | 0.1 | 4.6 | <0.001 | 1.8 | 0.006 |
| Anti-diabetic medication, all types (%) | 18.5 | 33.3 | 0.001 | 34.3 | <0.001 |
| Anti-diabetic medication, insulin (%) | 4.9 | 14.9 | 0.001 | 10.2 | 0.010 |
| Anti-hypertensive medication (%) | 36.0 | 51.7 | 0.004 | 47.6 | 0.004 |
| Lipid-modifying medication (%) | 33.2 | 44.8 | 0.027 | 42.3 | 0.016 |
| **Lifestyle factors** | | | | | |
| Smoking, never/former/current (%) | 36.6/53.2/10.2 | 24.1/49.4/26.5 | <0.001 | 28.5/52.1/19.4 | 0.002 |
| Alcohol use, none/low/high (%) | 15.2/57.5/27.3 | 31.3/44.6/24.1 | <0.001 | 25.5/54.5/20.0 | 0.001 |
| Physical activity (hours/week) | 14.2±7.9 | 13.7±9.3 | 0.580 | 12.0±7.8 | 0.001 |
| **Markers of microvascular function** | | | | | |
| Retinal arteriolar baseline diameter (MU) | 115.2±15.5 | 115.4±16.0 | 0.869 | 116.8±16.0 | 0.199 |
| Retinal arteriolar average dilation (%) | 3.1±2.8 | 2.5±2.7 | 0.058 | 2.4±2.6 | 0.001 |
| Retinal venular baseline diameter (MU) | 146.4±20.3 | 148.9±22.4 | 0.261 | 146.0±21.2 | 0.813 |
| Retinal venular average dilation (%) | 3.9±2.2 | 3.1±1.9 | 0.001 | 3.7±2.2 | 0.240 |
| Baseline skin blood flow (PU) | 11.0±6.3 | 11.4±6.9 | 0.698 | 11.7±7.2 | 0.365 |
| Skin hyperemic response (%) | 1164.5±811.0 | 942.6±550.1 | 0.055 | 1052.0±755.0 | 0.204 |
| sICAM-1 (ng/ml) | 351±89 | 394±162 | <0.001 | 374±105 | 0.002 |
| sVCAM-1 (ng/ml) | 426±97 | 429±128 | 0.789 | 448±127 | 0.009 |
| sE-selectin (ng/ml) | 114±58 | 137±83 | 0.001 | 124±92 | 0.074 |
| vWF (%) | 131±47 | 133±58 | 0.680 | 141±52 | 0.008 |
| ED score | -0.04±0.61 | 0.17±0.95 | 0.003 | 0.15±0.85 | <0.001 |

Data are presented as mean ± SD or percentage as appropriate, and stratified for clinically relevant depressive symptoms. PHQ indicates patient health questionnaire; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; LGI, low-grade inflammation; PU, perfusion units; MU, measurement units; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1; sE-selectin, soluble E-selectin; vWF; von Willebrand factor; ED, endothelial dysfunction. *Compared to no depressive symptoms at baseline and follow-up. †Study design is oversampled with individuals with type 2 diabetes for reasons of efficiency.

**Table S3.2 General characteristics and markers of microvascular dysfunction of the skin study population at baseline according to depression status**

| Characteristic | No depressive symptoms at baseline or follow up (PHQ9<10) (n=1,227) | Prevalent depressive symptoms (PHQ9≥10) (n=70) | *P*-value* | Incident depressive symptoms (PHQ9≥10) (n=128) | *P*-value* |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (years) | 60.3 ± 8.0 | 56.8 ± 7.5 | <0.001 | 60.3 ± 7.6 | 0.991 |
| Sex (% female) | 48.1 | 67.1 | 0.002 | 40.6 | 0.114 |
| Educational level, low/medium/high (%) | 29.9/28.0/42.2 | 45.5/31.8/22.7 | 0.001 | 38.4/39.2/20.0 | <0.001 |
| Partner status (% partner) | 86.9 | 77.6 | 0.042 | 80.0 | 0.040 |
| Depressive symptoms (PHQ-9 score) | 2.0 ± 2.1 | 13.7 ± 3.8 | <0.001 | 4.5 ± 2.8 | <0.001 |
| Major depressive disorder (MINI) (%) | 1.1 | 37.1 | <0.001 | 9.4 | <0.001 |
| **Cardiovascular risk factors** | | | | | |
| Body mass index (kg/m$^2$) | 26.7 ± 4.2 | 30.0 ± 6.1 | <0.001 | 27.9 ± 4.5 | 0.003 |
| Waist circumference (cm) | 95.1 ± 13.0 | 103.3 ± 17.2 | <0.001 | 99.0 ± 13.6 | 0.002 |
| Office systolic BP (mmHg) | 135.5 ± 17.9 | 139.1 ± 19.1 | 0.110 | 136.9 ± 19.6 | 0.419 |
| Office diastolic BP (mmHg) | 76.3 ± 9.3 | 80.6 ± 10.6 | <0.001 | 77.2 ± 11.3 | 0.279 |
| Hypertension (%) | 57.3 | 67.1 | 0.108 | 61.7 | 0.348 |
| Type 2 diabetes mellitus (%)† | 24.9 | 48.6 | <0.001 | 39.8 | 0.001 |
| HbA1c (mmol/mol) | 40.8 ± 8.9 | 46.7 ± 16.5 | <0.001 | 45.2 ± 12.1 | <0.001 |
| Total-to-HDL cholesterol | 3.6 ± 1.1 | 3.6 ± 1.0 | 0.919 | 4.0 ± 1.3 | 0.001 |
| Triglycerides (mmol/l) | 1.4 ± 0.8 | 1.7 ± 0.8 | 0.002 | 1.8 ± 1.5 | <0.001 |
| eGFR (ml/min/1.73m$^2$) | 88.4 ± 14.4 | 88.9 ± 15.4 | 0.775 | 87.7 ± 14.5 | 0.601 |
| Albuminuria, normal/micro/macro (%) | 93.2/6.2/0.6 | 82.5/17.5/0.0 | 0.002 | 87.6/12.4/0.0 | 0.025 |
| History of CVD (%) | 16.2 | 29.9 | 0.007 | 21.6 | 0.130 |
| LGI score | -0.02 ± 0.52 | 0.12 ± 0.51 | 0.031 | 0.08 ± 0.85 | 0.045 |
| **Medication use** | | | | | |
| Anti-depressive medication (%) | 5.6[b] | 31.4 | <0.001 | 14.8 | <0.001 |
| Anxiolytic medication (%) | 1.5 | 15.7 | <0.001 | 4.7 | 0.020 |
| Sleep medication (%) | 2.5 | 5.7 | 0.106 | 0.0 | 0.106 |
| Anti-psychotic medication (%) | 0.2 | 8.6 | <0.001 | 0.8 | 0.328 |
| Anti-diabetic medication, all types (%) | 20.0 | 42.9 | <0.001 | 35.9 | <0.001 |
| Anti-diabetic medication, insulin (%) | 5.7 | 20.0 | <0.001 | 12.5 | 0.006 |
| Anti-hypertensive medication (%) | 39.2 | 57.1 | 0.004 | 50.0 | 0.023 |
| Lipid-modifying medication (%) | 37.2 | 47.1 | 0.100 | 41.4 | 0.388 |
| **Life style factors** | | | | | |
| Smoking, never/former/current (%) | 33.8/55.7/10.4 | 23.9/47.8/28.4 | 0.002 | 28.0/56.8/15.2 | 0.101 |
| Alcohol use, none/low/high (%) | 14.6/55.9/29.4 | 39.4/37.9/22.7 | <0.001 | 28.8/53.6/17.6 | <0.001 |
| Physical activity (hours/week) | 14.0 ± 7.6 | 13.2 ± 9.9 | 0.443 | 13.4 ± 8.7 | 0.462 |
| **Markers of microvascular function** | | | | | |
| Retinal arteriolar baseline diameter (MU) | 116.0 ± 16.2 | 113.6 ± 15.0 | 0.316 | 116.0 ± 17.1 | 0.991 |
| Retinal arteriolar average dilation (%) | 3.1 ± 2.9 | 2.0 ± 2.6 | 0.011 | 2.4 ± 2.5 | 0.026 |
| Retinal venular baseline diameter (MU) | 147.1 ± 20.9 | 142.7 ± 22.6 | 0.151 | 146.1 ± 21.9 | 0.681 |
| Retinal venular average dilation (%) | 3.8 ± 2.1 | 2.8 ± 1.8 | 0.001 | 3.6 ± 2.1 | 0.214 |
| Baseline skin blood flow (PU) | 11.1 ± 6.5 | 11.4 ± 6.8 | 0.699 | 11.5 ± 6.7 | 0.490 |
| Skin hyperemic response (%) | 1147.9 ± 786.0 | 1021.15 ± 713.4 | 0.184 | 1027.9 ± 704.1 | 0.096 |
| sICAM-1 (ng/ml) | 354 ± 88 | 395 ± 170 | 0.001 | 370 ± 95 | 0.074 |
| sVCAM-1 (ng/ml) | 435 ± 96 | 434 ± 145 | 0.951 | 450 ± 131 | 0.094 |
| sE-selectin (ng/ml) | 115 ± 59 | 141 ± 85 | 0.002 | 126 ± 105 | 0.074 |
| vWF (%) | 132 ± 47 | 136 ± 57 | 0.440 | 135 ± 47 | 0.438 |
| ED score | -0.01 ± 0.61 | 0.21 ± 1.00 | 0.006 | 0.13 ± 0.88 | 0.029 |

Data are presented as means ± SD or percentage as appropriate, and stratified for clinically relevant depressive symptoms. PHQ indicates patient health questionnaire; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; LGI, low-grade inflammation; PU, perfusion units; MU, measurement units; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1; sE-selectin, soluble E-selectin; vWF; von Willebrand factor; ED, endothelial dysfunction. *Comparison to no depressive symptoms at baseline and follow-up. †Study design is oversampled with individuals with type 2 diabetes for reasons of efficiency.

**Table S3.3 General characteristics and markers of microvascular dysfunction of the plasma study population at baseline according to depression status**

| Characteristic | No depressive symptoms at baseline or follow up (PHQ9<10) (n=2,463) | Prevalent depressive symptoms (PHQ9≥10) (n=132) | *P*-value* | Incident depressive symptoms (PHQ9≥10) (n=251) | *P*-value* |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age (years) | 59.8 ± 8.1 | 55.9 ± 7.7 | <0.001 | 59.8 ± 8.2 | 0.952 |
| Sex (% female) | 48.9 | 59.1 | 0.025 | 47.8 | 0.791 |
| Educational level, low/medium/high (%) | 29.6/28.6/41.8 | 39.8/32.8/27.3 | 0.001 | 42.1/30.8/27.1 | <0.001 |
| Partner status (% partner) | 85.7 | 73.6 | 0.001 | 83.1 | 0.257 |
| Depressive symptoms (PHQ-9 score) | 2.0 ± 2.1 | 14.0 ± 4.0 | <0.001 | 4.6 ± 2.7 | <0.001 |
| Major depressive disorder (MINI) (%) | 0.9 | 40.2 | <0.001 | 7.6 | <0.001 |
| **Cardiovascular risk factors** | | | | | |
| Body mass index (kg/m$^2$) | 26.7 ± 4.3 | 29.4 ± 6.1 | <0.001 | 28.3 ± 5.0 | <0.001 |
| Waist circumference (cm) | 94.7 ± 13.1 | 101.9 ± 18.0 | <0.001 | 99.4 ± 14.8 | <0.001 |
| Office systolic BP (mmHg) | 134.6 ± 17.9 | 135.0 ± 17.1 | 0.820 | 135.7 ± 19.0 | 0.386 |
| Office diastolic BP (mmHg) | 76.1 ± 9.7 | 77.6 ± 10.7 | 0.091 | 76.1 ± 11.0 | 0.947 |
| Hypertension (%) | 54.5 | 62.1 | 0.089 | 62.2 | 0.020 |
| Type 2 diabetes mellitus (%)† | 23.1 | 41.7 | <0.001 | 39.8 | <0.001 |
| HbA1c (mmol/mol) | 40.2 ± 8.8 | 45.4 ± 16.4 | <0.001 | 44.6 ± 11.9 | <0.001 |
| Total-to-HDL cholesterol | 3.6 ± 1.1 | 3.9 ± 1.5 | 0.013 | 3.8 ± 1.3 | 0.007 |
| Triglycerides (mmol/l) | 1.4 ± 0.8 | 1.7 ± 0.9 | <0.001 | 1.7 ± 1.4 | <0.001 |
| eGFR (ml/min/1.73m$^2$) | 88.5 ± 14.3 | 90.0 ± 15.8 | 0.255 | 87.0 ± 16.8 | 0.125 |
| Albuminuria, normal/micro/macro (%) | 92.7/6.6/0.7 | 82.1/17.1/0.9 | <0.001 | 86.3/12.0/1.7 | 0.001 |
| History of CVD (%) | 14.5 | 22.8 | 0.015 | 26.9 | <0.001 |
| LGI score | -0.02 ± 0.53 | 0.08 ± 0.42 | 0.026 | 0.04 ± 0.63 | 0.069 |
| **Medication use** | | | | | |
| Anti-depressive medication (%) | 4.8 | 29.5 | <0.001 | 15.1 | <0.001 |
| Anxiolytic medication (%) | 1.5 | 16.7 | <0.001 | 6.8 | <0.001 |
| Sleep medication (%) | 1.9 | 4.5 | 0.046 | 2.8 | 0.333 |
| Anti-psychotic medication (%) | 0.2 | 7.6 | <0.001 | 1.2 | 0.031 |
| Anti-diabetic medication, all types (%) | 18.4 | 35.6 | <0.001 | 35.1 | <0.001 |
| Anti-diabetic medication, insulin (%) | 5.1 | 15.9 | <0.001 | 13.1 | <0.001 |
| Anti-hypertensive medication (%) | 37.2 | 50.0 | 0.004 | 49.8 | <0.001 |
| Lipid-modifying medication (%) | 33.6 | 42.4 | 0.047 | 42.6 | 0.005 |
| **Life style factors** | | | | | |
| Smoking, never/former/current (%) | 36.6/52.5/10.9 | 24.2/47.7/28.1 | <0.001 | 29.6/50.2/20.2 | <0.001 |
| Alcohol use, none/low/high (%) | 15.5/56.4/28.1 | 35.9/44.5/19.5 | <0.001 | 26.0/54.9/19.1 | <0.001 |
| Physical activity (hours/week) | 14.4 ± 8.0 | 13.2 ± 9.1 | 0.096 | 12.8 ± 8.8 | 0.004 |
| **Markers of microvascular function** | | | | | |
| Retinal arteriolar baseline diameter (MU) | 115.2 ± 15.4 | 115.6 ± 16.0 | 0.790 | 116.6 ± 15.6 | 0.253 |
| Retinal arteriolar average dilation (%) | 3.1 ± 2.8 | 2.6 ± 2.7 | 0.070 | 2.5 ± 2.6 | 0.004 |
| Retinal venular baseline diameter (MU) | 146.4 ± 20.4 | 149.1 ± 22.5 | 0.247 | 145.8 ± 21.4 | 0.692 |
| Retinal venular average dilation (%) | 3.9 ± 2.2 | 3.1 ± 1.9 | 0.001 | 3.8 ± 2.2 | 0.313 |
| Baseline skin blood flow (PU) | 11.1 ± 6.5 | 11.5 ± 6.9 | 0.682 | 11.6 ± 6.7 | 0.451 |
| Skin hyperemic response (%) | 1146.6 ± 784.8 | 1016.5 ± 717.5 | 0.175 | 1018.1 ± 693.8 | 0.077 |
| sICAM-1 (ng/ml) | 347 ± 88 | 388 ± 141 | <0.001 | 373 ± 100 | <0.001 |
| sVCAM-1 (ng/ml) | 425 ± 96 | 434 ± 129 | 0.288 | 443 ± 119 | 0.006 |
| sE-selectin (ng/ml) | 114 ± 57 | 133 ± 77 | <0.001 | 126 ± 89 | 0.003 |
| vWF (%) | 131 ± 47 | 134 ± 56 | 0.434 | 139 ± 50 | 0.008 |
| ED score | -0.06 ± 0.61 | 0.16 ± 0.86 | <0.001 | 0.14 ± 0.81 | <0.001 |

Data are presented as means ± SD or percentage as appropriate, and stratified for clinically relevant depressive symptoms. PHQ indicates patient health questionnaire; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; LGI, low-grade inflammation; PU, perfusion units; MU, measurement units; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1; sE-selectin, soluble E-selectin; vWF; von Willebrand factor; ED, endothelial dysfunction.

*Comparison to no depressive symptoms at baseline and follow-up.

†Study design is oversampled with individuals with type 2 diabetes for reasons of efficiency.

**Table S3.4 Cross-sectional associations of markers of microvascular dysfunction with prevalent depressive symptoms and major depressive disorder with replacement of office systolic blood pressure by 24h ambulatory systolic blood pressure and replacement of BMI by waist circumference**

| Model | **Depressive symptoms (PHQ-9 score)** Rate ratio (95% CI) | *P*-value | **Clinically relevant depressive symptoms (PHQ-9≥10)** Odds ratio (95% CI) | *P*-value | **Major depressive disorder (MINI)** Odds ratio (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.05 (1.00 to 1.11) | 0.073 | 1.14 (0.88 to 1.48) | 0.335 | 0.86 (0.65 to 1.13) | 0.277 |
| Model 2* | 1.04 (0.99 to 1.09) | 0.166 | 1.13 (0.89 to 1.44) | 0.327 | 0.87 (0.68 to 1.12) | 0.274 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.05 (0.99 to 1.11) | 0.095 | 1.36 (1.03 to 1.79) | 0.033 | 1.11 (0.81 to 1.52) | 0.502 |
| Model 2* | 1.05 (1.00 to 1.11) | 0.048 | 1.42 (1.09 to 1.84) | 0.009 | 1.10 (0.84 to 1.45) | 0.485 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | | | | | |
| Model 1 | 1.06 (0.99 to 1.13) | 0.104 | 1.25 (0.88 to 1.77) | 0.209 | 1.35 (0.89 to 2.05) | 0.156 |
| Model 2* | 1.05 (0.98 to 1.12) | 0.166 | 1.26 (0.92 to 1.72) | 0.159 | 1.22 (0.86 to 1.73) | 0.266 |
| **Higher ED score (per 1 SD)** | | | | | | |
| Model 1 | 1.08 (1.03 to 1.13) | 0.003 | 1.22 (1.01 to 1.47) | 0.035 | 1.04 (0.82 to 1.33) | 0.725 |
| Model 2* | 1.06 (1.01 to 1.11) | 0.019 | 1.14 (0.95 to 1.37) | 0.147 | 1.10 (0.90 to 1.35) | 0.362 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire; MINI, mini-international neuropsychiatric interview; ED, endothelial dysfunction. n=1,983 (retinal data), n=1,443 (skin data), and n=2,898 (plasma data). PHQ-9 ≥10 in n=82 (retinal data), n=66 (skin data), and n=127 (plasma data) and MDD is present in n=62 (retinal data), n=50 (skin data), and n=93 (plasma data).

**Model 1:** adjusted for age, sex, type 2 diabetes, 24h systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, waist circumference, smoking status and educational level.

**Model 2:** replaced 24h systolic blood pressure with waist circumference in model 1.

*Data on variables in model 2 were missing in n=220 (retinal data), n=183 (skin data), and n=334 (plasma data).

**Table S3.5 Cross-sectional associations of markers of microvascular dysfunction with prevalent depressive symptoms and major depressive disorder, additionally corrected for use of anti-depressive medication, anti-psychotic and anxiolytic medication, anti-diabetic and insulin medication, history of cardiovascular diseases, plasma markers of low-grade inflammation, physical activity, alcohol use, and cognitive functioning**

| Model | **Depressive symptoms (PHQ-9 score)** Rate ratio (95% CI) | *P*-value | **Clinically relevant depressive symptoms (PHQ-9≥10)** Odds ratio (95% CI) | *P*-value | **Major depressive disorder (MINI)** Odds ratio (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.04(0.99 to 1.09) | 0.168 | 1.13(0.89 to 1.44) | 0.327 | 0.87(0.68 to 1.12) | 0.270 |
| Model 2 | 1.03 (0.98 to 1.09) | 0.207 | 1.13 (0.88 to 1.45) | 0.329 | 0.87 (0.68 to 1.11) | 0.264 |
| Model 3 | 1.03 (0.98 to 1.09) | 0.249 | 1.08 (0.84 to 1.39) | 0.531 | 0.86 (0.67 to 1.10) | 0.230 |
| Model 4 | 1.03 (0.98 to 1.08) | 0.283 | 1.12 (0.88 to 1.43) | 0.353 | 0.85 (0.66 to 1.09) | 0.199 |
| Model 5* | 1.03 (0.98 to 1.09) | 0.205 | 1.11 (0.87 to 1.42) | 0.398 | 0.87 (0.67 to 1.11) | 0.261 |
| Model 6† | 1.04 (0.98 to 1.09) | 0.194 | 1.13 (0.88 to 1.45) | 0.332 | 0.87 (0.68 to 1.12) | 0.289 |
| Model 7‡ | 1.05 (1.00 to 1.11) | 0.072 | 1.30 (0.99 to 1.70) | 0.061 | 0.93 (0.70 to 1.24) | 0.625 |
| Model 8§ | 1.04 (0.98 to 1.09) | 0.188 | 1.12 (0.88 to1.44) | 0.363 | 0.84 (0.65 to 1.08) | 0.166 |
| Model 9‖ | 1.03 (0.98 to 1.09) | 0.274 | 1.11 (0.87 to 1.42) | 0.400 | 0.87 (0.68 to 1.12) | 0.270 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.05(1.00 to 1.11) | 0.049 | 1.42(1.09 to 1.84) | 0.009 | 1.10(0.84 to 1.45) | 0.482 |
| Model 2 | 1.05 (0.99 to 1.10) | 0.089 | 1.40 (1.08 to 1.83) | 0.012 | 1.08 (0.82 to 1.42) | 0.571 |
| Model 3 | 1.05 (1.00 to 1.10) | 0.075 | 1.42 (1.08 to 1.87) | 0.012 | 1.10 (0.82 to 1.42) | 0.513 |
| Model 4 | 1.05 (1.00 to 1.10) | 0.072 | 1.41 (1.08 to 1.83) | 0.012 | 1.07 (0.81 to 1.42) | 0.613 |
| Model 5* | 1.05 (1.00 to 1.11) | 0.059 | 1.43 (1.09 to 1.86) | 0.010 | 1.10 (0.83 to 1.45) | 0.516 |
| Model 6† | 1.05 (1.00 to 1.11) | 0.045 | 1.40 (1.08 to 1.83) | 0.012 | 1.11 (0.85 to 1.47) | 0.448 |
| Model 7‡ | 1.06 (1.01 to 1.12) | 0.031 | 1.54 (1.16 to 2.04) | 0.003 | 1.05 (0.78 to 1.40) | 0.758 |
| Model 8§ | 1.06 (1.00 to 1.11) | 0.036 | 1.44 (1.11 to 1.88) | 0.007 | 1.09 (0.82 to 1.44) | 0.550 |
| Model 9‖ | 1.06 (1.00 to 1.11) | 0.044 | 1.42 (1.08 to 1.84) | 0.012 | 1.09 (0.82 to 1.44) | 0.549 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | | | | | |
| Model 1 | 1.05(0.99 to 1.12) | 0.129 | 1.27(0.93 to 1.75) | 0.138 | 1.24(0.87 to 1.76) | 0.242 |
| Model 2 | 1.05 (0.99 to 1.12) | 0.121 | 1.36 (0.98 to 1.90) | 0.070 | 1.31 (0.90 to 1.89) | 0.156 |
| Model 3 | 1.05 (0.99 to 1.12) | 0.140 | 1.33 (0.96 to 1.84) | 0.090 | 1.22 (0.86 to 1.75) | 0.270 |
| Model 4 | 1.05 (0.99 to 1.12) | 0.116 | 1.27 (0.92 to 1.76) | 0.144 | 1.24 (0.87 to 1.77) | 0.238 |
| Model 5* | 1.05 (0.99 to 1.12) | 0.117 | 1.28 (0.92 to 1.77) | 0.138 | 1.23 (0.86 to 1.75) | 0.253 |
| Model 6† | 1.06 (0.99 to 1.13) | 0.093 | 1.30 (0.94 to 1.80) | 0.117 | 1.24 (0.87 to 1.77) | 0.241 |
| Model 7‡ | 1.06 (0.99 to 1.13) | 0.099 | 1.28 (0.92 to 1.79) | 0.144 | 1.29 (0.87 to 1.92) | 0.205 |
| Model 8§ | 1.06 (1.00 to 1.14) | 0.058 | 1.32 (0.95 to 1.83) | 0.104 | 1.36 (0.92 to 2.00) | 0.122 |
| Model 9‖ | 1.06 (0.99 to 1.13) | 0.076 | 1.29 (0.94 to 1.78) | 0.113 | 1.23 (0.87 to 1.74) | 0.249 |

**Table S3.5 (Continued)**

| Model | **Depressive symptoms (PHQ-9 score)** Rate ratio (95% CI) | *P*-value | **Clinically relevant depressive symptoms (PHQ-9≥10)** Odds ratio (95% CI) | *P*-value | **Major depressive disorder (MINI)** Odds ratio (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| **Higher ED score (per 1 SD)** | | | | | | |
| Model 1 | 1.06(1.01 to 1.11) | 0.013 | 1.16(0.97 to 1.39) | 0.106 | 1.11(0.91 to 1.36) | 0.317 |
| Model 2 | 1.05 (1.01 to 1.10) | 0.023 | 1.12 (0.93 to 1.35) | 0.227 | 1.06 (0.86 to 1.31) | 0.578 |
| Model 3 | 1.07 (1.02 to 1.11) | 0.007 | 1.16 (0.97 to 1.39) | 0.114 | 1.10 (0.90 to 1.36) | 0.341 |
| Model 4 | 1.05 (1.00 to 1.10) | 0.045 | 1.14 (0.95 to 1.37) | 0.152 | 1.08 (0.88 to 1.33) | 0.440 |
| Model 5* | 1.06 (1.01 to 1.11) | 0.017 | 1.13 (0.94 to 1.35) | 0.197 | 1.10 (0.89 to 1.35) | 0.379 |
| Model 6† | 1.06 (1.01 to 1.11) | 0.019 | 1.14 (0.95 to 1.37) | 0.161 | 1.12 (0.90 to 1.38) | 0.312 |
| Model 7‡ | 1.07 (1.02 to 1.13) | 0.003 | 1.20 (1.00 to 1.44) | 0.048 | 1.13 (0.92 to 1.40) | 0.255 |
| Model 8§ | 1.06 (1.01 to 1.11) | 0.023 | 1.12 (0.93 to 1.34) | 0.224 | 1.04 (0.84 to 1.29) | 0.701 |
| Model 9‖ | 1.06 (1.01 to 1.11) | 0.017 | 1.14 (0.95 to 1.37) | 0.158 | 1.08 (0.89 to 1.33) | 0.434 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire; MINI, mini-international neuropsychiatric interview; ED, endothelial dysfunction. n=1,983 (retinal data), n=1,443 (skin data), and n=2,900 (plasma data), PHQ-9 ≥10 in n=82 (retinal data), n=66 (skin data), and n=127 (plasma data) and MDD is present in n=62 (retinal data), n=50 (skin data), and n=93 (plasma data).

**Model 1:** adjusted for age, sex, type 2 diabetes, office systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status, and educational level

**Model 2:** model 1 additionally adjusted for anti-depressive medication (n=138)

**Model 3:** model 1 additionally adjusted for anti-psychotic (n=9) and anxiolytic medication (n=42)

**Model 4:** model 1 additionally adjusted for anti-diabetic (n=435) and insulin medication (n=125)

**Model 5:** model 1 additionally adjusted for history of cardiovascular diseases

**Model 6:** model 1 additionally adjusted for markers of low-grade inflammation

**Model 7:** model 1 additionally adjusted for physical activity

**Model 8:** model 1 additionally adjusted for alcohol use

**Model 9:** model 1 additionally adjusted for cognitive functioning

*Data on variables in model 5 were missing in n=26 (retinal data), n=16 (skin data), and n=38 (plasma data).

†Data on variables in model 6 were missing in n=16 (retinal data), n=13 (skin data), and n=1(plasma data).

‡Data on variables in model 7 were missing in n=127 (retinal data), n=94 (skin data), and n=192 (plasma data).

§Data on variables in model 8 were missing in n=8 (retinal data), n=7 (skin data), and n=10 (plasma data).

‖Data on variables in model 9 were missing in n=57 (retinal data), n=43 (skin data), and n=84 (plasma data).

**Table S3.6 Cross-sectional associations of markers of microvascular dysfunction with prevalent depressive symptoms and major depressive disorder, expressed as absolute retinal arteriolar and venular diameter corrected for baseline arteriolar and venular diameter and absolute skin blood flow corrected for baseline skin blood flow**

| Model | **Depressive symptoms (PHQ-9 score)** Rate ratio (95% CI) | *P*-value | **Clinically relevant depressive symptoms (PHQ-9≥10)** Odds ratio (95% CI) | *P*-value | **Major depressive disorder (MINI)** Odds ratio (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.06 (1.01 to 1.12) | 0.018 | 1.27 (1.00 to 1.61) | 0.048 | 0.91 (0.71 to 1.15) | 0.412 |
| Model 2 | 1.05 (0.99 to 1.10) | 0.091 | 1.21 (0.95 to 1.54) | 0.117 | 0.87 (0.68 to 1.10) | 0.245 |
| Model 3* | 1.04 (0.99 to 1.09) | 0.165 | 1.13 (0.89 to 1.44) | 0.329 | 0.84 (0.66 to 1.08) | 0.178 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.07 (1.01 to 1.12) | 0.012 | 1.41 (1.09 to 1.82) | 0.009 | 1.16 (0.89 to 1.51) | 0.277 |
| Model 2 | 1.06 (1.01 to 1.12) | 0.019 | 1.35 (1.05 to 1.74) | 0.021 | 1.13 (0.87 to 1.47) | 0.362 |
| Model 3* | 1.05 (1.00 to 1.11) | 0.054 | 1.31 (1.01 to 1.70) | 0.044 | 1.14 (0.86 to 1.50) | 0.361 |
| **Lower heat-induced skin hyperemic response (per SD)** | | | | | | |
| Model 1 | 1.07 (1.01 to 1.14) | 0.035 | 1.31 (0.99 to 1.74) | 0.062 | 1.20 (0.88 to 1.64) | 0.241 |
| Model 2 | 1.04 (0.98 to 1.11) | 0.228 | 1.20 (0.91 to 1.60) | 0.200 | 1.15 (0.84 to 1.56) | 0.387 |
| Model 3* | 1.03 (0.97 to 1.10) | 0.357 | 1.21 (0.89 to 1.64) | 0.230 | 1.13 (0.81 to 1.57) | 0.483 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire; MINI, mini-international neuropsychiatric interview. n=2,037 (retinal data), n=1,490 (skin data), and n=2,976 (plasma data). PHQ-9 ≥10 in n=87 (retinal data) and n=70 (skin data). MDD is present in n=66 (retinal data) and n=53 (skin data).

**Model 1:** adjusted for age and sex.

**Model 2:** additionally adjusted for type 2 diabetes.

**Model 3:** additionally adjusted for office systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level.

*Additional data on variables in model 3 were missing in n=37 (retinal data) and n=40 (skin data).

**Table S3.7 Cross-sectional associations of markers of microvascular dysfunction with prevalent depressive symptoms and major depressive disorder excluding participants with a major depression onset before the age of 40**

| Model | **Depressive symptoms (PHQ-9 score)** Rate ratio (95% CI) | *P*-value | **Clinically relevant depressive symptoms (PHQ-9≥10)** Odds ratio (95% CI) | *P*-value | **Major depressive disorder (MINI)** Odds ratio (95% CI) | *P*-Value |
|---|---|---|---|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.06 (1.00 to 1.12) | 0.042 | 1.25 (0.93 to 1.68) | 0.141 | 0.96 (0.71 to 1.30) | 0.800 |
| Model 2 | 1.04 (0.98 to 1.10) | 0.213 | 1.17 (0.87 to 1.58) | 0.298 | 0.92 (0.68 to 1.24) | 0.579 |
| Model 3* | 1.03 (0.98 to 1.09) | 0.249 | 1.06 (0.78 to 1.44) | 0.717 | 0.91 (0.66 to 1.25) | 0.550 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | | | | | |
| Model 1 | 1.05 (0.99 to 1.11) | 0.109 | 1.40 (1.03 to 1.90) | 0.032 | 1.05 (0.77 to 1.44) | 0.741 |
| Model 2 | 1.04 (0.98 to 1.10) | 0.213 | 1.34 (0.98 to 1.82) | 0.064 | 1.03 (0.76 to 1.40) | 0.863 |
| Model 3* | 1.03 (0.97 to 1.09) | 0.352 | 1.25 (0.91 to 1.72) | 0.163 | 1.07 (0.77 to 1.49) | 0.686 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | | | | | |
| Model 1 | 1.10 (1.01 to 1.19) | 0.025 | 1.85 (1.10 to 3.13) | 0.021 | 1.37 (0.84 to 2.24) | 0.205 |
| Model 2 | 1.08 (1.00 to 1.18) | 0.060 | 1.77 (1.04 to 3.02) | 0.035 | 1.34 (0.82 to 2.19) | 0.248 |
| Model 3* | 1.05 (0.96 to 1.14) | 0.281 | 1.71 (0.93 to 3.17) | 0.087 | 1.36 (0.79 to 2.33) | 0.272 |
| **Higher ED score (per 1 SD)** | | | | | | |
| Model 1 | 1.15 (1.09 to 1.21) | <0.001 | 1.44 (1.21 to 1.72) | <0.001 | 1.33 (1.09 to 1.63) | 0.005 |
| Model 2 | 1.09 (1.04 to 1.15) | <0.001 | 1.28 (1.06 to 1.55) | 0.011 | 1.21 (0.98 to 1.50) | 0.077 |
| Model 3* | 1.06 (1.00 to 1.11) | 0.034 | 1.14 (0.92 to 1.41) | 0.227 | 1.11 (0.88 to 1.41) | 0.377 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire; MINI, mini-international neuropsychiatric interview; ED, endothelial dysfunction. n= 1,762 (retina), n=1,269 (skin), and n=2,563 (plasma). PHQ-9 ≥10 in n=53 (retinal data), n=28 (skin data), and n=85 (plasma data). Major depressive disorder is present in n=43 (retinal data), n=25 (skin data), and n=68 (plasma data).

**Model 1:** adjusted for age and sex.

**Model 2:** additionally adjusted for type 2 diabetes.

**Model 3:** additionally adjusted for office systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level.

*Additional data on variables in model 3 were missing in n=37 (retinal data), n=40 (skin data), and n=54 (plasma data).

**Table S3.8 Longitudinal associations of markers of microvascular dysfunction with incident depressive symptoms with replacement of office systolic blood pressure by 24h ambulatory systolic blood pressure and replacement of BMI by waist circumference**

| Model | Incident depressive symptoms (PHQ-9≥10) Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | |
| Model 1 | 1.24 (1.04 to 1.48) | 0.018 |
| Model 2* | 1.23 (1.04 to 1.46) | 0.016 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | |
| Model 1 | 1.03 (0.87 to 1.22) | 0.719 |
| Model 2* | 1.05 (0.89 to 1.23) | 0.560 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | |
| Model 1 | 1.17 (0.95 to 1.44) | 0.149 |
| Model 2* | 1.17 (0.96 to 1.43) | 0.132 |
| **Higher ED score (per 1 SD)** | | |
| Model 1 | 1.22 (1.06 to 1.39) | 0.004 |
| Model 2* | 1.19 (1.04 to 1.35) | 0.009 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire; ED, endothelial dysfunction. n=1,820 (retina data), n=1,314 (skin data), and n=2,650 (plasma data). Incident depressive symptoms were presence in n=164 (retinal data), n=125 (skin data), and n=246 (plasma data).

**Model 1:** adjusted for age, sex, type 2 diabetes, 24h systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level.

**Model 2:** replaced 24h systolic blood pressure with waist circumference in model 1.

*Data on variables in model 1 were missing in n=199 (retinal data), n=162 (skin data), and n=295 (plasma data).

**Table S3.9 Longitudinal associations of markers of microvascular dysfunction with incident depressive symptoms, additionally corrected for use of anti-depressive medication, anti-psychotic and anxiolytic medication, anti-diabetic and insulin medication, history of cardiovascular diseases, plasma markers of low-grade inflammation, physical activity, alcohol use, and cognitive functioning**

| Model | Incident depressive symptoms (PHQ-9≥10) Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | |
| Model 1 | 1.23(1.04 to 1.46) | 0.018 |
| Model 2 | 1.20 (1.02 to 1.43) | 0.031 |
| Model 3 | 1.20 (1.01 to 1.42) | 0.036 |
| Model 4 | 1.22 (1.03 to 1.44) | 0.022 |
| Model 5* | 1.21 (1.02 to 1.44) | 0.027 |
| Model 6† | 1.21 (1.02 to 1.43) | 0.033 |
| Model 7‡ | 1.25 (1.05 to 1.50) | 0.014 |
| Model 8§ | 1.23 (1.04 to 1.45) | 0.018 |
| Model 9ll | 1.20 (1.02 to 1.43) | 0.033 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | |
| Model 1 | 1.05(0.89 to 1.23) | 0.238 |
| Model 2 | 1.03 (0.88 to 1.21) | 0.698 |
| Model 3 | 1.04 (0.89 to 1.22) | 0.630 |
| Model 4 | 1.04 (0.88 to 1.22) | 0.661 |
| Model 5* | 1.04 (0.88 to 1.22) | 0.680 |
| Model 6† | 1.03 (0.88 to 1.21) | 0.688 |
| Model 7‡ | 1.02 (0.86 to 1.20) | 0.842 |
| Model 8§ | 1.05 (0.90 to 1.23) | 0.536 |
| Model 9ll | 1.02 (0.86 to 1.19) | 0.857 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | |
| Model 1 | 1.17(0.96 to 1.43) | 0.130 |
| Model 2 | 1.19 (0.97 to 1.46) | 0.093 |
| Model 3 | 1.17 (0.96 to 1.43) | 0.121 |
| Model 4 | 1.16 (0.95 to 1.42) | 0.154 |
| Model 5* | 1.17 (0.95 to 1.43) | 0.134 |
| Model 6† | 1.17 (0.95 to 1.43) | 0.142 |
| Model 7‡ | 1.14 (0.92 to 1.40) | 0.229 |
| Model 8§ | 1.18 (0.97 to 1.45) | 0.098 |
| Model 9ll | 1.17 (0.96 to 1.43) | 0.137 |
| **Higher ED score (per 1 SD)** | | |
| Model 1 | 1.19(1.05 to 1.35) | 0.008 |
| Model 2 | 1.18 (1.04 to 1.33) | 0.011 |
| Model 3 | 1.19 (1.05 to 1.35) | 0.007 |
| Model 4 | 1.17 (1.03 to 1.33) | 0.015 |
| Model 5* | 1.16 (1.02 to 1.32) | 0.026 |
| Model 6† | 1.19 (1.05 to 1.36) | 0.009 |
| Model 7‡ | 1.15 (1.00 to 1.32) | 0.045 |
| Model 8§ | 1.17 (1.03 to 1.34) | 0.015 |
| Model 9ll | 1.18 (1.03 to 1.34) | 0.014 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire; ED, endothelial dysfunction. n=1,820 (retina data), n=1,314 (skin data), and n=2,650 (plasma data). Incident depressive symptoms were presence in n=164 (retinal data), n=125 (skin data), and n=246 (plasma data).

**Model 1:** adjusted for age, sex, type 2 diabetes, office systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status, and educational level.

**Model 2:** model 1 additionally adjusted for anti-depressive medication (n=113).

**Model 3:** model 1 additionally adjusted for anti-psychotic (n=5) and anxiolytic medication (n=30).

**Model 4:** model 1 additionally adjusted for anti-diabetic medication (n=372) and use of insulin (n=101).

**Model 5:** model 1 additionally adjusted for history of cardiovascular diseases.

**Model 6:** model 1 additionally adjusted for low-grade inflammation.

**Model 7:** model 1 additionally adjusted for physical activity.

**Model 8:** model 1 additionally adjusted for alcohol use.

**Model 9:** model 1 additionally adjusted for cognitive functioning.

*Data on variables in model 5 were missing in n=23 (retinal data), n=6 (skin data), and n=32 (plasma data).

†Data on variables in model 6 were missing in n=14 (retinal data), n= 11 (skin data), and n=1 (plasma data).

‡Data on variables in model 7 were missing in n=107 (retinal data), n= 75 (skin data), and n=162 (plasma data).

§Data on variables in model 8 were missing in n=7 (retinal data), n=6 (skin data), and n=9 (plasma data).

llData on variables in model 9 were missing in n=48 (retinal data), n=36 (skin data), and n=71 (plasma data).

**Table S3.10 Longitudinal associations of markers of microvascular dysfunction with incident depressive symptoms, expressed as absolute retinal arteriolar and venular diameter corrected for baseline arteriolar and venular diameter and absolute skin blood flow corrected for baseline skin blood flow**

| Model | Incident depressive symptoms (PHQ-9≥10) Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | |
| Model 1 | 1.30 (1.09 to 1.54) | 0.003 |
| Model 2 | 1.24 (1.05 to 1.47) | 0.014 |
| Model 3* | 1.24 (1.04 to 1.47) | 0.015 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | |
| Model 1 | 1.09 (0.93 to 1.28) | 0.282 |
| Model 2 | 1.06 (0.91 to 1.25) | 0.445 |
| Model 3* | 1.06 (0.91 to 1.25) | 0.454 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | |
| Model 1 | 1.13 (0.93 to 1.37) | 0.217 |
| Model 2 | 1.09 (0.90 to 1.32) | 0.386 |
| Model 3* | 1.08 (0.89 to 1.31) | 0.434 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire. n=1,865 (retina data), n=1,355 (skin data), and n=2,714 (plasma data). Incident depressive symptoms in n=166 (retinal data) and n=128 (skin data).

**Model 1:** adjusted for age and sex.

**Model 2:** additionally adjusted for type 2 diabetes.

**Model 3:** additionally adjusted for office systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level.

*Additional data on variables in model 3 were missing in n=45 (retinal data) and n=41 (skin data).

**Table S3.11 Longitudinal associations of markers of microvascular dysfunction with incident depressive symptoms excluding participants with a major depression at baseline**

| Model | Incident depressive symptoms (PHQ-9≥10) Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | |
| Model 1 | 1.32 (1.11 to 1.56) | 0.008 |
| Model 2 | 1.32 (1.10 to 1.57) | 0.002 |
| Model 3 | 1.26 (1.06 to 1.50) | 0.008 |
| Model 4* | 1.26 (1.05 to 1.50) | 0.011 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | |
| Model 1 | 1.12 (0.95 to 1.32) | 0.170 |
| Model 2 | 1.12 (0.95 to 1.32) | 0.182 |
| Model 3 | 1.09 (0.92 to 1.28) | 0.320 |
| Model 4* | 1.07 (0.90 to 1.26) | 0.439 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | |
| Model 1 | 1.20 (0.98 to 1.47) | 0.077 |
| Model 2 | 1.17 (0.95 to 1.44) | 0.130 |
| Model 3 | 1.13 (0.92 to 1.39) | 0.237 |
| Model 4* | 1.16 (0.94 to 1.43) | 0.172 |
| **Higher ED score (per 1 SD)** | | |
| Model 1 | 1.36 (1.22 to 1.53) | <0.001 |
| Model 2 | 1.38 (1.23 to 1.55) | <0.001 |
| Model 3 | 1.28 (1.13 to 1.44) | <0.001 |
| Model 4* | 1.20 (1.06 to 1.37) | 0.006 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire. n=1,836 (retina data), n= 1,330 (skin data), and n= 2,673 (plasma data). Incident depressive symptoms in n=156 (retinal data), n=116 (skin data), n= 232 (plasma data).

**Model 1:** unadjusted

**Model 2:** adjusted for age and sex.

**Model 3:** model 2 additionally adjusted for type 2 diabetes.

**Model 4:** model 3 additionally adjusted for office systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level.

*Additional data on variables in model 4 were missing in n=44 (retinal data), n=40 (skin data), and n=62 (plasma data).

**Table S3.12 Longitudinal associations of markers of microvascular dysfunction with incident depressive symptoms excluding participants with a major depression onset before the age of 40**

| Model | Incident depressive symptoms (PHQ-9≥10) Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| **Lower flicker light-induced retinal arteriolar dilation (per 1 SD)** | | |
| Model 1 | 1.32 (1.09 to 1.60) | 0.004 |
| Model 2 | 1.30 (1.07 to 1.58) | 0.008 |
| Model 3 | 1.25 (1.03 to 1.52) | 0.025 |
| Model 4* | 1.24 (1.02 to 1.52) | 0.030 |
| **Lower flicker light-induced retinal venular dilation (per 1 SD)** | | |
| Model 1 | 1.18 (0.98 to 1.43) | 0.079 |
| Model 2 | 1.17 (0.97 to 1.41) | 0.098 |
| Model 3 | 1.14 (0.95 to 1.38) | 0.169 |
| Model 4* | 1.12 (0.93 to 1.36) | 0.241 |
| **Lower heat-induced skin hyperemic response (per 1 SD)** | | |
| Model 1 | 1.24 (0.97 to 1.58) | 0.081 |
| Model 2 | 1.19 (0.93 to 1.52) | 0.177 |
| Model 3 | 1.15 (0.90 to 1.47) | 0.272 |
| Model 4* | 1.17 (0.91 to 1.50) | 0.223 |
| **Higher ED score (per 1 SD)** | | |
| Model 1 | 1.46 (1.29 to 1.65) | <0.001 |
| Model 2 | 1.44 (1.27 to 1.64) | <0.001 |
| Model 3 | 1.34 (1.17 to 1.53) | <0.001 |
| Model 4* | 1.26 (1.09 to 1.45) | 0.002 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire. n=1,622 (retina data), n= 1,173 (skin data), and n= 2,343 (plasma data). Incident depressive symptoms in n=123 (retinal data), n=86 (skin data), n= 173 (plasma data).

**Model 1:** unadjusted

**Model 2:** adjusted for age and sex .

**Model 3:** additionally adjusted for type 2 diabetes.

**Model 4:** additionally adjusted for office systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level.

*Additional data on variables in model 4 were missing in n=39 (retinal data), n=34 (skin data), and n=55 (plasma data).

**Table S3.13. Cross-sectional and longitudinal associations of overall microvascular dysfunction with prevalent and incident depressive symptoms**

| Model | **Depressive symptoms (PHQ-9 score)** Rate ratio (95% CI) | *P*-value | **Clinically relevant depressive symptoms (PHQ-9≥10)** Odds ratio (95% CI) | *P*-value | **Major depressive disorder (MINI)** Odds ratio (95% CI) | *P*-value | **Incident depressive symptoms (PHQ-9≥10)** Hazard ratio (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|---|
| Model 1 | 1.12(1.05;1.20) | 0.001 | 1.88 (1.41 to 2.51) | <0.001 | 1.29(0.94;1.78) | 0.122 | 1.42(1.13;1.78) | 0.002 |
| Model 2 | 1.19(1.11;1.28) | <0.001 | 1.31 (1.68 to 3.16) | <0.001 | 1.33(0.95;1.86) | 0.093 | 1.39(1.10;1.77) | 0.007 |
| Model 3 | 1.16(1.08;1.25) | <0.001 | 2.06 (1.49 to 2.85) | <0.001 | 1.22(0.87;1.71) | 0.250 | 1.33(1.05;1.70) | 0.021 |
| Model 4* | 1.10(1.02;1.19) | 0.012 | 1.78 (1.26 to 2.51) | <0.001 | 1.02(0.72;1.45) | 0.897 | 1.25(0.98;1.59) | 0.071 |

CI indicates confidence interval; PHQ-9, 9-item patient health questionnaire; MINI, mini-international neuropsychiatric interview. Overall microvascular dysfunction is calculated as the standardized average of all included microvascular markers (standardized retinal arteriolar dilatation, retinal venular dilatation, skin hyperemic response, and plasma endothelial dysfunction score). Cross-sectional analyses n=1,084, PHQ-9 ≥10 in n=49 and major depressive disorder is present in n=39. Longitudinal analyses n=988, incident depressive symptoms in n=86.

**Model 1:** unadjusted

**Model 2:** adjusted for age and sex.

**Model 3:** additionally adjusted for type 2 diabetes.

**Model 4:** additionally adjusted for office systolic blood pressure, anti-hypertensive medication, total-to-HDL cholesterol ratio, lipid-modifying medication, body mass index, smoking status and educational level.

*Additional data on variables in model 4 were missing in n=32 (cross-sectional) and n=27 (longitudinal).

# Chapter 4

## The relation of depression with structural brain abnormalities and cognitive functioning: The Maastricht Study

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## Abstract

### Background

Individuals with depression often experience widespread and persistent cognitive deficits, which might be due to brain atrophy and cerebral small vessel disease (CSVD). We therefore studied the associations between depression, markers of brain atrophy and CSVD, and cognitive functioning.

### Methods

We used cross-sectional data from the population-based Maastricht study (n = 4734; mean age 59.1 ± 8.6 years, 50.2% women), which focuses on type 2 diabetes. A current episode of major depressive disorder (MDD, n = 151) was assessed by the Mini-International Neuropsychiatric Interview. Volumes of cerebral spinal fluid, white matter, gray matter and white matter hyperintensities, presence of lacunar infarcts and cerebral microbleeds, and total CSVD burden were assessed by 3 T magnetic resonance imaging. Multiple linear and logistic regression analyses tested the associations between MDD, brain markers and cognitive functioning in memory, information processing speed, and executive functioning & attention, and presence of cognitive impairment. Structural equation modeling was used to test mediation.

### Results

In fully adjusted models, MDD was associated with lower scores in information processing speed [mean difference = –0.18(–0.28;–0.08)], executive functioning & attention [mean difference=–0.13(–0.25;–0.02)], and with higher odds of cognitive impairment [odds ratio (OR) = 1.60(1.06;2.40)]. MDD was associated with CSVD in participants without type 2 diabetes [OR = 1.65(1.06;2.56)], but CSVD or other markers of brain atrophy or CSVD did not mediate the association with cognitive functioning.

### Conclusions

MDD is associated with more impaired information processing speed and executive functioning & attention, and overall cognitive impairment. Furthermore, MDD was associated with CSVD in participants without type 2 diabetes, but this association did not explain an impaired cognitive profile.

## Introduction

Several studies have shown that depression is strongly related to impaired cognition [1]. Around two-thirds of individuals with depression experience impaired cognitive functioning [1], and studies in patients with clinical depression have shown that cognitive deficits persist despite remission of depressive symptoms [2,3]. Several prospective cohort studies suggest that individuals with depression show accelerated cognitive decline and have a two times higher risk for Alzheimer's disease (AD) and a three times higher risk for vascular dementia [4].

Underlying mechanisms that are involved in the aetiology of dementia such as brain atrophy[5] and cerebral small vessel disease (CSVD) [6] have also been linked to depression. Volume reductions in total grey matter (GM) [7], the hippocampus [8], and several prefrontal regions [8], were reported to be associated with depression. Studies have also shown that depression is related to markers of CSVD, including white matter hyperintensities (WMH), lacunar infarcts, and cerebral microbleeds [9]. Small clinical studies have demonstrated that these cerebral changes are related to cognitive functioning in memory, executive functions and processing speed in patients with depression [10-13]. However, studies generally were small and confined to the more severely depressed spectrum such as inpatients, hence there is a lack of population-based cohort studies that generalize findings to the wider population with depression. Furthermore, most studies only corrected for a limited number of confounders [10-13] and associations found could be spurious; studies mostly included a limited number of brain markers [10,11], which might have resulted in less sensitivity; and studies were often performed in elderly populations (>59years) [11-13], while the development of structural brain damage may already start at middle age [14].

Therefore, the aim of this study is to investigate the association between depression, brain volume (white matter (WM), GM), markers of generalized atrophy (cerebrospinal fluid (CSF volume) and CSVD (WMH, lacunar infarcts, and cerebral microbleeds), cognitive impairment and functioning (memory, information processing speed, and executive function & attention). In addition, we assess whether markers of brain atrophy and CSVD mediate the association between depression and cognition. Previous studies that related structural brain abnormalities to depression and cognition mainly included elderly populations, and sex differences are found in both MDD [15] and structural brain abnormalities [16]. Furthermore, it has been shown that type 2 diabetes mellitus (T2DM) is associated with MDD [17], cognitive functioning [18], and

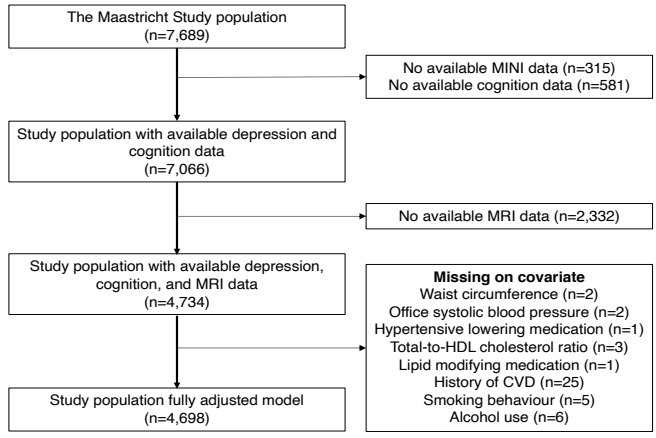
structural brain abnormalities [19]. Because of this, we tested whether associations differed according to sex, age, and T2DM status in a cohort enriched for T2DM. We hypothesized that depression is associated with worse cognitive functioning and that these associations are partly explained by markers of brain atrophy and CSVD. In addition, we expected that the associations are similar between the individuals with and without T2DM.

## Methods

### *Study population and Design*

We used cross-sectional data from The Maastricht Study, an observational population-based cohort study. The rationale and methodology have been described previously [20]. In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of T2DM, heart disease, and other chronic conditions, 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, the municipal registries, and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency. Figure 4.1 shows the flowchart of the study population. Baseline surveys were completed between November 2010 and January 2018. From the initial 7,689 participants, depression and cognitive functioning data was available in n=7,066 participants. MRI measurements were implemented from December 2013 onwards until February 2017 and were available in 4,734 participants. We performed complete case analyses in which 4,734 participants were included in the key analyses and 4,698 participants in the fully adjusted analyses. All participants gave written informed consent.

**Figure 4.1 Flowchart of the study population**




MINI indicates Mini-International Neuropsychiatric Interview; MRI, magnetic resonance imaging; HDL, high-density lipoprotein; CVD, cardiovascular disease.

### *Major depressive disorder*

Current and lifetime episodes of major depressive disorder (MDD) were assessed by the Mini-International Neuropsychiatric Interview (MINI) [21]. The MINI is a short diagnostic structured interview used to assess the presence of MDD in the preceding two weeks, in line with the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). MDD is diagnosed if participants had (1) one core symptom (i.e. depressed mood or loss of interest) and at least four other symptoms of depression (i.e. significant weight change of change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, guilt or worthlessness, diminished ability to think or concentrate or indecisiveness and suicidal thoughts or plans), or (2) two core symptoms and at least three other symptoms, for a period of more than two weeks. The MINI was conducted by trained staff members.

### *Cognitive Performance*

Cognitive performance was assessed by a concise (30-minute) neuropsychological test battery [20]. For conceptual clarity, test scores were standardized and divided into three cognitive domains (memory function, information processing speed, and executive function & attention). Briefly, memory function was evaluated using the Verbal Learning Test [22], and a

memory domain score was derived by calculating the average of total immediate and delayed recall standardized scores. An information processing speed domain score was derived from standardized scores of the Stroop Color-Word Test Part I and II [23], the Concept Shifting Test Part A and B [24], and the Letter-Digit Substitution Test [25]. The executive function & attention domain score was calculated the average of the Stroop Color-Word Test Part III and the Concept Shifting Test Part C. If necessary, individual test scores were log-transformed to reduce skewness of distributions and/or inverted so that higher scores indicated better cognitive performance. In addition, participants were categorized as cognitively impaired (yes/no) based on a regression-based normalization procedure per test that predicted expected scores for each individual given their age, sex and level education from a published normative sample [22-25]. The difference between observed and expected scores and their standard deviation were used to calculate z-scores, which were then averaged per domains and re-standardized. Individuals performing <-1.5 standard deviations below their norm-based expected score in any domain were categorized as having significant cognitive impairment (CogImp).

***Brain magnetic resonance imaging***

Brain magnetic resonance imaging (MRI) was performed on a 3 Tesla MRI scanner (MAGNETOM Prismafit Syngo MR D13D; Siemens Healthcare, Erlangen, Germany) by use of a 64-element head coil for parallel imaging, as previously described [26]. The MRI protocol consists of a 3D $T_1$-weighted sequence (TR/TE/TI2300/2.98/900ms, 1.00mm cubic voxel, 176 continuous slices, matrix size of 240x250 and reconstructed matrix size of 512x512), a $T_2$-weighted fluid-attenuated inversion recovery (TR/TE/TI 5000/394/1800ms, 0.98x0.98x1.26mm acquisition voxel and 0.49x0.49x1.00 mm reconstructed voxel, 176 continuous slices, acquisition matrix size of 250x250 and reconstructed matrix size of 512x512), and a gradient recalled echo pulse sequence with susceptibility-weighted imaging. The protocols for MRI acquisition and analysis are in line with current STRIVE V2 imaging standards [27].

$T_1$ images and $T_2$-weighted fluid-attenuated inversion recovery images were analysed by use of an ISO- 13485:2012–certified, automated method [28,29]. $T_1$-weighted images were segmented into white matter, grey matter, and cerebrospinal fluid (CSF), volumes (1 voxel=1.00mm3=0.001 ml). Intracranial volume was calculated as the sum of white matter (including WMH volume),

grey matter, and CSF volume. Volumes of white matter, grey matter, CSF, and intracranial volume were standardized.

$T_1$ images and $T_2$-weighted fluid-attenuated inversion recovery images were used to quantify deep, periventricular and total WMH volume. Periventricular WMH were automatically defined as WMH <3 mm, and deep cortical WMH as WMH ≥3 mm from the CSF volume. WMH volumes were log-transformed and standardized. In addition, WMH were visually rated with the Fazekas scale [30]. The location and the number of lacunar infarcts are manually rated on T2 and fluid-attenuated inversion recovery images and defined as focal lesions of ≥3mm and <15mm in size with a similar signal intensity as cerebrospinal fluid on all sequences and a hyperintense rim [27]. The location and the number of cerebral microbleeds are manually rated on 3D T2* gradient recalled echo-weighted imaging with susceptibility-weighted imaging by use of the Microbleed Anatomical Rating Scale [31] and defined as focal lesions of ≥2mm and ≤10mm in size with a hypointense signal on T2* gradient recalled echo and susceptibility-weighted images [27]. Lacunar infarcts and cerebral microbleeds were rated manually by three neuroradiologists. The intraclass correlation coefficient for the three raters based on 50 randomly selected scans was 0.84 (0.74; 0.91) and 0.83 (0.72; 0.90) for the presence of lacunar infarcts and cerebral microbleeds, respectively. Presence of CSVD was defined as (1) presence of lacunar infarct, (2) presence of cerebral microbleeds, and/or (3) Fazekas score ≥2.

Because MRI assessment did not always take place at the same time as the baseline assessment for logistic reasons, we adjusted for MRI lag time, i.e., the time between baseline assessment and MRI assessment.

***General characteristics and covariates***

General characteristics and covariates were measured as described elsewhere [20]. Educational level (low, intermediate, high), partner status (partner/no partner), history of cardiovascular diseases (CVD), smoking status (never, current, former), alcohol consumption (none, low, high), physical activity, and Mediterranean diet score were assessed by questionnaires [20]. We measured height, weight, waist circumference, blood pressure (measured in office and via ambulatory 24-h blood pressure monitoring at home (WatchBP03; Microlife AG, Widnau, Switzerland)), serum creatinine, 24-h urinary albumin excretion (twice), and plasma lipid profile as described elsewhere [20]. Estimated glomerular filtration rate (eGFR; in mL/min/1.73 $m^2$) was calculated with the Chronic Kidney

Disease Epidemiology Collaboration equation based on both serum creatinine and serum cystatin C [32]. Medication use was assessed in a medication interview where generic name, dose, and frequency were registered. To determine T2DM status, all participants (except those who used insulin) underwent an oral glucose tolerance test (OGTT) after an overnight fast as previously described [20]. T2DM was defined according to the World Health Organization 2006 criteria (fasting blood glucose ≥7.0 mmol/L or a 2-h post-load blood glucose ≥11.1 mmol/L or used oral glucose-lowering medication or insulin) [33].

***Statistical Analyses***

All statistical analyses were performed by use of the Statistical Package for Social Sciences (version 25.0; IBM, Chicago, IL, USA), Stata (version 13; StataCorp LLC, College Station, TX, USA), and Mplus (version 8.4; Muthén & Muthén, Los Angeles, CA, USA). To assess associations of MDD with cognitive functioning and MRI markers, we used multiple linear and logistic regression analyses reporting the unstandardized regression coefficient B and the odds ratio (OR), respectively, with their 95% confidence interval (CI). The associations were adjusted for potential confounders: model 1 included MDD (for cognitive outcome measures) or MDD + MRI time lag (for categorical MRI outcome measures) or MDD + MRI time lag + intracranial volume (for MRI volume outcome measures); model 2 additionally adjusted for age, sex and educational level; model 3 additionally adjusted for T2DM (because of oversampling); model 4 additionally adjusted for waist circumference, office systolic blood pressure, hypertensive medication, total-to-high-density lipoprotein cholesterol ratio, lipid-modifying medication, and history of cardiovascular diseases, and model 5 additionally adjusted for smoking behaviour and alcohol use. Model 3 was considered the main model. Models 4 and 5 were tested separately as covariates might well be on the causal pathway with potential overcorrection [34]. We also tested the interactions of MDD with age, sex, and T2DM on cognitive functioning and on the brain markers. These interactions were first tested in main model 3, and later in models 4 and 5 that may include variables that are on the causal pathway. To test for mediation of the association between depression and cognition by brain markers, structural equation modelling was used to decompose total effects of depression into direct and indirect effects using maximum likelihood estimation for continuous and mean and variance corrected weighted least squares robust estimation for categorical dependent variables. Also, these analyses were performed in main model 3, as models 4 and 5 may include variables that might

be on the causal pathway. A two-sided P-value < 0.05 was considered statistically significant.

## Results

### *General characteristics of the study population*

Table 4.1 shows the general characteristics of the study population (n=4,734), stratified for MDD status. Participants had a mean age of 59.1±8.6 years and 50.2% were women. Participants with MDD were lower educated and had a worse cardiometabolic risk profile compared to participants without MDD. Participants without MINI and cognition data (n=623) were significantly older, were more often men, had a lower level of education, a worse cardiometabolic risk profile, more often T2DM, lower cognitive functioning scores, smaller brain volumes, and larger volumes of WMH than participants with MINI and cognition data. Participants without MRI data (n=2,332) were significantly older, had a lower level of education, a worse cardiometabolic risk profile, more often T2DM, a higher depressive symptoms score, and lower cognitive functioning scores as compared to participants with MRI data (data not shown).

**Table 4.1 General characteristics study population according to depression status**

| Characteristic | No major depressive disorder (n=4,583) | Major depressive disorder (n=151) | *P*-value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 59.2±8.6 | 58.3±8.4 | 0.233 |
| Sex, n (% female) | 2,30(50.2) | 75(49.7) | 0.934 |
| Educational level, low/medium/high, n (%) | 1,397/1,308/1,878 (30.5/28.5/41.0) | 71/48/32 (47.0/31.8/21.2) | <0.001 |
| Partner status, n (% partner) | 3,901(85.2) | 107(70.9) | <0.001 |
| **Depression** | | | |
| Depressive symptoms (PHQ-9 score) | 2[0-4] | 9[6-15] | <0.001 |
| Anti-depressive medication, n (%) | 273(6.0) | 43(28.5) | <0.001 |
| Sleeping medication, n (%) | 93(2.0) | 9(6.0) | 0.005 |
| Anxiolytic medication, n (%) | 90(2.0) | 16(10.6) | <0.001 |
| Anti-psychotic medication, n (%) | 22(0.5) | 8(5.3) | <0.001 |
| **Cardiovascular risk factors** | | | |
| Body mass index (kg/m$^2$) | 26.4±4.1 | 28.3±5.1 | <0.001 |
| Waist circumference (cm) | 93.5±12.6 | 98.2±15.2 | <0.001 |
| Office systolic BP (mmHg) | 132.7±17.3 | 134.6±17.2 | 0.194 |
| Office diastolic BP (mmHg) | 75.4±9.7 | 77.1±10.4 | 0.042 |
| Antihypertensive medication, n (%) | 1,465(32.0) | 64(42.4) | 0.010 |
| Hypertension, n (%) | 2,230(48.7) | 90(59.6) | 0.010 |
| Total/high density cholesterol ratio | 3.6±1.2 | 3.8±1.3 | 0.012 |
| Triglycerides (mmol/l) | 1.4±0.8 | 1.5±0.8 | 0.005 |
| Lipid-modifying medication, n (%) | 1,225(26.7) | 49(32.5) | 0.135 |
| eGFR (ml/min/1.73m$^2$) | 89.1±14.1 | 89.7±14.8 | 0.714 |
| Albuminuria, normal/micro/macro, n (%) | 1,716/111/6 (93.6/6.1/0.3) | 55/9/0 (85.9/14.1/0.0) | 0.016 |
| History of CVD, n (%) | 549(12.0) | 25(16.7) | 0.098 |
| Type 2 diabetes mellitus, n (%) | 864(18.9) | 49(32.5) | <0.001 |
| Diabetes medication (all types), n (%) | 630(13.7) | 37(24.5) | <0.001 |
| HbA1c (mmol/mol) | 38.5±8.4 | 42.2±12.8 | <0.001 |
| **Life style factors** | | | |
| Smoking, never/former/current, n (%) | 1,814/2,232/534 (39.6/48.7/11.7) | 54/66/29 (36.2/44.3/19.5) | 0.078 |
| Alcohol use, none/low/high, n (%) | 750/2,682/1,146 16.4/58.6/25.0 | 47/79/24 31.3/52.7/16.0 | <0.001 |
| Physical activity (hours/week) | 14.2±8.0 | 12.8±8.3 | 0.047 |
| Mediterranean diet score | 4.5±1.7 | 4.1±1.8 | 0.001 |
| **Cognitive functioning** | | | |
| Memory score | 0.09±0.93 | -0.06±0.89 | 0.061 |
| Information processing speed score | 0.09±0.75 | -0.18±0.82 | <0.001 |
| Executive functioning & attention score | 0.09±0.78 | -0.15±0.86 | <0.001 |
| Cognitive impairment, n (%) | 648(14.1) | 35(23.2) | 0.003 |
| **Markers of brain atrophy and CSVD** | | | |
| Cerebrospinal fluid (ml) | 252.2±47.7 | 244.8±48.7 | 0.062 |
| White matter (ml) | 476.2±58.4 | 464.4±63.8 | 0.015 |
| Grey matter (ml) | 662.5±60.6 | 649.6±68.6 | 0.010 |
| Intracranial volume (ml) | 1391.8±133.4 | 1359.7±147.4 | 0.004 |
| WMH (ml) | 0.21[0.06-0.66] | 0.25[0.08-0.72] | 0.161 |
| Deep cortical WMH (ml) | 0.04[0.01-0.19] | 0.04[0.01-0.19] | 0.559 |
| Periventricular WMH (ml) | 0.14[0.04-0.46] | 0.16[0.05-0.52] | 0.120 |
| Fazekas score ≥2, n (%) | 1,054(23.0) | 38(25.2) | 0.556 |
| Cerebral lacunar infarct, n (%) | 197(4.3) | 8(5.3) | 0.539 |
| Cerebral microbleeds, n (%) | 458(10.0) | 15(9.9) | 1.000 |
| CSVD, n (%) | 1,437(31.4) | 52(34.4) | 0.424 |
| MRI lag time (years) | 0.70[0.02-1.30] | 0.80[0.23-2.08] | 0.482 |

Data are presented as means ± standard deviation (SD), number (%) or median [interquartile range], and evaluated using independent T-tests, Mann–Whitney U tests or $\chi 2$ tests. PHQ-9 indicates 9 item Patient Health Questionnaire; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; CSVD, cerebral small vessel disease; HbA1c, glycated hemoglobin A1c; WMH, white matter hyperintensities

***Association between MDD and cognitive functioning***

Table 4.2 shows the associations between MDD and cognitive functioning. MDD was associated with higher odds of CogImp (OR=1.60[1.06;2.40]) after full adjustment for demographic, cardiovascular, and lifestyle risk factors (model 5). Furthermore, MDD was associated with lower scores in information processing speed (B=-0.18[-0.28;-0.08]) and executive functioning & attention (B=-0.13[-0.25;-0.02]), but not with memory (B=-0.02[-0.15;0.11]) in model 5. We did not find interactions of MDD with age, sex, or T2DM on CogImp or cognitive domain scores (Supplementary Table S4.1).

***Association between MDD and markers of brain atrophy and CSVD***

Table 4.3 shows the associations between MDD and markers of brain atrophy and CSVD. MDD was not associated with white matter volume (B=0.00[-0.08;0.07]), grey matter volume (B=-0.01[-0.09;0.06]), or CSF volume (B=0.02[-0.08;0.12]), after adjustment for demographic risk factors (model 2). MDD was associated with larger WMH volume (B=0.16[0.02 to 0.30]) after adjustment for demographic risk factors (model 2), but not after additional adjustment for T2DM in model 3 (B=0.14[0.00;0.28]). However, the association between MDD and periventricular WMH volume remained significant after additional adjustment for T2DM in model 3 (B=0.15[0.01;0.29]), and became non-significant after additional adjustment for potentially mediating cardiovascular risk factors in model 4 (B=0.14[0.00;0.28]). MDD was not associated with deep cortical WMH volume (B=0.11[-0.03;0.26]) or presence of CSVD (OR=1.32[0.91;1.91]) after adjustment for demographic risk factors in model 2.

Next, we tested whether above associations differ by age, sex and T2DM in model 3 (Supplementary Table S4.2). We found an interaction of MDD with age for white matter volume in model 3 (p=0.029), suggesting MDD is associated with a larger white matter volume in older participants only. The interaction attenuated and became non-significant in model 4 (p=0.082), which could be attributed to differences in blood pressure between young and old individuals with MDD. Next, an interaction of MDD with age for grey matter existed in model 3 (p=0.013) which remained statistically significant in model 5 (p=0.023). Results of stratified analyses were suggestive for an association between MDD and a lower grey matter volume in older participants (≥65 years, model 3: B=-0.12[-0.29;0.06]), while no association was observed in younger participants (<65 years, model 3: B=0.03[-0.05;0.10]). However, results in the older age group were statistically non-significant. Finally, we found an interaction of MDD

with T2DM on CSVD score in model 3 (p=0.026) which remained statistically significant in the fully adjusted model 5 (p=0.023). Stratified analyses of model 5 showed that MDD was associated with presence of CSVD in participants without T2DM (OR=1.65[1.06;2.56]), but not in participants with T2DM (OR=0.68[0.34;1.38]). In the former, MDD was also significantly associated with WHM volume (B=0.17[0.01;0.34]) and periventricular WMH volume (B=0.18[0.01;0.35]) in model 3, but not after adjustment for cardiovascular and lifestyle factors.

**Table 4.2 Associations of major depressive disorder with different domains of cognitive functioning**

| **Model** | **Memory score** Mean difference (95% CI) | *P*-value | **Information processing speed score** Mean difference (95% CI) | *P*-value | **Executive functioning & attention score** Mean difference (95% CI) | *P*-value | **Cognitive impairment (yes/no)** OR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|---|
| Model 1 | -0.15(-0.30;0.01) | 0.061 | -0.27(-0.40;-0.15) | <0.001 | -0.23(-0.36;-0.11) | <0.001 | 1.83(1.24;2.70) | 0.002 |
| Model 2 | -0.08(-0.21;0.06) | 0.257 | -0.22(-0.33;-0.12) | <0.001 | -0.18(-0.29;-0.06) | 0.002 | 1.89(1.28;2.79) | 0.001 |
| Model 3 | -0.06(-0.19;0.07) | 0.373 | -0.21(-0.31;-0.10) | <0.001 | -0.17(-0.28;-0.05) | 0.005 | 1.79(1.21;2.66) | 0.004 |
| Model 4 | -0.05(-0.18;0.08) | 0.447 | -0.20(-0.30;-0.10) | <0.001 | -0.16(-0.27;-0.04) | 0.008 | 1.74(1.17;2.59) | 0.007 |
| Model 5 | -0.02(-0.15;0.11) | 0.735 | -0.18(-0.28;-0.08) | 0.001 | -0.13(-0.25;-0.02) | 0.026 | 1.60(1.06;2.40) | 0.024 |

n=4,734. Major depressive disorder cases n=151. Regression results are presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CI indicates confidence interval; OR, odds ratio.

**Model 1:** crude.

**Model 2:** adjusted for age, sex, and educational level.

**Model 3:** additionally adjusted for type 2 diabetes mellitus.

**Model 4:** additionally adjusted for waist circumference, office systolic blood pressure, hypertensive medication, total/high density cholesterol ratio, lipid modifying medication, and history of cardiovascular disease (n=4,701).

**Model 5:** additionally adjusted for smoking behaviour and alcohol use (n=4,698).

**Table 4.3 Associations of major depressive disorder with markers of brain atrophy and cerebral small vessel disease**

| Model | CSF volume (per 1 SD) Mean difference (95% CI) | WM volume (per 1 SD) Mean difference (95% CI) | GM volume (per 1 SD) Mean difference (95% CI) | WMH volume (per 1 SD) Mean difference (95% CI) | DWMH volume (per 1 SD) Mean difference (95% CI) | PWMH volume (per 1 SD) Mean difference (95% CI) | CSVD (yes/no) OR (95% CI) |
|---|---|---|---|---|---|---|---|
| **Model 1** | -0.01(-0.14;0.12) | 0.01(-0.07;0.09) | -0.01(-0.09;0.08) | 0.11(-0.05;0.27) | 0.06(-0.10;0.22) | 0.13(-0.04;0.29) | 1.13(0.80;1.59) |
| **Model 2** | 0.02(-0.08;0.12) | 0.00(-0.08;0.07) | -0.01(-0.09;0.06) | 0.16(0.02;0.30) | 0.11(-0.03;0.26) | 0.18(0.04;0.32) | 1.27(0.88;1.83) |
| **Model 3** | -0.01(-0.11;0.10) | 0.01(-0.07;0.08) | 0.00(-0.07;0.07) | 0.14(-0.00;0.28) | 0.09(-0.06;0.23) | 0.15(0.01;0.29) | 1.24(0.86;1.79) |
| **Model 4** | -0.01(-0.11;0.09) | 0.00(-0.07;0.08) | 0.00(-0.07;0.08) | 0.12(-0.02;0.26) | 0.08(-0.07;0.22) | 0.14(0.00;0.28) | 1.22(0.84;1.76) |
| **Model 5** | -0.01(-0.11;0.09) | -0.02(-0.14;0.10) | 0.01(-0.07;0.08) | 0.12(-0.02;0.26) | 0.07(-0.08;0.21) | 0.13(-0.01;0.27) | 1.23(0.85;1.79) |

n=4,734. Major depressive disorder cases n=151. Regression results are presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CSF indicates cerebrospinal fluid; WM, white matter; GM, grey matter; SD, standard deviation; WMH, white matter hyperintensity; DWMH, deep cortical white matter hyperintensities; PWMH, periventricular white matter hyperintensities; CSVD, cerebral small vessel disease.
**Model 1:** adjusted for intracranial volume (except CSVD composite score) and MRI lag time.
**Model 2:** additionally adjusted for age, sex, and educational level.
**Model 3:** additionally adjusted for type 2 diabetes mellitus.
**Model 4:** additionally adjusted for waist circumference, office systolic blood pressure, hypertensive medication, total/high density cholesterol ratio, lipid modifying medication, and history of cardiovascular disease (n=4,701).
**Model 5:** additionally adjusted for smoking behaviour and alcohol use (n=4,698).

**Table 4.4 Decomposed associations of major depressive disorder with different domains of cognitive functioning in the subpopulation without type 2 diabetes**

| | Memory score | Information processing speed score | Executive functioning & attention score | Cognitive impairment (yes/no) |
|---|---|---|---|---|
| **Model** | Mean difference (95% CI) | Mean difference (95% CI) | Mean difference (95% CI) | OR (95% CI) |
| **WMH** | | | | |
| Direct | -0.08(-0.23;0.07) | -0.18(-0.30;-0.06)* | -0.12(-0.25;0.02) | 1.19(0.89;1.61) |
| Indirect | -0.02(-0.03;0.00) | -0.01(-0.02;0.00) | -0.01(-0.02;0.00) | 1.02(1.00;1.05) |
| Total | -0.10(-0.25;0.06) | -0.18(-0.31;-0.06)* | -0.13(-0.26;0.01) | 1.22(0.91;1.64) |
| **DWMH** | | | | |
| Direct | -0.08(-0.24;0.07) | -0.18(-0.30;-0.06)* | -0.12(-0.26;0.01) | 1.20(0.89;1.61) |
| Indirect | -0.01(-0.03;0.00) | -0.01(-0.02;0.00) | -0.01(-0.01;0.00) | 1.02(1.00;1.05) |
| Total | -0.10(-0.25;0.06) | -0.18(-0.31;-0.06)* | -0.13(-0.26;0.01) | 1.22(0.91;1.64) |
| **PWMH** | | | | |
| Direct | -0.08(-0.23;0.07) | -0.18(-0.30;-0.06)* | -0.12(-0.25;0.02) | 1.20(0.89;1.62) |
| Indirect | -0.02(-0.03;-0.00)* | -0.01(-0.01;0.00) | -0.01(-0.02;0.00) | 1.02(1.00;1.04) |
| Total | -0.10(-0.25;0.06) | -0.18(-0.31;-0.06)* | -0.13(-0.26;0.01) | 1.22(0.91;1.64) |
| **CSVD** | | | | |
| Direct | -0.07(-0.25;0.10) | -0.19(-0.31;-0.07)* | -0.14(-0.28;-0.00)* | 1.21(0.91;1.62) |
| Indirect | -0.01(-0.03;0.00) | -0.01(-0.02;0.00) | -0.00(-0.01;0.01) | 1.03(0.99;1.06) |
| Total | -0.08(-0.26;0.09) | -0.20(-0.32;-0.08)* | -0.15(-0.28;-0.01)* | 1.25(0.93;1.67) |

Regression results are decomposed in direct, indirect and total effects and presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CI indicates confidence interval; OR, odds ratio; MDD, major depressive; WMH, white matter hyperintensities; DWMH, deep cortical white matter hyperintensities; PWMH, periventricular white matter hyperintensities; CSVD, cerebral small vessel disease. Model 2 is adjusted for adjusted for age, sex, educational level. n=3,821, MDD cases n=102. *$p < 0.05$ (two-sided).

### *Mediation analyses of the association between MDD, CSVD and cognition*

In the above results we only found an association between MDD and markers of CSVD in the subpopulation without T2DM. Therefore, only mediation analyses in the subpopulation without T2DM are shown in Table 4.4. Mediation analyses of the total study population are shown in Supplementary Table S4.4. There was a modest indirect effect for periventricular WMH (model 2: B=-0.02[-0.03;-0.00]) on memory, in which 20% of the total effect of MDD on memory score could be attributed to its relation with periventricular WMH. Since the total effect itself was not significant itself, this is a marginal association. There were no mediation effects for other cognitive outcomes (Table 4.4).

### *Additional analyses*

Results of additional analyses are shown in Supplementary Tables S4.5-7. Since more participants had data on cognitive functioning than on MRI, we inspected potential selection bias by including only those with available MRI. Overall, associations between MDD and cognitive functioning were attenuated in the sample with available MRI compared to the full sample analyses (Table S4.5). Next, we performed several sensitivity analyses. First, to reduce potential misclassification of depression, we 1) additionally adjusted for anti-depressant medication, 2) exclude participants who used anti-depressant medication from the control group, 3) exclude participants with moderate to high depressive symptoms (PHQ-9 score ≥10) from the control group, and 4) exclude participants without MDD at baseline who did report a lifetime diagnosis of MDD from the control group. Second, we additionally adjusted for physical activity, Mediterranean diet score, and eGFR, which were missing in more participants and therefore not included in the main analyses. Third, we replaced office systolic blood pressure for 24h systolic blood pressure, waist circumference for BMI, and total-to-HDL cholesterol ration for triglycerides. All these adjustments did not materially change our results (Table S4.6). Previous studies that investigated structural brain abnormalities often focused on late-life depression above the age of 60 years [35]. To investigate whether associations between MDD and markers of brain atrophy and CSVD become stronger with age, we tested these association in several age categories (Table S4.7). This showed that associations between MDD and markers of brain atrophy and CSVD indeed became stronger with increasing age.

## Discussion

In this population-based imaging study, MDD was associated with higher odds of cognitive impairment, and more impaired performance in information processing speed and executive functioning & attention, but not memory. These associations were independent of demographic, cardiovascular, and lifestyle-related risk factors, and were similar in women and men, and in participants with and without T2DM. Contrary to our expectations, MDD was not associated with markers of brain atrophy or CSVD in the total study population. However, MDD was associated with CSVD in participants without T2DM, but this relation could not explain the associations between MDD and cognitive functioning.

Our finding that MDD is associated with generalized cognitive impairment corroborates previous evidence of a relation between depression and cognitive deficits [1], and are in line with studies that show that these cognitive deficits are often persistent [3] and can increase over time [4]. Cognitive impairment persists in 45% of patients even after remission of MDD [36].

We found participants with MDD and no T2DM had more evidence for CSVD, which mirrors previous findings [9]. The association between MDD and total WMH volume was statistically non-significant, while the association between MDD and periventricular WMH volume was statistically significant, after adjustment for demographic risk factors and T2DM. However, the difference in the strength of the association between MDD with respectively total WMH volume and periventricular WMH volume is <7%. In addition, the confidence intervals of these association are almost identical. The non-significant association with total WMH can be explained by the absence of an association between MDD and deep cortical WMH volume in our study population, which diluted the association between MDD and total WMH volume. Although some studies differentiate between periventricular and deep cortical WMH volume, results of a meta-analysis suggested that this categorical distinction may be arbitrary [37].

Others also found an association between depression and brain atrophy [7], but studies into whole brain grey matter volume have shown mixed results [8]. More consistent evidence has been found for volume reductions in specific brain areas such as the hippocampus, prefrontal cortex, insula, putamen, amygdala, and anterior cingulate-, prefrontal, and temporal cortex [8]. Moreover, it has been shown that the effect of depression on frontal and temporal grey matter volume reductions increases with age [38], for which we found tentative support as the

interaction between MDD and age on grey matter suggested that MDD is more strongly related to lower grey matter volumes in older age [7]. The reduced statistical power in the stratified analyses can explain the non-significant association between MDD and lower grey matter volume in the older subgroup. It may be that our study population was still too young (mean age 59.1±8.6 years) with limited variation in brain volumes to find an association between MDD and markers of brain atrophy, and consequently, a mediation of brain atrophy on the association between MDD and cognitive impairment as brain volume loss might have been subtle. Our finding that MDD is stronger associated with information processing speed and executive functioning & attention as compared to memory is more in line with an underlying vascular mechanism than a neurodegenerative mechanism involving the hippocampus[2].

As said, depressed participants without T2DM more often had signs of CSVD. In addition, total WMH and periventricular WHM load was higher. This was partly explained by their worse general vascular health profile, since associations with WMH and periventricular WMH became non-significant after adjustment for cardiovascular factors. Previous studies that adjusted for factors such as hypertension also reported modest associations [9]. The relatively young age and general absence of large confluent WHM (Fazekas score ≥3, n=37) in our sample may explain the subtler associations. The use of the categorical CSVD variable might have allowed a sharper contrast between those with high and low CSVD burden. As a consequence, associations between MDD and CSVD were comparable with a recent meta-analysis on the presence of significant WMH in MDD [9].

Despite above associations, neither CSVD nor markers of brain atrophy explained the worse cognitive profile of individuals with MDD in the total sample or among those without T2DM. It is possible that markers of CSVD and cognitive impairment are only related within a subgroup of depression (so-called vascular depression) [39], but such associations might be diluted at the population-average level. Contrary to our expectation, we did not observe an association between MDD and markers of brain atrophy or CSVD in individuals with T2DM. This might be because vascular burden in T2DM is already high. Although it has been shown that comorbid depression in T2DM is related to the development of macro- and microvascular complications [40], the presence of MDD might add little to the variation in the observed association with CSVD [41].

Several mechanisms have been suggested to be explain the higher risk of cognitive impairment in individuals with MDD. This includes neurobiological

effects of depression such as chronically increased cortisol levels and glutamatergic neurotoxicity [42], and decreased in heartrate variability and an increase in platelet activation and pro-inflammatory factors [43]. On the other hand, brain atrophy or ischemic damage in affect regulating centers (fronto-subcortical loop) might be a common etiological factor for both MDD and cognitive impairment. In that case, brain markers could be seen as a classical confounder for the association between MDD and cognitive impairment, though reported direct effects of MDD on cognition remained significant in models including the MRI markers. Next, lower grey matter volumes might be a marker of impending dementia [44] and the association be due to reverse causation. The stronger association in older age groups between MDD and grey matter seems in line with this, though we would have expected to find associations with intracranial CSF volumes, as a proxy of generalized brain atrophy, in particular. Finally, cognitive impairments might be a state effect of a current depressive episode. Yet, several studies suggest impairments are highly persistent or worsening in depression [36]. Importantly, above explanations are not mutually exclusive and different pathways might act in different individuals with accumulation and interaction of their effects.

Strengths of our study include its large sample size and population-based design; the oversampling of individuals with T2DM which provides insights of the investigated associations in this population with a high burden of depression [45], cognitive impairment and brain changes; the comparable prevalence rate of depression to other population-based studies; the use of the MINI diagnostic interview to assess MDD; the extensive assessment cognitive functioning by means of a comprehensive neuropsychological test battery with available norm scores to define cognitive impairment; inclusion of a broad range of potential confounders; and the performance of several sensitivity analyses to test the robustness of findings.

This study also has some limitations. First, the data were cross-sectional. Therefore, we cannot exclude reverse causality. Second, the study population was relatively young, with an upper age range of 75 years, and despite the oversampling of T2DM relatively healthy, which may have led to an underestimation of the associations with brain atrophy and CSVD. These effects appear to be more pronounce in older adults, as most studies who found these effects included participants above the age of 65 years. In addition, functional MRI research has linked MDD to abnormal functioning of cognition-related brain networks in individuals with an MDD onset below the age of 50 years [46]. Research into more subtle markers of brain changes, like brain

connectivity or functional measures, is therefore recommended for younger populations. Third, we adjusted for a range of potential confounders, but due to the cross-sectional assessment, we could not differentiate between cause and effect. Cardiovascular and lifestyle factors might very well be on the causal pathway from depression to brain changes, especially CSVD. This overadjustment might explain the loss of significant associations in models 4 and 5 in the analyses with WMH and periventricular WMH, and therefore we kept these factors in separate models [34]. Fourth, we performed multiple analyses in which we did not correct for multiple testing. Correction for multiple testing reduces the chance of type 1 error at the cost of increasing the risk for type 2 error. The markers for brain atrophy, CSVD, and cognitive impairment are correlated and based on the same shared risk factors and disease mechanisms. Furthermore, the magnitude of the associations is consistent and associations are directionally similar. Therefore, it is unlikely that our findings are a result of mere chance, against which multiple testing would safeguard. Fifth, we did not find an association between MDD and memory in our study sample with available MRI data, but the fact this association was present in the larger study sample including participants without MRI data suggests that depressed participants with MDD and poor memory were less likely to undergo MRI, leading to selection bias. This likely also applies to other population-imaging studies [47]. Finally, we did not study segmented brain areas to assess region-specific differences such as hippocampal or prefrontal lobar volumes. Most evidence for brain atrophy in depression is found in focal volume loss rather than generalized volume loss [48].

In a large cohort of community-dwelling participants aged between 40 and 75 years, MDD was associated with overall cognitive impairment and more impaired information processing speed and executive functioning & attention. MDD was further associated with CSVD in participants without T2DM, but this relation was insufficient to explain the associations between MDD and cognitive functioning. Longitudinal studies are needed to establish the mediation of structural brain damage in the development of cognitive impairment and dementia in MDD.

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## Supplemental Material to Chapter 4

### Supplemental Tables

**Table S4.1 Interaction analyses of associations of major depressive disorder with different domains of cognitive functioning**

| | Memory score | | Information processing speed score | | Executive functioning & attention score | | Cognitive impairment (yes/no) | |
|---|---|---|---|---|---|---|---|---|
| **Model 3** | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| **MDD*age** | -0.01(-0.21;0.11) | 0.526 | -0.01(-0.02;0.00) | 0.187 | 0.01(-0.01;0.02) | 0.448 | 1.00(0.96;1.05) | 0.955 |
| **MDD*women** | -0.04(-0.30;0.22) | 0.762 | 0.01(-0.20;0.21) | 0.934 | 0.01(-0.22;0.24) | 0.943 | 0.67(0.30;1.50) | 0.330 |
| **MDD*T2DM** | 0.08(-0.20;0.36) | 0.563 | -0.03(-0.25;0.19) | 0.762 | -0.07(-0.31;0.18) | 0.586 | 1.66(0.74;3.72) | 0.216 |

n=4,734. Major depressive disorder cases n=151. Regression results are presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CI indicates confidence interval; SD, standard deviation; OR, odds ratio; MDD, major depressive; T2DM, type 2 diabetes mellitus.
**Model 3:** adjusted for intracranial volume (except CSVD composite score), MRI lag time, age, sex, educational level, and type 2 diabetes mellitus.

**Table S4.2 Interaction analyses of associations of major depressive disorder with markers of brain atrophy**

| | CSF volume (per 1 SD) | | WM volume (per 1 SD) | | GM volume (per 1 SD) | |
|---|---|---|---|---|---|---|
| **Model 3** | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value |
| **MDD*age** | 0.00(-0.01;0.01) | 0.776 | 0.01(0.00;0.02) | 0.029 | -0.01(-0.02;-0.00) | 0.013 |
| **MDD*women** | 0.10(-0.10;0.31) | 0.334 | -0.08(-0.23;0.07) | 0.290 | -0.00(-0.15;0.14) | 0.961 |
| **MDD*T2DM** | -0.09(-0.32;0.13) | 0.402 | -0.03(-0.19;0.13) | 0.689 | 0.12(-0.04;0.27) | 0.142 |

n=4,734. Major depressive disorder cases n=151. Regression results are presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CSF indicates cerebrospinal fluid; WM, white matter; GM, grey matter; SD, standard deviation; MDD, major depressive disorder; T2DM, type 2 diabetes mellitus.
**Model 3:** adjusted for intracranial volume (except CSVD composite score), MRI lag time, age, sex, educational level, and type 2 diabetes mellitus.

**Table S4.3 Interaction analyses of associations of major depressive disorder with markers of cerebral small vessel disease**

| | WMH volume (per 1 SD) | | DWMH volume (per 1 SD) | | PWMH volume (per 1 SD) | | CSVD (yes/no) | |
|---|---|---|---|---|---|---|---|---|
| **Model 3** | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| **MDD*age** | 0.01(-0.01;0.03) | 0.330 | 0.01(-0.01;0.03) | 0.330 | 0.14(-0.00;0.03) | 0.110 | 0.99(0.95;1.04) | 0.774 |
| **MDD*women** | -0.13(-0.41;0.16) | 0.390 | -0.13(-0.41;0.16) | 0.390 | 0.02(-0.26;0.30) | 0.874 | 1.23(0.59;2.55) | 0.583 |
| **MDD*T2DM** | -0.14(-0.44;0.16) | 0.355 | -0.21(-0.52;0.10) | 0.186 | -0.12(-0.42;0.18) | 0.422 | 0.40(0.18;0.90) | 0.026 |

n=4,734. Major depressive disorder cases n=151. Regression results are presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). WMH indicates white matter hyperintensity; DWMH, deep cortical white matter hyperintensities; PWMH, periventricular white matter hyperintensities; CSVD, cerebral small vessel disease; SD, standard deviation; MDD, major depressive disorder; T2DM, type 2 diabetes mellitus.
**Model 3:** adjusted for intracranial volume (except CSVD composite score), MRI lag time, age, sex, educational level, and type 2 diabetes mellitus.

**Table S4.4 Decomposed associations of major depressive disorder with different domains of cognitive functioning in the total study population**

| | Memory score | Information processing speed score | Executive functioning & attention score | Cognitive impairment (yes/no) |
|---|---|---|---|---|
| **Model** | Mean difference (95% CI) | Mean difference (95% CI) | Mean difference (95% CI) | OR (95% CI) |
| **WMH** | | | | |
| Direct | -0.07(-0.20;0.06) | -0.18(-0.28;-0.08)* | -0.14(-0.26;0.03)* | 1.35(1.07;1.70)* |
| Indirect | -0.01(-0.02;0.00) | -0.01(-0.01;0.00) | -0.01(-0.01;0.00) | 1.02(1.00;1.03) |
| Total | -0.08(-0.21;0.05) | -0.19(-0.29;-0.09)* | -0.15(-0.26;-0.03)* | 1.37(1.09;1.73)* |
| **DWMH** | | | | |
| Direct | -0.07(-0.20;0.06) | -0.19(-0.29;-0.08)* | -0.14(-0.26;-0.03)* | 1.35(1.07;1.71)* |
| Indirect | -0.01(-0.02;0.00) | -0.00(-0.01;0.00) | -0.00(-0.01;0.00) | 1.01(0.99;1.03) |
| Total | -0.08(-0.21;0.05) | -0.19(-0.29;-0.09)* | -0.15(-0.26;-0.03)* | 1.37(1.08;1.73)* |
| **PWMH** | | | | |
| Direct | -0.07(-0.20;0.06) | -0.18(-0.29;-0.08)* | -0.14(-0.25;-0.03)* | 1.35(1.07;1.70)* |
| Indirect | -0.01(-0.02;0.00) | -0.01(-0.02;0.00) | -0.01(-0.02;0.00) | 1.01(1.00;1.03) |
| Total | -0.08(-0.21;0.05) | -0.19(-0.29;-0.09)* | -0.15(-0.26;-0.03)* | 1.36(1.08;1.72)* |
| **CSVD** | | | | |
| Direct | -0.06(-0.20;0.08) | -0.21(-0.31;-0.12)* | -0.20(-0.30;-0.10)* | 1.37(1.09;1.73)* |
| Indirect | -0.00(-0.01;0.00) | -0.00(-0.01;0.00) | -0.00(-0.01;0.00) | 1.01(0.99;1.03) |
| Total | -0.07(-0.21;0.07) | -0.22(-0.32;-0.12)* | -0.20(-0.30;-0.11)* | 1.39(1.10;1.75)* |

Regression results are decomposed in direct, indirect and total effects and presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CI indicates confidence interval; OR, odds ratio; MDD, major depressive; WMH, white matter hyperintensities; DWMH, deep cortical white matter hyperintensities; PWMH, periventricular white matter hyperintensities; CSVD, cerebral small vessel disease. Model 2 is adjusted for adjusted for age, sex, educational level. n=4,734, MDD cases n=151. *$p < 0.05$ (two-sided).

**Table S4.5 Associations of major depressive disorder with different domains of cognitive functioning in participants with and without missing MRI data**

| | Memory score | | Information processing speed score | | Executive functioning & attention score | | Cognitive impairment (yes/no) | |
|---|---|---|---|---|---|---|---|---|
| **Model** | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| **Study population with MRI data**[a] | | | | | | | | |
| Model 1 | -0.15(-0.30;0.01) | 0.061 | -0.27(-0.40;-0.15) | <0.001 | -0.23(-0.36;-0.11) | <0.001 | 1.83(1.24;2.70) | 0.002 |
| Model 2 | -0.08(-0.21;0.06) | 0.257 | -0.22(-0.33;-0.12) | <0.001 | -0.18(-0.29;-0.06) | 0.002 | 1.89(1.28;2.79) | 0.001 |
| Model 3 | -0.06(-0.19;0.07) | 0.373 | -0.21(-0.31;-0.10) | <0.001 | -0.17(-0.28;-0.05) | 0.005 | 1.79(1.21;2.66) | 0.004 |
| Model 4 | -0.05(-0.18;0.08) | 0.447 | -0.20(-0.30;-0.10) | <0.001 | -0.16(-0.27;-0.04) | 0.008 | 1.74(1.17;2.59) | 0.007 |
| Model 5 | -0.02(-0.15;0.11) | 0.735 | -0.18(-0.28;-0.08) | 0.001 | -0.13(-0.25;-0.02) | 0.026 | 1.60(1.06;2.40) | 0.024 |
| **Study population with missing MRI data**[b] | | | | | | | | |
| Model 1 | -0.25(-0.37;-0.13) | <0.001 | -0.35(-0.45;-0.25) | <0.001 | -0.35(-0.45;-0.24) | <0.001 | 2.73(2.07;3.61) | <0.001 |
| Model 2 | -0.18(-0.28;-0.07) | 0.001 | -0.29(-0.38;-0.21) | <0.001 | -0.28(-0.38;-0.19) | <0.001 | 2.80(2.11;3.70) | <0.001 |
| Model 3 | -0.16(-0.26;-0.05) | 0.003 | -0.27(-0.35;-0.19) | <0.001 | -0.26(-0.36;-0.17) | <0.001 | 2.64(1.99;3.50) | <0.001 |
| Model 4 | -0.14(-0.25;-0.04) | 0.008 | -0.26(-0.35;-0.18) | <0.001 | -0.26(-0.35;-0.16) | <0.001 | 2.57(1.93;3.43) | <0.001 |
| Model 5 | -0.11(-0.22;-0.00) | 0.044 | -0.24(-0.32;-0.15) | <0.001 | -0.23(-0.32;-0.14) | <0.001 | 2.37(1.77;3.17) | <0.001 |

[a]n=4,734. Major depressive disorder cases n=151.

[b]n=7,066. Major depressive disorder cases n=236.

Regression results are presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CI indicates confidence interval; SD, standard deviation; OR, odds ratio.

**Model 1:** crude.

**Model 2:** adjusted for age, sex, and educational level.

**Model 3:** additionally adjusted for type 2 diabetes mellitus.

**Model 4:** additionally adjusted for waist circumference, office systolic blood pressure, hypertensive medication, total/high density cholesterol ratio, lipid modifying medication, and history of cardiovascular disease (n=4,701 and n=7,006 in study population without and with missing MRI data respectively).

**Model 5:** additionally adjusted for smoking behaviour and alcohol use (n=4.698 and n=6,998 in study population without and with missing MRI data respectively).

**Table S4.6 Sensitivity analyses of associations of major depressive disorder with different domains of cognitive functioning**

| | Memory score | | Information processing speed score | | Executive functioning & attention score | | Cognitive impairment (yes/no) | |
|---|---|---|---|---|---|---|---|---|
| **Model** | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | Mean difference (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Model 5 | -0.02(-0.15;0.11) | 0.735 | -0.18(-0.28;-0.08) | 0.001 | -0.13(-0.25;-0.02) | 0.026 | 1.60(1.06;2.40) | 0.024 |
| Model 6: model 5 + antidepressant medication | 0.00(-0.13;0.13) | 0.994 | -0.16(-0.26;-0.05) | 0.003 | -0.10(-0.22;0.01) | 0.083 | 1.50(1.00;2.27) | 0.053 |
| Model 7: model 5 excl. antidepressant users from controls | -0.02(-0.15;0.11) | 0.735 | -0.18(-0.28;-0.08) | 0.001 | -0.13(-0.25;-0.02) | 0.026 | 1.60(1.06;2.40) | 0.024 |
| Model 8: model 5 excl. PHQ-9 score ≥10 from control | -0.02(-0.15;0.11) | 0.735 | -0.18(-0.28;-0.08) | 0.001 | -0.13(-0.25;-0.02) | 0.026 | 1.86(1.05;3.31) | 0.035 |
| Model 9: model 5 excl. lifetime MDD from controls | -0.02(-0.15;0.11) | 0.735 | -0.18(-0.28;-0.08) | 0.001 | -0.13(-0.25;-0.02) | 0.026 | 1.86(1.05;3.31) | 0.035 |
| Model 10: model 5 + physical activity[a] | -0.05(-0.18;0.10) | 0.529 | -0.21(-0.32;-0.10) | <0.001 | -0.15(-0.27;-0.02) | 0.019 | 1.62(1.04;2.53) | 0.034 |
| Model 11: model 5 + Mediterranean diet score[b] | -0.03(-0.16;0.11) | 0.690 | -0.21(-0.32;-0.10) | 0.001 | -0.13(-0.25;-0.01) | 0.031 | 1.66(1.09;2.53) | 0.018 |
| Model 12: model 5 + eGFR[c] | -0.03(-0.22;0.17) | 0.798 | -0.13(-0.29;0.02) | 0.093 | -0.18(-0.35;-0.01) | 0.037 | 2.07(1.18;3.66) | 0.012 |
| Model 13: model 5 replacing office SBP for 24h SBP[d] | -0.08(-0.30;0.14) | 0.485 | -0.12(-0.29;0.05) | 0.158 | -0.15(-0.34;0.04) | 0.127 | 1.57(0.80;3.07) | 0.191 |
| Model 14: model 5 replacing waist circumference for BMI | -0.02(-0.15;0.11) | 0.734 | -0.18(-0.28;-0.07) | 0.001 | -0.13(-0.25;-0.01) | 0.027 | 1.59(1.06;2.39) | 0.025 |
| Model 15: model 5 replacing total-to-HDL cholesterol ratio for triglycerides | -0.02(-0.15;0.11) | 0.742 | -0.18(-0.28;-0.08) | 0.001 | -0.13(-0.25;-0.02) | 0.025 | 1.60(1.07;2.40) | 0.023 |

Regression results are presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CI indicates confidence interval; SD, standard deviation; OR, odds ratio; MDD, major depressive; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure. Model 5 (n=4,734, MDD cases n=151) is adjusted for adjusted for age, sex, educational level, type 2 diabetes mellitus, waist circumference, office systolic blood pressure, hypertensive medication, total/high density cholesterol ratio, lipid modifying medication, history of cardiovascular disease, smoking behavior and alcohol use. [a]n=4,249, [b]n=4,459, [c]n=2,024, [d]n=1,805.

**Table S4.7 Age trend for the associations of major depressive disorder with markers of brain atrophy and cerebral small vessel disease**

| | CSF volume (per 1 SD) | WM volume (per 1 SD) | GM volume (per 1 SD) | WMH volume (per 1 SD) | DWMH volume (per 1 SD) | PWMH volume (per 1 SD) | CSVD (yes/no) |
|---|---|---|---|---|---|---|---|
| **Model 3** | Mean difference (95% CI) | Mean difference (95% CI) | Mean difference (95% CI) | Mean difference (95% CI) | Mean difference (95% CI) | Mean difference (95% CI) | OR (95% CI) |
| **Aged 40-50 years** | -0.09(-0.31;0.13) | -0.06(-0.23;0.11) | 0.13(-0.02;0.29) | -0.22(-0.51;0.06) | 0.01(-0.24;0.26) | -0.29(0.57;0.00) | 2.45(0.94;6.42) |
| **Aged 50-60 years** | -0.02(-0.17;0.14) | -0.03(-0.14;0.09) | 0.04(-0.07;0.15) | 0.20(-0.01;0.42) | -0.02(-0.23;0.19) | 0.27(0.06;0.48) | 0.85(0.46;1.57) |
| **Aged 60-70 years** | 0.09(-0.10;0.28) | 0.01(-0.13;0.15) | -0.08(-0.22;0.06) | 0.25(-0.02;0.52) | 0.25(-0.04;0.54) | 0.25(-0.02;0.51) | 1.44(0.79;2.63) |
| **Aged 70-80 years** | -0.03(-0.40;0.35) | 0.23(-0.02;0.48) | -0.20(-0.47;0.07) | 0.18(-0.30;0.65) | 0.26(-0.32;0.83) | 0.17(-0.30;0.63) | 1.16(0.39;3.46) |

[a]n=891. Major depressive disorder cases n=28.
[b]n=1,573. Major depressive disorder cases n=63.
[c]n=1,841. Major depressive disorder cases n=46.
[d]n=429. Major depressive disorder cases n=14.
Regression results are presented as mean difference or odds ratio (OR) with 95% confidence intervals (95% CI). CSF indicates cerebrospinal fluid; WM, white matter; GM, grey matter; SD, standard deviation; WMH, white matter hyperintensity; DWMH, deep cortical white matter hyperintensities; PWMH, periventricular white matter hyperintensities; CSVD, cerebral small vessel disease; SD, standard deviation.
**Model 3:** adjusted for intracranial volume (except CSVD composite score), MRI lag time, age, sex, educational level, and type 2 diabetes mellitus.

# Chapter 5

## The association of hyperglycaemia and insulin resistance with incident depressive symptoms over 4 years of follow-up: The Maastricht Study

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## Abstract

### Aims/hypothesis

Depression is twice as common in individuals with type 2 diabetes as in the general population. However, it remains unclear whether hyperglycaemia and insulin resistance are directly involved in the aetiology of depression. Therefore, we investigated the association of markers of hyperglycaemia and insulin resistance, measured as continuous variables, with incident depressive symptoms over 4 years of follow-up.

### Methods

We used data from the longitudinal population-based Maastricht Study (n=2848; mean age 59.9±8.1 years, 48.8% women, 265 incident depression cases, 10,932 person-years of follow-up). We assessed hyperglycaemia by fasting and 2 h post-load OGTT glucose levels, $HbA_{1c}$ and skin autofluorescence (reflecting AGEs) at baseline. We used the Matsuda insulin sensitivity index and HOMA-IR to calculate insulin resistance at baseline. Depressive symptoms (nine-item Patient Health Questionnaire score ≥10) were assessed at baseline and annually over 4 years. We used Cox regression analyses, and adjusted for demographic, cardiovascular and lifestyle risk factors.

### Results

Fasting plasma glucose, 2 h post-load glucose and $HbA_{1c}$ levels were associated with an increased risk for incident depressive symptoms after full adjustment (HR 1.20 [95% CI 1.08, 1.33]; HR 1.25 [1.08, 1.44]; and HR 1.22 [1.09, 1.37] per SD, respectively), while skin autofluorescence, insulin sensitivity index and HOMA-IR were not (HR 0.99 [0.86, 1.13]; HR 1.02 [0.85, 1.25]; and HR 0.93 [0.81, 1.08], per SD, respectively).

### Conclusions/interpretation

The observed temporal association between hyperglycaemia and incident depressive symptoms in this study supports the presence of a mechanistic link between hyperglycaemia and the development of depressive symptoms.

## Introduction

The prevalence of depression is nearly doubled in individuals with type 2 diabetes as compared with the general population, with prevalence rates of 6.5% to 33% [1]. Comorbid depression in type 2 diabetes is associated with impaired quality of life [2], worse self-care, suboptimal blood glucose levels and an increased risk for macro- and microvascular complications, mortality [3] and dementia [4]. In addition, their co-occurrence has an adverse economic impact with increased healthcare costs and decreased work productivity [5]. Furthermore, depression appears to be highly persistent and/or recurrent in type 2 diabetes [6]. Although there is evidence for a bidirectional association between type 2 diabetes and depression, the exact nature and the aetiological direction of the relationship remain unknown [1].

Hyperglycaemia and insulin resistance are key features of type 2 diabetes, and have been proposed as underlying mechanisms involved in the aetiology of depression [7]. Both fluctuations in plasma glucose and prolonged hyperglycaemia may be involved in the development of depression. The brain is particularly vulnerable to fluctuations in plasma glucose levels because neurons do not possess an active glucose transporter. As a consequence, high extracellular glucose levels lead to high intracellular glucose levels. The resulting biochemical changes, for instance the formation of reactive oxygen species (ROS) or AGEs, and accumulation of the resulting damage over the years, may lead to neuronal damage and/or disturbances of the hypothalamic–pituitary–adrenal axis, which eventually may lead to depression [7]. However, current evidence on the temporality of these associations remains scarce. A recent meta-analysis of prospective studies found an association between prevalent diabetes and incident depression but not between impaired glucose metabolism (IGM) or newly diagnosed type 2 diabetes and incident depression, compared with normal glucose metabolism (NGM) [8]. However, numbers for incident depression with IGM [9-11] or newly diagnosed type 2 diabetes were relatively small [10-13] and thus confidence intervals were large, and all studies used categorical instead of continuous values of glucose metabolism.

With regard to insulin resistance, only four prospective studies examined the association with incident depression. One study found an association [14], while the others did not [15-17]. However, these studies have important methodological limitations, such as a single follow-up assessment of depression [14,16,17], inclusion of only men [15] or only elderly men [14], a small study population [17] or a small number of incident depression cases [14].

In summary, there is a need for methodologically well-conducted prospective studies to assess whether hyperglycaemia and insulin resistance are temporally related to the development of depression. Therefore, the aim of this study was to examine the associations of markers of hyperglycaemia and insulin resistance measured as continuous variables with incident clinically relevant depressive symptoms within the population-based Maastricht Study. In addition, we assessed whether these associations were independent of demographic, cardiovascular and lifestyle risk factors, or differed between women and men. We hypothesised that hyperglycaemia and higher levels of insulin resistance are independently associated with incident clinically relevant depressive symptoms, and that these associations are similar in women and men.

## Methods

### *Study population and design*

The Maastricht Study is an observational population-based cohort study. The rationale and methodology have been described previously [18]. In brief, the study focuses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes and is characterised 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, the 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 baseline data from 3124 participants, who completed the baseline survey between November 2010 and September 2013. Figure 5.1 gives an overview of the study design. The baseline examinations of each participant were performed within a time window of 3 months. Follow-up data were only available for depression data and were available in 91.9%, 85.4%, 79.9% and 71.4% of the participants with available baseline data at, respectively, 1, 2, 3 and 4 years of follow-up. 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.

**Figure 5.1 Study design**

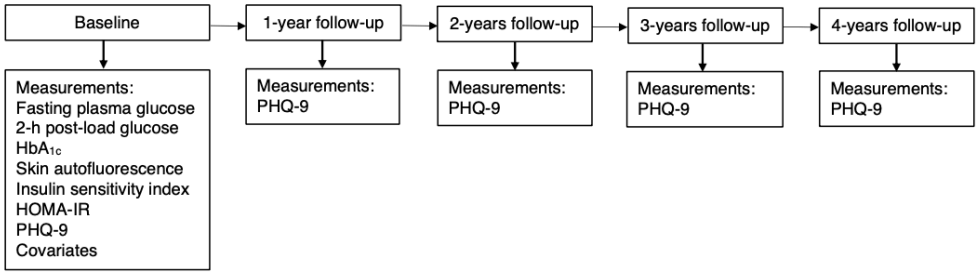
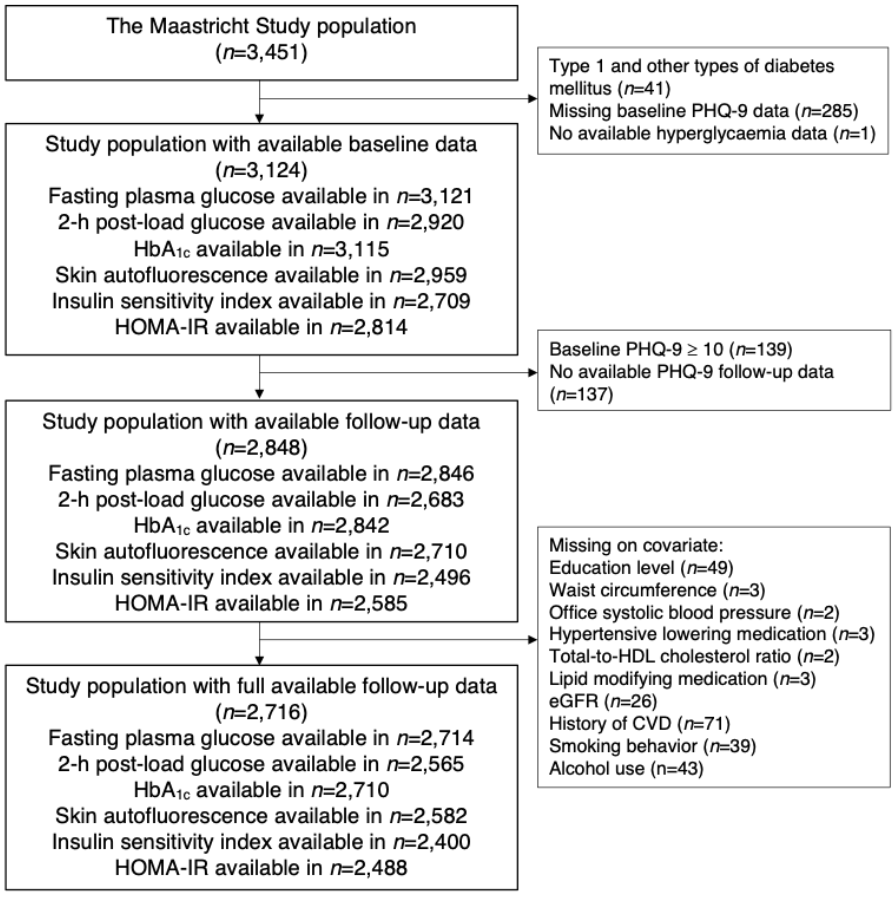



Figure 5.2 shows the flowchart of the study population. From the initial 3451 participants we excluded individuals with other types of diabetes than type 2 diabetes (*n*=41). For the cross-sectional analyses we included participants with available hyperglycaemia, insulin resistance and nine-item Patient Health Questionnaire (PHQ-9) data at baseline (*n*=3124). For the longitudinal analyses, we excluded participants with clinically relevant depressive symptoms at baseline (PHQ-9 score ≥10, *n*=139) or without any follow-up PHQ-9 data (*n*=137) to investigate the associations with newly developed depressive symptoms during follow-up, resulting in a study population of 2848 participants with an average follow-up duration of 3.8±1.0 years.

**Figure 5.2 Flowchart of study population**




Missing data on covariates are not mutually exclusive

### *Hyperglycaemia*

Markers of hyperglycaemia were measured at baseline. Participants, except those who used insulin (as endogenous insulin production is limited), underwent a standardised 2 h 75 g OGTT to determine fasting and 2 h post-load blood glucose levels 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*=42). Venous fasting and 2 h post-load plasma glucose levels were measured by the enzymatic hexokinase method on two automatic analysers, the Beckman Synchron LX20 (Beckman Coulter, CA, USA) for samples obtained between November 2010 and April 2012, and the Roche

Cobas 6000 (Roche Diagnostics, Mannheim, Germany) for samples obtained thereafter. Glucose metabolism status was defined according to the World Health Organization 2006 criteria as NGM, prediabetes (fasting glucose 6.1–7.0 mmol/l or 2 h post-load blood glucose 7.8–11.1 mmol/l) or type 2 diabetes (fasting blood glucose ≥7.0 mmol/l or 2 h post-load blood glucose ≥11.1 mmol/l, or used oral glucose-lowering medication or insulin) [19]. Type 1 diabetes and other types of diabetes were determined by use of a clinical interview. $HbA_{1c}$ was determined in fasting venous blood samples by ion-exchange high performance liquid chromatography [18]. Skin autofluorescence (SAF) was measured with the AGE Reader (DiagnOptics Technologies, Groningen, the Netherlands), which is a desktop device that uses ultra-violet light to excite autofluorescence in human skin tissue to estimate the level of AGE accumulation in the skin, as described elsewhere [20].

### *Insulin resistance*

Insulin resistance was assessed by the Matsuda insulin sensitivity index (ISI) and the HOMA-IR [21] at baseline only. The ISI was calculated as suggested by DeFronzo and Matsuda [22]: $ISI=10{,}000/(G_0 \times I_0 \times G_{mean} \times I_{mean})1/2$, where G and I represent plasma glucose ($mmol\,dl^{-1}$) and insulin ($mU\,l^{-1}$) concentrations, respectively, and '0' and 'mean' indicate fasting value and mean value during OGTT, respectively. The reciprocal (i.e., 1/ISI) was used to reflect insulin resistance as a risk factor. The ISI is strongly correlated ($r=0.73$, $p<0.0001$) with the rate of whole-body glucose disposal during the euglycaemic insulin clamp [23].

HOMA-IR was calculated with the HOMA2 calculator version 2.2.3 for Windows [24]. HOMA-IR is the most widely used and validated surrogate marker of insulin resistance and corresponds reasonably well to clamp-derived measures of insulin sensitivity [25]. Neither measure was calculated for participants receiving insulin treatment (*n*=169); as endogenous insulin levels will be close to zero, ISI and HOMA-IR calculations will result in zero as well.

### *Depressive symptoms*

Depressive symptoms were assessed by a validated Dutch version of the PHQ-9 [26] both at baseline and during annual follow-up over 4 years. The PHQ-9 is a self-administered questionnaire that assesses the presence of the nine symptoms for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a major depressive disorder (MDD) [27] on a four-point Likert-scale ranging from 0, 'not at all', to 4, 'nearly every day'. When one or two items were missing, the total score was calculated as 9×(total points/9–number of missing

items) and rounded to the nearest integer. When more items were missing, the total score was scored as missing.

A cut-off score of ≥10 is most often used as a dichotomous scoring system for defining clinically relevant depressive symptoms, with sensitivity and specificity of, respectively, 88% and 78% [28]. Online PHQ-9 questionnaires were completed annually during a follow-up period of 4 years. Prevalent depressive symptoms were defined as clinically relevant depressive symptoms at baseline (PHQ-9≥10). Incident depressive symptoms were defined as no depressive symptoms at baseline (PHQ-9 <10) and presence of clinically relevant depressive symptoms on at least one follow-up moment (PHQ-9≥10). In addition, at baseline only, current and lifetime diagnosis of MDD was assessed by the Mini-International Neuropsychiatric Interview (MINI) [29].

### *General characteristics and covariates*

General characteristics and covariates were measured at baseline. Educational level (low, intermediate, high), partner status (partner/no partner), history of CVD, smoking status (never, current, former), alcohol consumption (none, low, high), physical activity and Mediterranean diet score were assessed by questionnaires [18]. We measured height, weight, waist circumference, office blood pressure, plasma lipid profile, eGFR (in ml $min^{-1}$ 1.73 $m^{-2}$) and 24 h urinary albumin excretion (twice). Urinary albumin excretion was defined as normal (<15 mg/24 h), microalbuminuria (15 to <30 mg/24 h) or macroalbuminuria (≥30 mg/24 h). Medication use was assessed in a medication interview where generic name, dose and frequency were registered. More details about these general characteristics and covariates are provided in the electronic supplementary material (ESM) methods.

### *Statistical analysis*

All statistical analyses were performed by use of the Statistical Package for Social Sciences (version 25.0; IBM, Chicago, Illinois, USA). General characteristics of the study population were evaluated using independent *t* tests, Mann–Whitney *U* tests or $\chi^2$ tests. Negative binomial and logistic regression analyses were used to investigate the cross-sectional associations of markers of hyperglycaemia and insulin resistance per SD with, respectively, depressive symptoms and clinically relevant depressive symptoms. We used Cox proportional regression analyses to assess the association of markers of hyperglycaemia and insulin resistance per SD with incident depressive symptoms (PHQ-9≥10), with time-in-study as time axis. Participants were

censored at the date of the event or, in case of attrition, the last available date of follow-up, whichever came first. Hazard ratios indicate the increased risk for incident depressive symptoms per SD higher marker of hyperglycaemia or insulin resistance. We performed complete case analyses in which associations were adjusted for potential confounders in four models: model 1, crude; model 2, adjusted for demographic confounders (age, sex and educational level); model 3, additionally adjusted for cardiovascular risk factors (waist circumference, office systolic blood pressure, blood pressure-lowering medication, total-to-HDL-cholesterol ratio, lipid-modifying medication, eGFR and history of CVD); and model 4, additionally adjusted for modifiable lifestyle-related risk factors (smoking behaviour and alcohol use). We also investigated whether there was an interaction with sex in the fully adjusted model.

Several additional analyses were performed. To study whether the associations were driven by the oversampling of individuals with diagnosed type 2 diabetes, we additionally adjusted for type 2 diabetes, and excluded participants with type 2 diabetes from the analyses. To reduce potential misclassification of participants with subthreshold depression (MDD but low PHQ-9 scores due to remission or treatment), we performed the following sensitivity analyses; first, we additionally adjusted for use of antidepressant medication at baseline; second, we excluded participants who used antidepressant medication at baseline; and third, we excluded participants who had an MDD diagnosis at baseline. To restrict analyses to 'de novo' depression, we excluded participants who had a lifetime MDD diagnosis. We also applied stricter rules on the follow-up data, allowing no or a maximum of one missing follow-up measurement. Furthermore, we additionally adjusted for physical activity and Mediterranean diet score, as these data were missing in more participants. Finally, we replaced office systolic blood pressure with 24 h ambulatory systolic blood pressure, waist circumference with BMI and total-to-HDL-cholesterol ratio with triacylglycerols. A two-sided p value $<0.05$ was considered statistically significant.

## Results

### *General characteristics of the study population*

During 10,932 person-years of follow-up, 265 (9.3%) participants developed clinically relevant depressive symptoms (PHQ-9≥10; average follow-up time of 2.5±1.2 years), which yields an incidence rate of 24 cases per 1000 person-years. Participants not included in the analyses (n=603) were statistically significantly younger, had a lower level of education, less often had a partner,

had higher levels of hyperglycaemia and insulin resistance, and had a worse cardiometabolic risk profile than participants included in the analyses (data not shown).

Table 5.1 shows the general characteristics of the study population at baseline, stratified for incident depressive symptoms. Participants had a mean age of 59.9± 8.1 years and 48.8% were women. Participants with incident depressive symptoms had a worse cardiometabolic risk profile compared with participants free of depressive symptoms.

**Table 5.1 General characteristics and markers of hyperglycaemia and insulin resistance according to incident depression status**

| Characteristic | No depressive symptoms at baseline and follow-up (n=2583) | Incident depressive symptoms (PHQ-9≥10) (n=265) | *P*-value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 59.9±8.1 | 59.8±8.2 | 0.768 |
| Sex, n (% female) | 1263 (48.9) | 127 (47.9) | 0.796 |
| Educational level, low/medium/high, n (%) | 766/723/1048 (30.2/28.5/41.3) | 114/79/69 (43.5/30.2/26.3) | <0.001 |
| Partner status, n (%) (partner) | 2187 (85.8) | 218 (82.9) | 0.116 |
| **Depression** | | | |
| Depressive symptoms (PHQ-9 score) | 2.0±2.1 | 4.5±2.8 | <0.001 |
| MDD (MINI), n (%) | 23 (1.0) | 18 (7.1) | <0.001 |
| Anti-depressive medication, n (%) | 124 (4.8) | 40 (15.1) | <0.001 |
| **Cardiovascular risk factors** | | | |
| BMI (kg/m$^2$) | 26.7±4.3 | 28.5±5.2 | <0.001 |
| Waist circumference (cm) | 94.7±13.1 | 100.0±15.2 | <0.001 |
| Office systolic BP (mmHg) | 134.6±17.9 | 135.6±19.5 | 0.397 |
| Office diastolic BP (mmHg) | 76.1±9.7 | 76.6±11.2 | 0.480 |
| Antihypertensive medication, n (%) | 953 (37.0) | 133 (50.2) | <0.001 |
| Hypertension, n (%) | 1405 (54.5) | 165 (62.3) | 0.016 |
| Total-to-HDL-cholesterol ratio | 3.6±1.1 | 3.9±1.3 | 0.003 |
| Triacylglycerols (mmol/l) | 1.4±0.8 | 1.7±1.3 | <0.001 |
| Lipid-modifying medication, n (%) | 860 (33.4) | 109 (41.1) | 0.012 |
| eGFR (ml min$^{-1}$ 1.73 m$^{-2}$) | 88.3±14.3 | 86.6±16.6 | 0.124 |
| Albuminuria, normal/micro/macro, n (%) | 2238/157/15 (92.9/6.5/0.6) | 214/29/4 (86.6/11.7/1.6) | <0.001 |
| History of CVD, n (%) | 376 (15.0) | 66 (25.4) | <0.001 |
| Type 2 diabetes mellitus, n (%) | 612 (23.7) | 110 (41.5) | <0.001 |
| Diabetes medication (all types), n (%) | 456 (17.7) | 92 (34.7) | <0.001 |
| Diabetes medication (insulin), n (%) | 102 (3.9) | 32 (12.1) | <0.001 |
| **Life style factors** | | | |
| Smoking, never/former/current, n (%) | 929/1,340/278 (36.5/52.6/10.9) | 77/129/56 (29.4/49.2/21.4) | <0.001 |
| Alcohol use, none/low/high, n (%) | 399/1,443/702 15.7/56.7/27.6 | 68/144/49 26.1/55.2/18.8 | <0.001 |
| Physical activity (h/week) | 14.4±8.0 | 13.0±8.8 | 0.008 |
| Mediterranean diet score | 4.5±1.7 | 4.2±1.6 | 0.008 |
| **Markers of hyperglycaemia and insulin resistance** | | | |
| Fasting plasma glucose (mmol/l) | 5.9±1.4 | 6.6±2.2 | <0.001 |
| 2 h post-load glucose (mmol/l) | 7.6±4.0 | 8.9±4.9 | <0.001 |
| $HbA_{1c}$ (mmol/mol) | 39.9±8.5 | 44.4±11.5 | <0.001 |
| $HbA_{1c}$ (%) | 5.8±0.8 | 6.2±1.1 | <0.001 |
| SAF (AU) | 2.4±0.5 | 2.5±0.6 | 0.010 |
| HOMA-IR | 1.7±1.1 | 1.9±1.2 | 0.021 |
| ISI | 4.1±2.7 | 3.6±2.4 | 0.008 |

Data are presented as mean±SD or number and percentage, as appropriate. AU, arbitrary units.

In cross-sectional analyses, markers of hyperglycaemia and insulin resistance were associated with prevalent depressive symptoms. However, associations with insulin resistance were attenuated after adjustment for cardiovascular and lifestyle factors, in particular waist circumference (Table 5.2).

**Table 5.2 Cross-sectional associations of markers of hyperglycaemia and insulin resistance with prevalent depressive symptoms**

| Model | Prevalent depressive symptoms<br>Rate ratio (95% CI) | *P*-value | Prevalent clinically relevant depressive symptoms (PHQ-9≥10)<br>OR (95% CI) | *P*-value |
|---|---|---|---|---|
| **Markers of hyperglycaemia** | | | | |
| **Fasting plasma glucose (per 1 SD)** | | | | |
| Model 1 | **1.08 (1.04, 1.12)** | **<0.001** | **1.30 (1.15, 1.46)** | **<0.001** |
| Model 2 | **1.15 (1.10, 1.20)** | **<0.001** | **1.41 (1.25, 1.60)** | **<0.001** |
| Model 3 | **1.08 (1.03, 1.13)** | **0.001** | **1.17 (1.00, 1.36)** | **0.045** |
| Model 4 | **1.07 (1.02, 1.12)** | **0.008** | 1.13 (0.97, 1.32) | 0.130 |
| **2 h post-load glucose (per 1 SD)** | | | | |
| Model 1 | **1.04 (1.00, 1.08)** | **0.074** | **1.19 (1.01, 1.41)** | **0.042** |
| Model 2 | **1.10 (1.05, 1.15)** | **<0.001** | **1.35 (1.13, 1.61)** | **0.001** |
| Model 3 | 1.03 (0.98, 1.09) | 0.298 | 1.06 (0.84, 1.33) | 0.619 |
| Model 4 | 1.02 (0.97, 1.08) | 0.407 | 1.05 (0.84, 1.33) | 0.656 |
| **$HbA_{1c}$ (per 1 SD)** | | | | |
| Model 1 | **1.12 (1.07, 1.16)** | **<0.001** | **1.42 (1.26, 1.61)** | **<0.001** |
| Model 2 | **1.18 (1.13, 1.23)** | **<0.001** | **1.54 (1.35, 1.75)** | **<0.001** |
| Model 3 | **1.11 (1.06, 1.16)** | **<0.001** | **1.30 (1.11, 1.52)** | **0.001** |
| Model 4 | **1.08 (1.03, 1.13)** | **0.002** | **1.21 (1.03, 1.42)** | **0.022** |
| **SAF (per 1 SD)** | | | | |
| Model 1 | 1.03 (0.99, 1.08) | 0.122 | 1.18 (1.00, 1.39) | 0.051 |
| Model 2 | **1.11 (1.06, 1.16)** | **<0.001** | **1.43 (1.19, 1.72)** | **<0.001** |
| Model 3 | **1.07 (1.02, 1.13)** | **0.004** | **1.31 (1.07, 1.60)** | **0.009** |
| Model 4 | 1.04 (0.99, 1.09) | 0.152 | 1.18 (0.95, 1.45) | 0.129 |
| **Markers of insulin resistance** | | | | |
| **ISI (per SD)** [a] | | | | |
| Model 1 | 1.04 (1.00, 1.09) | .056 | 1.16 (0.93, 1.45) | 0.182 |
| Model 2 | **1.10 (1.05, 1.15)** | **<0.001** | **1.29 (1.02, 1.63)** | **0.033** |
| Model 3 | 1.02 (0.96, 1.07) | 0.598 | 0.89 (0.69, 1.15) | 0.363 |
| Model 4 | 1.01 (0.96, 1.07) | 0.621 | 0.88 (0.68, 1.14) | 0.323 |
| **HOMA-IR (per SD)** | | | | |
| Model 1 | **1.07 (1.02, 1.12)** | **0.004** | **1.20 (1.02, 1.42)** | **0.032** |
| Model 2 | **1.12 (1.07, 1.17)** | **<0.001** | **1.28 (1.08, 1.53)** | **0.005** |
| Model 3 | 1.03 (0.97, 1.09) | 0.345 | 0.95 (0.75, 1.20) | 0.665 |
| Model 4 | 1.02 (0.96, 1.08) | 0.485 | 0.93 (0.73, 1.18) | 0.561 |

Total number of participants included in model 1: n=3121 (fasting plasma glucose); n=2920 (2 h post-load glucose); n=3,115 ($HbA_{1c}$); n=2959 (SAF); n=2709 (ISI); and n=2814 (HOMA-IR).
Number of prevalent depression cases in model 1: n=138 (fasting plasma glucose); n=113 (2 h post-load glucose); n=139 ($HbA_{1c}$); n=131 (SAF); n=101 (ISI); and HOMA-IR (n=110).
**Model 1:** crude.
**Model 2:** adjusted for age, sex and educational level. Data missing, *n*=60 (fasting plasma glucose).
**Model 3:** additionally adjusted for waist circumference, office systolic blood pressure, hypertensive medication, total-to-HDL-cholesterol ratio, lipid-modifying medication and history of CVD. Additional missing data, *n*=128 (fasting plasma glucose).
**Model 4;** additionally adjusted for smoking behaviour and alcohol use. Additional missing data, *n*=97 (fasting plasma glucose).
[a] The reciprocal was used for the ISI (1/ISI)

### *Associations of hyperglycaemia with incident depressive symptoms*

Table 5.3 shows the associations of markers of hyperglycaemia with incident depressive symptoms. Fasting plasma glucose, 2 h post-load glucose and $HbA_{1c}$ levels were associated with an increased risk for incident depressive symptoms after full adjustment (HR 1.20 [95% CI 1.08, 1.33]; HR 1.25 [1.08, 1.44]; and HR 1.22 [1.09, 1.37] per SD, respectively). SAF was not associated with incident depressive symptoms (HR 0.99 [0.86, 1.13] per SD). No interactions were found with regard to sex for fasting plasma glucose (*p*-interaction=0.981), 2 h post-load glucose (*p*-interaction=0.234) and $HbA_{1c}$ (*p*-interaction=0.686). There was an interaction with sex for SAF (*p*-interaction=0.031); however, associations were not significant in stratified analyses for men (HR 1.13 [0.94, 1.37] per SD) or women (HR 0.83 [0.67, 1.02] per SD).

**Table 5.3 Associations of markers of hyperglycaemia and insulin resistance with incident depressive symptoms**

| Model | Incident depressive symptoms (PHQ-9≥10) HR (95% CI) | *P*-value |
|---|---|---|
| **Markers of hyperglycaemia** | | |
| **Fasting plasma glucose (per 1 SD)** | | |
| Model 1 | **1.35 (1.25, 1.46)** | **<0.001** |
| Model 2 | **1.33 (1.22, 1.45)** | **<0.001** |
| Model 3 | **1.21 (1.09, 1.34)** | **<0.001** |
| Model 4 | **1.20 (1.08, 1.33)** | **0.001** |
| **2 h post-load glucose (per 1 SD)** | | |
| Model 1 | **1.32 (1.18, 1.47)** | **<0.001** |
| Model 2 | **1.29 (1.14, 1.45)** | **<0.001** |
| Model 3 | **1.26 (1.09, 1.46)** | **0.002** |
| Model 4 | **1.25 (1.08, 1.44)** | **0.003** |
| **$HbA_{1c}$ (per 1 SD)** | | |
| Model 1 | **1.44 (1.32, 1.57)** | **<0.001** |
| Model 2 | **1.40 (1.27, 1.53)** | **<0.001** |
| Model 3 | **1.28 (1.15, 1.43)** | **<0.001** |
| Model 4 | **1.22 (1.09, 1.37)** | **0.001** |
| **SAF (per 1 SD)** | | |
| Model 1 | **1.15 (1.02, 1.30)** | **0.019** |
| Model 2 | 1.12 (0.99, 1.28) | 0.075 |
| Model 3 | 1.06 (0.93, 1.22) | 0.401 |
| Model 4 | 0.99 (0.86, 1.13) | 0.831 |
| **Markers of insulin resistance** | | |
| **ISI (per SD)** [a] | | |
| Model 1 | **1.22 (1.05, 1.43)** | **0.010** |
| Model 2 | **1.21 (1.03, 1.42)** | **0.018** |
| Model 3 | 1.03 (0.86, 1.23) | 0.748 |
| Model 4 | 1.03 (0.86, 1.23) | 0.783 |
| **HOMA-IR (per SD)** | | |
| Model 1 | **1.19 (1.06, 1.34)** | **0.003** |
| Model 2 | **1.19 (1.05, 1.34)** | **0.006** |
| Model 3 | 0.99 (0.84, 1.17) | 0.962 |
| Model 4 | 0.98 (0.83, 1.15) | 0.766 |

Total number of participants included in model 1: n=2846 (fasting plasma glucose); n=2683 (2 h post-load glucose); n=2842 ($HbA_{1c}$); n=2710 (SAF); n=2496 (ISI); and n=2585 (HOMA-IR)
Number of incident depression cases in model 1: n=265 (fasting plasma glucose); n=226 (2 h post-load glucose); n=264 ($HbA_{1c}$); n=254 (SAF); n=212 (ISI); and n=220 (HOMA-IR)
**Model 1:** crude
**Model 2:** adjusted for age, sex and educational level. Data missing, *n*=49 (fasting plasma glucose)
**Model 3:** additionally adjusted for waist circumference, office systolic blood pressure, hypertensive medication, total-to-HDL-cholesterol ratio, lipid-modifying medication and history of CVD. Additional missing data, *n*=71 (fasting plasma glucose)
**Model 4:** additionally adjusted for smoking behaviour and alcohol use. Additional missing data, *n*=133 (fasting plasma glucose)
[a] The reciprocal was used for the ISI to define it as risk factor (1/ISI)

### *Associations of insulin resistance with incident depressive symptoms*

Table 5.3 shows the associations of insulin resistance with incident depressive symptoms. A lower ISI and a higher HOMA-IR were associated with an increased risk for incident depressive symptoms after adjustment for age, sex and educational level (HR 1.20 [1.03, 1.41] and HR 1.19 [1.05, 1.34] per SD, respectively). After additional adjustment for cardiovascular risk factors, these associations were attenuated (HR 1.03 [0.86, 1.23] and HR 0.99 [0.84, 1.17] per SD, respectively). These attenuations were mainly caused by waist circumference (model 2 additionally adjusted for waist circumference: HR 1.04 [0.87, 1.24] and HR 1.02 [0.87, 1.19] per SD, respectively). No interaction with regard to sex was found for ISI (*p*-interaction=0.589) and HOMA-IR (*p*-interaction=0.621).

### *Additional analyses*

Results of additional analyses are shown in Table 5.4. Additional adjustment for type 2 diabetes, and excluding participants with type 2 diabetes from the analyses, did not materially change the associations. As expected, additional adjustment for type 2 diabetes attenuated the associations, but HRs remained directionally similar. Adjustments to reduce potential misclassification of participants with subthreshold depression did not materially change our results. Furthermore, applying stricter rules on the follow-up data, allowing no or a maximum of one missing follow-up measurement for the control participants, did not materially change our results (data not shown). Similar strengths of the associations were found after additional adjustment for physical activity or Mediterranean diet score. Furthermore, our results were not materially changed by replacing office systolic blood pressure with 24 h ambulatory systolic blood pressure, replacing waist circumference with BMI or replacing total-to-HDL-cholesterol ratio with triacylglycerols.

**Table 5.4 Additional analyses for associations of markers of hyperglycaemia with incident depressive symptoms**

| Model | Incident clinically relevant depressive symptoms (PHQ-9≥10) HR (95% CI) | *P*- value |
|---|---|---|
| **Fasting plasma glucose (per 1 SD)** | | |
| Model 4 | **1.20 (1.08, 1.33)** | **0.001** |
| Model 5: model 4 + type 2 diabetes | 1.12 (0.99, 1.27) | 0.085 |
| Model 6: model 4 excl. type 2 diabetes (excluded data n=683) | 1.35 (0.81, 2.25) | 0.255 |
| Model 7: model 4 + antidepressant medication | **1.20 (1.08, 1.33)** | **0.001** |
| Model 8: model 4 excl. antidepressant users (missing data n=152) | **1.18 (1.05, 1.33)** | **0.006** |
| Model 9: model 4 excl. baseline MDD (excluded data n=150) | **1.19 (1.06, 1.33)** | **0.003** |
| Model 10: model 4 excl. lifetime MDD (excluded data n=897) | 1.06 (0.87, 1.29) | 0.580 |
| Model 11: model 4 + physical activity (missing data n=160) | **1.19 (1.07, 1.33)** | **0.002** |
| Model 12: model 4 + Mediterranean diet (missing data n=123) | **1.18 (1.06, 1.32)** | **0.002** |
| Model 13: model 4 replacing office SBP for 24 h SBP (missing data n=294) | **1.19 (1.06, 1.33)** | **0.003** |
| Model 14: model 4 replacing waist circumference for BMI | **1.21 (1.09, 1.34)** | **<0.001** |
| Model 15: model 4 replacing total-to-HDL-cholesterol ratio for triacylglycerols | **1.17 (1.05, 1.30)** | **0.004** |
| **2 h post-load glucose (per 1 SD)** | | |
| Model 4 | **1.25 (1.08, 1.44)** | **0.003** |
| Model 5: model 4 + type 2 diabetes | 1.16 (0.93, 1.45) | 0.192 |
| Model 6: model 4 excl. type 2 diabetes (excluded data n=539) | 1.19 (0.78, 1.83) | 0.419 |
| Model 7: model 4 + antidepressant medication | **1.27 (1.10, 1.47)** | **0.001** |
| Model 8: model 4 excl. antidepressant users (missing data n=132) | **1.26 (1.08, 1.47)** | **0.003** |
| Model 9: model 4 excl. baseline MDD (excluded data n=143) | **1.23 (1.05, 1.44)** | **0.009** |
| Model 10: model 4 excl. lifetime MDD (excluded data n=840) | 1.18 (0.94, 1.49) | 0.163 |
| Model 11: model 4 + physical activity (missing data n=153) | **1.22 (1.04, 1.42)** | **0.014** |
| Model 12: model 4 + Mediterranean diet (missing data n=116) | **1.24 (1.06, 1.44)** | **0.006** |
| Model 13: model 4 replacing office SBP for 24 h SBP (missing data n=274) | **1.23 (1.05, 1.44)** | **0.008** |
| Model 14: model 4 replacing waist circumference for BMI | **1.25 (1.08, 1.44)** | **0.002** |
| Model 15: model 4 replacing total-to-HDL-cholesterol ratio for triacylglycerols | **1.21 (1.04, 1.40)** | **0.015** |
| **$HbA_{1c}$ (per 1 SD)** | | |
| Model 4 | **1.22 (1.09, 1.37)** | **0.001** |
| Model 5: model 4 + type-2 diabetes | 1.14 (1.00, 1.31) | 0.057 |
| Model 6: model 4 excl. type-2 diabetes (excluded data n=684) | 1.23 (0.82, 1.83) | 0.318 |

**Table 5.4 (Continued)**

| Model | Incident clinically relevant depressive symptoms (PHQ-9≥10) HR (95% CI) | *P*- value |
|---|---|---|
| Model 7: model 4 + antidepressant medication | **1.23 (1.10, 1.38)** | **<0.001** |
| Model 8: model 4 excl. antidepressant users (missing data n=152) | **1.18 (1.03, 1.34)** | **0.017** |
| Model 9: model 4 excl. baseline MDD (excluded data n=150) | **1.21 (1.07, 1.37)** | **0.003** |
| Model 10: model 4 excl. lifetime MDD (excluded data n=894) | 1.08 (0.87, 1.33) | 0.486 |
| Model 11: model 4 + physical activity (missing data n=160) | **1.25 (1.11, 1.41)** | **<0.001** |
| Model 12: model 4 + Mediterranean diet (missing data n=123) | **1.20 (1.06, 1.35)** | **0.004** |
| Model 13: model 4 replacing office SBP for 24 h SBP (missing data n=294) | **1.23 (1.08, 1.41)** | **0.002** |
| Model 14: model 4 replacing waist circumference for BMI | **1.23 (1.10, 1.38)** | **<0.001** |
| Model 15: model 4 replacing total-to-HDL-cholesterol ratio for triacylglycerols | **1.20 (1.07, 1.35)** | **0.002** |
| **SAF (per 1 SD)** | | |
| Model 4 | 0.99 (0.86, 1.13) | 0.831 |
| Model 5: model 4 + type-2 diabetes | 0.94 (0.85, 1.11) | 0.606 |
| Model 6: model 4 excl. type-2 diabetes (excluded data n=658) | 0.87 (0.72, 1.05) | 0.154 |
| Model 7: model 4 + antidepressant medication | 1.00 (0.87, 1.15) | 0.975 |
| Model 8: model 4 excl. antidepressant users (missing data n=147) | 1.01 (0.87, 1.18) | 0.852 |
| Model 9: model 4 excl. baseline MDD (excluded data n=145) | 1.01 (0.87, 1.17) | 0.876 |
| Model 10: model 4 excl. lifetime MDD (excluded data n=854) | 1.00 (0.81, 1.25) | 0.985 |
| Model 11: model 4 + physical activity (missing data n=150) | 1.03 (0.89, 1.19) | 0.696 |
| Model 12: model 4 + Mediterranean diet (missing data n=117) | 1.00 (0.87, 1.16) | 0.986 |
| Model 13: model 4 replacing office SBP for 24 h SBP (missing data n=280) | 0.93 (0.81, 1.08) | 0.353 |
| Model 14: model 4 replacing waist circumference for BMI | 0.99 (0.86, 1.14) | 0.897 |
| Model 15: model 4 replacing total-to-HDL-cholesterol ratio for triacylglycerols | 0.98 (0.86, 1.13) | 0.800 |

Total number of participants in model 4: n=2714 (fasting plasma glucose); n=2565 (2 h post-load glucose); n=2710 ($HbA_{1c}$); n=2582 (SAF)
Incident depressive symptoms in model 4: n=254 (fasting plasma glucose); n=217 (2 h post-load glucose); n=253 ($HbA_{1c}$); and n=244 (SAF)
Model 4 is adjusted for age, sex, educational level, waist circumference, office systolic blood pressure, hypertensive medication, total-to-HDL-cholesterol ratio, lipid-modifying medication, history of CVD, smoking behaviour and alcohol use
Excl., excluding; SBP, systolic blood pressure

## Discussion

This population-based study demonstrates that fasting plasma glucose, 2 h post-load glucose and $HbA_{1c}$ were associated with incident depressive symptoms, with an increased risk of ~20% per SD higher level of hyperglycaemia markers. These associations were independent of demographical, cardiovascular and lifestyle-related risk factors, and were similar in women and men. The association of insulin resistance with incident depressive symptoms was explained by cardiovascular risk factors (waist circumference). Our results suggest that hyperglycaemia precedes the development of depression, and may be directly involved in its aetiology.

Our finding that hyperglycaemia is associated with incident depressive symptoms corroborates and further extends previous evidence of an association between type 2 diabetes and incident depression [30], and provides additional evidence that hyperglycaemia as such may be involved in the development of depression. This is in line with results of a large-scale cross-sectional study that showed an association between both diagnosed and undiagnosed diabetes and higher prevalence of depression [31]. Although a previous meta-analysis concluded that hyperglycaemia is unlikely to be causally related to incident depressive symptoms [8], this study did not investigate a linear contribution of hyperglycaemia to the incidence of depression.

Several pathophysiological pathways may explain the association between hyperglycaemia and incident depression. Hyperglycaemia is associated with generalised microvascular dysfunction [32], which may consequently lead to cerebral small vessel disease and subsequent depression [33]. Indeed, a recent meta-analysis showed that cerebrovascular damage was associated with incident depression [34]. Optimising blood glucose levels is the most effective therapy to prevent the development of microvascular complications in type 2 diabetes, and could potentially also contribute to preventing or slowing down the development of depressive symptoms. Alternatively, suboptimal blood glucose levels may also identify those individuals at high risk for depression. Furthermore, hyperglycaemia has been associated with low-grade inflammation [35], which in turn has been associated with cerebrovascular damage [36] and incident depression as well [37]. In support of this potential mechanism, several studies have shown that treatment resistance to antidepressants is associated with low-grade inflammation [38] and that anti-inflammatory therapy may be beneficial to individuals with depression [39]. Moreover, hyperglycaemia may activate the polyol pathway which induces oxidative stress, increases lipid peroxidation and

imbalances the generation of ROS [40]. These processes may lead to apoptosis in the brain, which may eventually lead to depression via shrinkage of specific brain structures (atrophy) [41]. This assumption is supported by a stronger association between oxidative stress and depression in individuals with IGM and type 2 diabetes than in those with NGM [42]. Furthermore, previous studies have assumed that diabetes may increase risk of depression because of disease burden [8]. However, disease burden alone may be not sufficient to explain the association between hyperglycaemia and incident depression, since 65% of the association remained after additional adjustment for type 2 diabetes. In addition, the suggestion that somatic symptoms may explain this association is unlikely, as a previous study of our group has shown that affective and somatic symptoms do not differ between individuals with and individual without type 2 diabetes [43].

We found no association between SAF and incident depressive symptoms, although earlier cross-sectional analyses in a smaller dataset (n=866) from The Maastricht Study did show an association between higher SAF and prevalent depression [20]. SAF is thought to represent the accumulation of fluorescent AGEs in the skin, but may be a less specific measure of hyperglycaemia, as it also measures other fluorescent proteins in the skin and does not reflect non-fluorescent AGEs [44]. Nevertheless, there are currently no other prospective studies available that have assessed this association. Therefore, this finding warrants replication in other prospective population-based studies in order to draw firm conclusions.

We found that the association of insulin resistance with incident depression was explained by CVD risk factors, in particular central obesity. This is in contrast with results of the Whitehall II Study, the Caerphilly Study and the Pittsburgh Healthy Heart Project, which did not show an association between insulin resistance and incident depression after adjustment for age only [15,16]. Furthermore, our results contrast with the results of the Health in Men Study, which did show an association between higher insulin resistance and incident depression after adjustment for cardiovascular risk factors including central obesity [14]. However, the Health in Men Study only included older men aged 70-93 years, which hinders direct comparison with our somewhat younger population. There are several explanations for the attenuation of the association between insulin resistance and incident depressive symptoms after adjustment for central obesity. First, central obesity may be on the causal pathway from insulin resistance to depression, which might have resulted in overadjustment. Second, as performing clamps is not feasible in large-scale studies, we used surrogate markers of insulin resistance. These markers moderately reflect hepatic and muscular insulin

resistance, which may or may not coincide with cerebral insulin resistance [45]. Consequently, we cannot fully exclude the possibility that cerebral insulin resistance is involved in the development of depression. Third, insulin resistance is less precisely measured than hyperglycaemia. The use of surrogate markers of insulin resistance may have created more noise in the data as compared with the direct markers of hyperglycaemia. Alternatively, hyperglycaemia may be one of the mechanisms linking insulin resistance to depression. Obesity is associated with the development of insulin resistance, but only individuals who lack sufficient insulin secretion to match the degree of insulin resistance will develop type 2 diabetes [46].

The association of hyperglycaemia with an increased risk of depressive symptoms has important clinical implications. First, professionals in diabetes care should be aware of the prevalence of depression, and use diagnostic skills to recognise and treat depression properly. For this, specific guidelines to identify and manage depressive symptoms in diabetes care have been developed [47]. In addition to these guidelines, it is important to distinguish between need for treatment and a high score on a questionnaire [48]. Since depression in individuals with type 2 diabetes is often persistent [6], and is related to suboptimal blood glucose levels [3], early recognition and treatment of depressive symptoms could have a favourable effect on the outcome of both diseases [49]. Considering the high comorbidity of depression and type 2 diabetes, integrated care approaches that treat these conditions jointly need to be implemented in diabetes care.

Strengths of our study include its large sample size and population-based longitudinal design; the oversampling of individuals with type 2 diabetes which results in more variability within the high ranges of hyperglycaemia; the annual assessment of the PHQ-9 to assess depressive symptoms over a 4 year period; the comparable incidence rate of depression to other population-based studies; the use of multiple continuous markers of hyperglycaemia; the extensive assessment of potential confounders; and the execution of several sensitivity analyses.

This study has some limitations. First, there could have been selection and/or attrition bias, which is inherent to prospective population-based studies; individuals with more severe depressive symptoms or with greater comorbidity may have been more likely not to participate or to withdraw, which may have led to an underestimation of the observed associations. Second, the study population was relatively well treated with regard to glucose metabolism, which may mean that the effects of fasting plasma glucose, 2 h post-load glucose and $HbA_{1c}$ on

incident depression were suppressed. Estimates of post-load glucose, ISI and HOMA-IR, did not include insulin users, which may have led to an underestimation of the observed findings in more severe type 2 diabetes. Third, the population was mainly of white ethnicity and aged 40–75 years, which should be considered when extrapolating these findings to other populations. Fourth, we measured depressive symptoms with the PHQ-9 questionnaire. High scores on this questionnaire are suggestive for depressive symptoms, but do not necessarily equate with MDD. Finally, because follow-up data were only available for depression data, we could not rule reverse causality; there might be a reciprocal relation in which depression may also lead to hyperglycaemia.

**Conclusion**

In conclusion, we showed that higher levels of hyperglycaemia were associated with incident depressive symptoms in a population-based setting, independent of major demographical, cardiovascular and lifestyle risk factors. The association of insulin resistance with incident depressive symptoms was dependent on cardiovascular risk factors, in particular, central obesity. These findings establish a temporal relation between hyperglycaemia and incident depressive symptoms, supporting the concept that hyperglycaemia itself is involved in the aetiology of depression, and thus may provide a potential target for the prevention of depression in individuals with and without type 2 diabetes.

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## Supplemental Material to Chapter 5

## Supplemental Methods

### Measurements of cardiovascular risk factors

History of cardiovascular disease was assessed with a modified version of the Rose Questionnaire for the diagnosis of ischemic heart pain and intermittent claudication [1] and defined as self-reported myocardial infarction, and/or cerebrovascular infarction or hemorrhage, and/or percutaneous artery angioplasty of, or vascular surgery on, the coronary arteries, abdominal arteries, peripheral arteries or carotid arteries. Waist circumference was measured with a flexible plastic tape measure (Seca, Hamburg, Germany) midway between the lower rib margin and the iliac crest at the end of expiration. 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), and calculated BMI as weight (kg) divided by height ($m^2$). Venous fasting and 2 h post-load plasma glucose levels were measured by the enzymatic hexokinase method on two automatic analyzers, the Beckman Synchron LX20 (Beckman Coulter, CA, USA) for samples obtained between November 2010 and April 2012, and the Roche Cobas 6000 (Roche Diagnostics, Mannheim, Germany) for samples obtained thereafter. HbA1c was determined by ion-exchange high performance liquid chromatography. Serum concentrations of total cholesterol, HDL cholesterol, and triacylglycerols were measured by use of an automatic analyzer (Beckman Synchron LX20, Beckman Coulter Inc. Brea, USA). Office blood pressure was calculated as the mean of at least three blood pressure readings (Omron 705IT, Japan) performed after a minimum of 10 min rest. We measured serum creatinine and cystatin C [2], and 24 h urinary albumin excretion (twice) as described previously [3]. Estimated glomerular filtration rate (eGFR; ml min–1 1.73 m–2) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on both serum creatinine and serum cystatin C.

### Measurements of covariates

Educational level was assessed by web-based questionnaire and divided into three categories: low (none, primary or lower vocational education only), intermediate (intermediate general secondary, intermediate vocational or higher general secondary education), and high (higher vocational education or university level of education) [4]. Alcohol consumption is assessed as part of the food frequency questionnaire [5] and categorized into three categories: 1) nonconsumers, 2) low consumers (less than or equal to seven glasses per week for women and $\leq$ 14 glasses per week for men), and 3) high consumers (more than seven glasses per week for women and >14 glasses per week for men) [6]. All participants received an extensive web-based community healthy activities model program for seniors (CHAMPS) physical activity questionnaire [3,7]. Activities included walking, cycling, gardening, household work, jogging/running, swimming, tennis,

team sport, light and intensive exercise. The total number of hours of physical activity in the past week was used to calculate a sum score of total physical activity.

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# Chapter 6

## The bidirectional longitudinal association between depressive symptoms and HbA1c: a systematic review and meta-analysis

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## Abstract

### Aim

To investigate whether there is a bidirectional longitudinal association of depression with HbA1c.

### Methods

We conducted a systematic literature search in PubMed, PsycINFO, CINAHL and EMBASE for observational, longitudinal studies published from January 2000 to September 2020, assessing the association between depression and HbA1c in adults. We assessed study quality with the Newcastle-Ottawa-Scale. Pooled effect estimates were reported as partial correlation coefficients ($r_p$) or odds ratios (OR).

### Results

We retrieved 1,642 studies; 26 studies were included in the systematic review and eleven in the meta-analysis. The majority of studies (16/26) focused on type 2 diabetes. Study quality was rated as good (n=19), fair (n=2) and poor (n=5). Of the meta-analysed studies, six investigated the longitudinal association between self-reported depressive symptoms and HbA1c and five the reverse longitudinal association, with a combined sample size of n = 48,793 and a mean follow-up of 2 years. Higher levels of baseline depressive symptoms were associated with subsequent higher levels of HbA1c (partial r = 0.07; [95% CI 0.03, 0.12]; I2 38%). Higher baseline HbA1c values were also associated with 18% increased risk of (probable) depression (OR = 1.18; [95% CI 1.12, 1.25]; I2 0.0%).

### Conclusions

Our findings support a bidirectional longitudinal association between depressive symptoms and HbA1c. However, the observed effect sizes were small and future research in large-scale longitudinal studies is needed to confirm this association. The results may have clinical implications, as depressive symptoms and HbA1c levels could be targeted concurrently in the prevention and treatment of diabetes and depression.

## Introduction

Depression and diabetes mellitus are among the leading causes of disability worldwide. The most recent estimates, available for 2017, suggest worldwide 264 million people living with depression and 476 million with diabetes; these figures are expected to rise.[1] The co-occurrence of type 2 diabetes and depression is frequently reported, and their association is suggested to be bidirectional.[2–7] Meta-analyses report a 15% increased risk of depression in individuals with diabetes.[2] For incident diabetes in individuals with depression, risk estimates in meta-analyses vary from 38-60%.[2,8] Individuals with comorbid depression and diabetes have shown a greatly reduced health-related quality of life, compared to individuals with only depression or only diabetes.[9] Moreover, depression in the presence of diabetes has been linked to an increased risk of incident diabetes complications such as retinopathy, neuropathy, and nephropathy,[10] as well as cardiac events,[11] cardiovascular mortality [11,12] and all-cause mortality.[12]

A possible mechanism linking depression to these adverse health outcomes are suboptimal blood glucose levels, measured with HbA1c. HbA1c levels are a key target in diabetes therapy because persistent or recurrent high glucose levels can damage blood vessels resulting in vascular complications. However, prior studies that investigated the association between depression and HbA1c have yielded inconsistent findings and faced methodological limitations. A landmark meta-analysis by Lustman and colleagues[13] reported a small to moderate association between depression and suboptimal HbA1c for type 1 and type 2 diabetes. However, the meta-analysis included mainly cross-sectional studies, limiting the ability to infer temporality. This seminal review was published in 2000; since then, a substantial number of new studies has become available.

The reverse association on impaired glucose metabolism and the risk of incident depression has been recently addressed by Tong et al.[14] In this meta-analysis, individuals with previously diagnosed diabetes had a higher risk of developing depressive symptoms compared to individuals with normal glucose metabolism. For individuals with newly diagnosed diabetes or impaired glucose metabolism, no significant association with depression was found. However, the numbers of individuals with incident depression within the impaired glucose metabolism or newly diagnosed type 2 diabetes groups were relatively small and thus confidence intervals were wide and the power to detect differences was low. Furthermore, this meta-analysis explored categories of glucose metabolism as opposed to continuous glucose measures and did not include individuals with type 1 diabetes.

In summary, prior evidence regarding depression as a risk factor for suboptimal HbA1c levels revealed mixed findings, is mainly based on cross-sectional data and needs updating, whereas the evidence regarding suboptimal HbA1c levels as a risk factor for depression needs increased power to assess the association of early hyperglycaemia with depression. Further, there is a need to assess whether the association is truly bidirectional which requires (large scale) longitudinal data. Therefore, we conducted a systematic review and meta-analysis to investigate (I) whether there is a longitudinal association between depression and HbA1c levels, and (II) whether there is a longitudinal association between HbA1c levels and depression. We hypothesized that higher HbA1c levels will be associated with a higher risk for depression, and vice versa.

## Methods

### *Search strategy*

We performed a systematic literature search in the following databases: PubMed, PsycINFO (Ebsco), CINAHL (Ebsco), and EMBASE (OVID). Searches were conducted for studies indexed between January 1, 2000 to July 29, 2019 and were updated until September 30, 2020. We restricted to articles written in English, Dutch, German, Spanish or French. Studies published before January 2000 were not included due to the previous meta-analysis by Lustman et al. including studies up until that date.[13]

This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42019147551) and is performed in accordance with the MOOSE guidelines[15] and the PRISMA guidelines.[16] A search strategy was developed based on the following search terms including their variants: (I) glycaemic/glycemic control, (II) depression/depressive symptoms and (III) cohort/longitudinal studies. The search terms are provided in detail in Table S6.1.

### *Selection criteria*

Two pairs of reviewers (MB and MS, RM and AG) independently screened the titles and abstracts retrieved. Subsequently, full-text screening was performed in parallel by MB and RM based on predefined in- and exclusion criteria. Any disagreement was resolved by consulting a third reviewer. Additionally, we hand-searched reference lists of papers eligible for inclusion. The core criteria for inclusion were a prospective cohort study design with two or more measurements, a study sample size of > 50 participants, and an adult (≥ 18

years) study population. Only studies that partially or solely included individuals with type 1 or type 2 diabetes were eligible for inclusion. Studies had to include a variable for depression (all types) or depressive symptoms, and a continuous variable for HbA1c levels, and report an estimate of the longitudinal association between them. The determinant had to be assessed at one or more time points and the outcome at two or more time points. As we looked at both depressive symptoms based on self-report questionnaires and clinical diagnosis of major depressive disorder, we use the term 'depression' to refer to both. Randomised controlled trials and other intervention studies were excluded because they would answer a different research question and require different methodology.

***Data extraction***

We pilot tested the data extraction form independently (MB and RM) using six studies to minimise bias and errors. As the extractions were highly comparable, one reviewer (MB) completed the data extraction. AG extracted the data from the new studies identified during the repeated search. The following characteristics of the included studies were extracted: Authors, year of publication, country, age, sex, detailed description of the study population, sample size, assessment method for depression, diabetes type, assessment method for HbA1c, use of medication for depression/diabetes, diabetes distress, study duration, number and time of follow-up measurements, reasons for exclusion/loss to follow up, statistical analysis, effect measures (crude and adjusted) with confidence intervals, standard errors or p-values, confounding factors, and stratified analyses including results.

***Quality assessment***

The quality of the included studies was assessed by use of the Newcastle-Ottawa-Scale (NOS) which examines three domains: selection, comparability, and outcome. The slightly adjusted version of the NOS including a rationale for adjustments can be found in the Supporting Information. One reviewer (MB) conducted the quality assessment which was independently assessed by a second reviewer for 30% of the included articles (RM). In order to judge the overall quality of a study, results were converted to the Agency for Healthcare Research and Quality Standards (see Supporting Information - Methods).

***Statistical analysis***

All statistical analyses were conducted in R by use of the metafor package (R version 3.6.2).[17] Studies were stratified based on whether HbA1c or depression

was used as outcome variable and two meta-analyses were conducted by use of a random-effects model. If both the crude and adjusted effect estimate were presented in the article, the adjusted effect estimate was chosen, as advised by the COSMOS-E guidelines.[18] In order to enable pooling of the results, regression coefficients were transformed into partial correlation coefficients (rp).[19,20] Fisher's r-to-z transformation was applied to stabilise variances of the $r_p$.[21] For studies with depression as outcome variable, effect measures were transformed into ORs, if needed. For this purpose, ORs were log-transformed to normalise their distribution. The pooled estimates and 95% CI were displayed in forest plots. We assessed heterogeneity using $I^2$ statistics (low (25%), moderate (50%), high (75%)) and determined the risk of publication bias by visual inspection of funnel plots. We explored heterogeneity and the robustness of our results by iteratively removing one study to assess each study's influence on the pooled estimate for both outcomes. We also intended conducting sensitivity analyses such as comparing studies with different types of depression assessment and exploring heterogeneity using meta-regression. However, the limited number of available studies did not allow for such exploration.

## Results

### *Study selection and characteristics*

We retrieved 1,642 studies, of which 173 full-text articles were assessed for eligibility. Of these, 26 studies met the inclusion criteria and were included in the systematic review. Inter-rater reliability for the full-text screening was 0.68 (Cohen's kappa). The results of eleven studies could be subjected to meta-analysis. Fifteen studies[22–36] had to be excluded from the meta-analysis as the reported effect measures could not be pooled in a meta-analysis. The exact reasons for exclusion can be found in Tables S6.4 and S6.5. Of the studies included in the meta-analysis, six investigated the longitudinal association between depressive symptoms and HbA1c[24,37–41] and five assessed the longitudinal association between HbA1c and major depressive disorder/depressive symptoms[42–46] (see Figure 6.1). Thereof, two studies assessed the reciprocal association.[37,38] For these two studies, we only considered the association between depressive symptoms and HbA1c as an outcome due to missing information for the transformation of the effect measure on the reversed association.

**Figure 6.1 Flowchart of the study selection process**

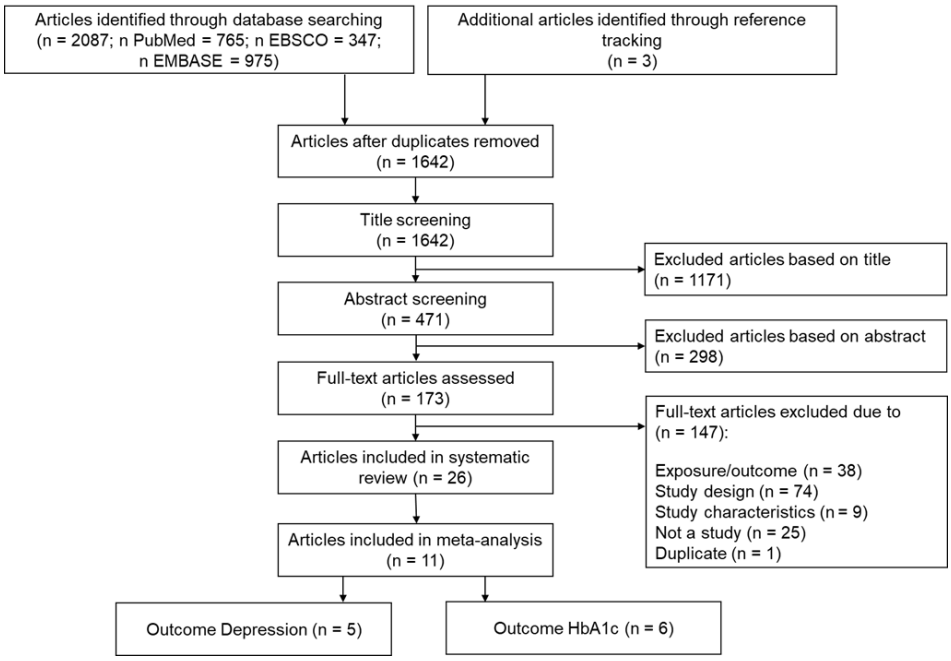



Table S6.2 presents the characteristics of the 26 studies in the systematic review. Sixteen studies consisted of individuals with type 2 diabetes[24–26,29–33,37–40,43–46], six with type 1 diabetes[22,28,34–36,41], two included a mixed population[27,47] and two did not specify the type of diabetes.[23,42] The mean age of participants ranged from 22.6 to 67.9 years. Study sample sizes varied with a range from 79 to 40,214 participants with a median of 598 individuals. Study duration varied from 6 months up to twelve years with two to six follow-up time points. Three studies used a retrospective study design[30,32,46]; nonetheless, we decided to include them as neither depression nor HbA1c were relevant for the selection of the exposed and non-exposed study participants. Six studies did not report adjusted outcome measures, and 13 studies did not report 95% CI.

### *Quality assessment*

For studies with HbA1c as the outcome variable, we rated thirteen as having good quality, one as fair and five as having poor quality according to NOS. Inter-rater reliability for quality assessment was 0.79 (Gwet's Agreement Coefficient 1). For studies with depression as outcome variable, eight were evaluated as good, one as fair and three received a poor rating (see Table S6.3). The main reason for a poor rating was lack of adjustments for sex, age, BMI or

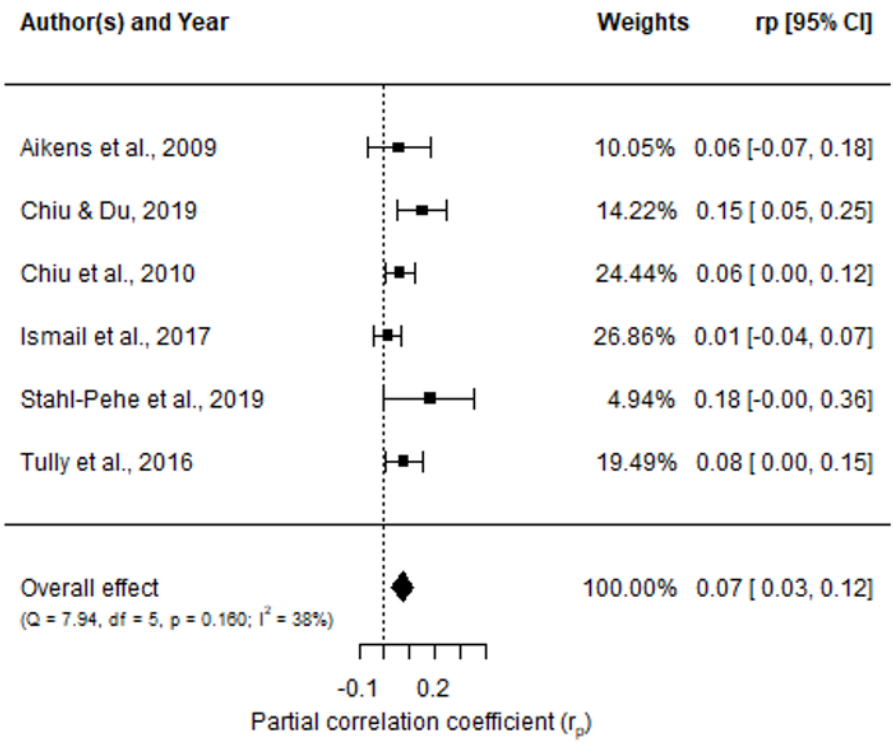
antidepressant medication use, or not adjusting for baseline values or disease status of the relevant dependent variable. Three studies used a selective study population such as only including men,[24] mainly including women with microalbuminuria,[45] or individuals with a longer disease duration and a low prevalence of probable depression in the study sample,[47]

***Longitudinal association of depressive symptoms with HbA1c***

Six studies that investigated the longitudinal association of depressive symptoms with HbA1c with a combined sample size of 3,683 individuals were included in the meta-analysis. The follow-up periods ranged from six months to five years with a mean follow-up period of 37 months. Results showed a small significant association between depressive symptoms (at baseline) and HbA1c levels (at follow-up) ($r_p$ = 0.07; [95% CI 0.03, 0.12], p = 0.002; Figure 6.2). Between-study heterogeneity was found to be moderate and non-significant ($I^2$ = 38%, [95%CI 00.00, 91.88], p = 0.159). When we removed one study at a time, $r_p$ ranged from 0.05 – 0.09. We saw no indication of publication bias at visual inspection of the funnel plot.

Thirteen studies with HbA1c as an outcome could not be included in the meta-analysis due to the reported effect measures (e.g., regression coefficient not standardized, depression as binary outcome variable, or no formula available for transformation). The results of these studies and reasons for exclusion are summarised in Table S6.4. Out of these thirteen studies, five reported that major depressive disorder/higher levels of depressive symptoms were longitudinally associated with higher levels of HbA1c,[26,28–30,36] while eight did not find an association.[22,25,27,32–35,47] One study described their results without reporting an effect estimate.[47]

**Figure 6.2 Forest plot showing the weighted mean partial correlation between depression scores and HbA1c values**



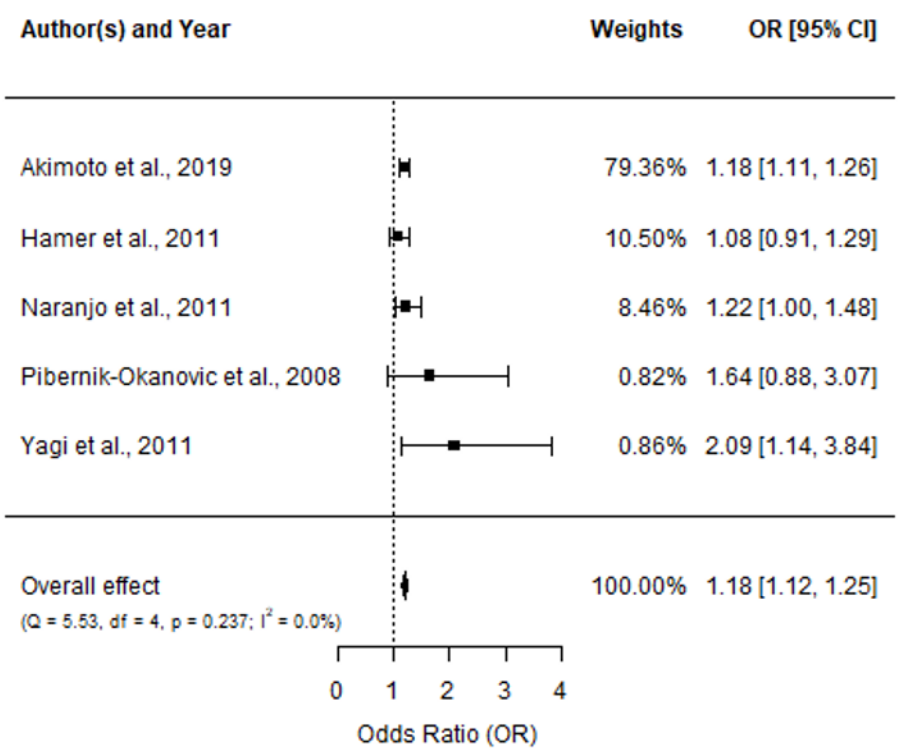

### *Longitudinal association of HbA1c with major depressive disorder/depressive symptoms*

Five studies that investigated the longitudinal association of HbA1c with major depressive disorder/depressive symptoms with a combined sample size of 45,110 individuals were included in the meta-analysis. The follow-up periods ranged from six months to three years with a mean follow-up period of 19.7 months. A one-point higher baseline HbA1c level was associated with a 18% increased risk of (probable) depression at follow-up (pooled OR = 1.18; [95% CI 1.12, 1.25], $p < 0.001$; Figure 6.3). The heterogeneity of the included studies was low and non-significant ($I^2 = 0.04\%$; [95%CI 0.00, 98.33], $p = 0.237$). When we removed one study at a time, ORs ranged from 1.18 – 1.25. We saw no indication of publication bias at visual inspection of the funnel plot.

Seven studies could not be included in the meta-analyses due to the reported effect measures (e.g., results presented for quintiles of HbA1c). Of these, three

found that higher HbA1c levels were associated with an increased risk for subsequent (probable) depression[23,26,31]; four reported no significant association.[22,35,37,38] The results and reasons for exclusion are presented in detail in Table S6.5.

**Figure 6.3 Forest plot showing the association of higher HbA1c values with increased depression risk in weighted odds**




## Discussion

In this meta-analysis and systematic review, we extensively and systematically assessed the longitudinal association between depression and HbA1c levels, and between HbA1c levels and depression. We found a significant bidirectional association, despite the relatively small number of studies that could be included in the meta-analysis. Our findings support the temporality of both associations, further emphasising that both depression and HbA1c are important treatment targets in individuals with depression and diabetes.

***Longitudinal association of depressive symptoms with HbA1c***

We found a small, but significant association between depressive symptoms and HbA1c scores at follow-up as an outcome in our meta-analysis. Importantly, these results provide evidence for the temporality of this association. Our finding extends previous research on cross-sectional studies by Lustman and colleagues where the authors found a small-to-moderate significant association.[13] A possible explanation for the somewhat reduced magnitude of the effect could be that longitudinal studies are often subject to attrition bias with healthier individuals less likely to drop-out, leading to an underestimation of the effect size. Five out of six studies had a fair-to-good quality, supporting the credibility of our results. In addition, studies from our systematic review that found an association between lower depression scores and higher HbA1c levels were of good quality whereas the studies that did not support an association received mixed quality ratings.

A potential pathway linking depression to the development of hyperglycaemia is via behavioural mediation. Higher depressive symptoms have been associated with less optimal diabetes self-management which has in turn been related to hyperglycaemia.[48] A meta-analysis found a moderate association between depression and reduced diabetes self-management with the strongest association found for keeping medical appointments and dietary self-care.[49] In addition, a depressed mood may lead to physical inactivity and unhealthy dietary behaviour.[6,50] Physical inactivity and an unhealthy diet may further lead to weight gain which in turn negatively affects blood glucose levels.[S51-52] Furthermore, pharmacological therapies for depression can also lead to weight gain. Prior evidence demonstrated a 5% increased risk of weight gain in individuals on antidepressant treatment compared to those without.[S53]

Since associations with depressive symptoms were often measured as a secondary analysis, most studies in this review did not report on adjustments for diabetes self-management and health behaviours. The studies that did adjust for these factors mentioned that depressive symptoms might improve with better glycaemic control once barriers to insulin treatment have been addressed.[11] Chiu et al. found that a variety of health behaviors explained a large part of the association of depressive symptoms with HbA1c. However, they still found a significant direct association of baseline depressive symptoms on HbA1c levels at follow-up above and beyond health behaviours.[17] Based on a mediation analysis, Schmitz et al. suggested that cardiometabolic factors and lifestyle-related behaviours might mediate the association between depressive symptoms and HbA1c.[18]

***Longitudinal association of HbA1c with depression***

Our meta-analysis on the association between HbA1c and depression as an outcome yielded a significant association between higher HbA1c and higher risk for (probable) depression. This finding contradicts results from a previous meta-analysis,[14] which concluded that hyperglycaemia or hyperinsulinemia is unlikely to be related to the development of depression. However, this study did not investigate a linear contribution of HbA1c to the incidence of depression. The use of HbA1c as a continuous measure gave us more statistical power to detect a difference. Moreover, the size of our pooled effect estimate was within the range reported by Tong et al.[14] Four out of five studies in our meta-analysis were of good quality, supporting the credibility of our results. The studies that were excluded from the meta-analysis showed mixed results with two studies supporting and four studies failing to support our findings. Studies which found an association had a good quality rating. One study with a poor, two studies with a fair and one study with a good quality rating did not find an association. A worse quality rating was based on lack of adjustment for important confounding factors and baseline values of HbA1c or depression.

Several biological mechanisms could explain the association between hyperglycaemia and incident depression. Neurons in the brain do not possess active glucose transporters. Consequently, prolonged, high levels of plasma glucose directly affect intraneuronal glucose levels. These high glucose concentrations can activate the polyol pathway, inducing an overgeneration of reactive oxygen species, and cause the generation of advanced glycation end products. [S54] These processes induce oxidative stress which may lead to neuronal apoptosis. Neuronal apoptosis may subsequently lead to brain atrophy which could eventually cause depression.[S54-55] Moreover, hyperglycaemia might lead to increased cortisol levels,[S54] which has been associated with incident depression. [S56] Other potential mechanisms include low-grade inflammation,[S57] reductions in serum brain-derived neurotrophic factor[S57] or vascular damage in brain regions implicated in mood regulation.[S54] The association between hyperglycaemia and incident depression may also be explained by psychological demands or psychological factors (e.g. social support, coping skills) related to the illness or its treatment. Depression may also be triggered from seeing high blood glucose levels all the time, resulting in a sense of personal failure to get the number down.[S58]

Importantly, both HbA1c levels and depression have been linked to diabetes distress.[S59] Diabetes distress refers to negative behavioural and emotional

reactions due to suffering from diabetes. It can be induced by the diagnosis itself, fear or experience of complications, struggle with self-management or other factors that are specific to their disease.[S60] Evidence from cross-sectional analyses suggests that diabetes-distress might mediate the association between depression and glycaemic control.[S61-62] From the studies included in this review, seven analysed the role of diabetes distress.[22,29,33–35,40,41] Thereof, three did not find evidence for an association for depressive symptoms or diabetes distress with HbA1c[22,40,S56] and two found an association for both depressive symptoms and diabetes distress.[29,41] In one study, the association between depressive symptoms and HbA1c attenuated when diabetes distress was entered into the model.[41] In two studies, neither depressive symptoms nor major depressive disorder showed an association with HbA1c.[33,34] Interestingly, diabetes distress was associated with HbA1c levels cross-sectionally and in the time-varying analysis but not in the prospective analysis in both studies. Based on these results, no firm conclusion on mediation can be drawn. Further research in longitudinal studies is needed to entangle this complex relationship.

***Limitations and strengths***

The quality of our meta-analyses is highly dependent on the quality of available literature. We only found a few studies that have investigated the association between depression and HbA1c and vice versa. Based on the limited number of studies, we could not formally assess publication bias,[S63] conduct meta-regression or sensitivity analyses that would discriminate between type of diabetes, assessment of depression (clinical diagnosis of major depressive disorder versus self-reported depressive symptoms), adjustment for diabetes distress, or between users and non-users of insulin, antidepressants or other types of medication. As the majority of pooled studies were in individuals with type 2 diabetes, conclusions about individuals with type 1 diabetes are limited. With regards to comparing users and non-users of insulin, potential differences were only analysed in the study by Aikens et al. The results suggested that HbA1c is only associated with depressive symptoms among insulin-users compared to individuals on oral medication alone.[37]

Moreover, most studies in the meta-analysis assessed depression by use of a self-report questionnaire. Self-report questionnaires are widely used in research to assess ‘depression’ because clinical diagnoses are often not available.[S59] Although cut-off scores on self-report questionnaires have been validated to identify depressive symptoms, a one-point increase or decrease in score of a questionnaire is difficult to clinically interpret. Aside from that, self-report

questionnaires have a lower specificity to identify depression.[S64] Structured clinical interviews remain the gold standard method to establish a diagnosis of major depressive disorder.

However, several strengths should be acknowledged as well. Our systematic review and meta-analysis were based on a comprehensive search including four databases, addressing both directions of the association between depression and HbA1c. Moreover, searches included papers in Dutch, German, Spanish, and French aside from English language papers, increasing the scope of the review. Another strength of this study is the inclusion of longitudinal studies which are of higher empirical evidence than cross-sectional studies and are able to assess the temporality of events. Most studies were of high quality and adjusted for multiple confounding factors. We also solely included studies that used continuous measures of HbA1c, increasing the power to detect a potential association.

Furthermore, despite the dissent in the current literature on how to best pool regression coefficients (e.g. ([S65–68])) and the lack of information on converting effect sizes, we found a solution for pooling regression coefficients.[19,20] The studies included in our meta-analyses adjusted for different sets of independent variables. The use of partial effect sizes allowed us to account for the influence of these variables. However, caution is needed when making inferences about population effect sizes. The size of the individual partial effects might be influenced by the complexity of the models that the effects derive from.[19]

***Recommendations and future perspectives***

The results of our systematic review and meta-analysis support a bidirectional association between depression/depressive symptoms and HbA1c. Further research is needed to investigate whether this offers treatment opportunities, because improvements in HbA1c levels could have a favourable effect on depression outcomes and vice versa. However, more high-quality, large-scale longitudinal studies on the bidirectional association between depression and HbA1c are firstly needed.

Future observational longitudinal studies on the current topic should pay attention to a coherent reporting of effect estimates, as is already advised for reporting in clinical trials,[S69] as well as to deciding on a commonly reported metric. This would enable the pooling of additional studies and avoid the introduction of noise due to the translation of effect estimates. A way in which the quality of future research can also be improved is through adequate adjustment for important confounding

factors, especially age,[S70] sex[S71] and antidepressant medication,[S72] which have been suggested to play an important role in this association. Additionally, assessment of type of diabetes treatment and stratified analyses based on insulin-use are recommended. Another subject that requires attention is the long-term effect of high glucose levels on depression. Based on our systematic search, we conclude that there is a need for studies assessing the impact of high HbA1c levels on depression at multiple time points over a longer follow-up period. Aside from that, mediation analyses based on longitudinal data could provide further inside into the role of diabetes distress, diabetes self-management and health behaviours in the association between depression and HbA1c.

The bidirectional association between depression and HbA1c levels may also have important clinical implications. Routine screening for depressive symptoms by diabetes health care teams is recommended in individuals with all types of diabetes. Special attention needs to be paid to ensure that, if symptom scores indicate the presence of depressive symptoms, affected individuals actually want help in dealing with them[S73-74] and that processes are in place to ensure appropriate management and treatment.[S75] Prior research suggests that clinical vigilance of HbA1c levels, especially shortly after a diagnosis of major depressive disorder, is particularly important to avoid hospital admissions due to hyper- or hypoglycaemic episodes.[S76] Research has also suggested to simultaneously treat depression and suboptimal HbA1c levels.[S75] In their comprehensive overview of interventions for depression and diabetes, Petrak et al. highlight the need to conduct active comparison studies that elucidate the effectiveness of individual intervention components.[S75] Moreover, depression and suboptimal HbA1c levels might share the same antecedents such as physical inactivity or inflammation. Consequently, prevention efforts could aim at targeting these antecedents to concurrently prevent depression and suboptimal HbA1c levels.

### *Conclusion*

This meta-analysis suggests that depressive symptoms are associated with an increased risk for the development of higher HbA1c levels over time and that HbA1c levels are associated with an increased risk for the development of (probable) depression over time. These findings support a longitudinal bidirectional association between depressive symptoms and HbA1c. However, the observed effect sizes were small and the number of eligible studies low. Further research in large-scale longitudinal studies is needed to confirm this association and to explore the role of diabetes distress and diabetes self-management behaviours. In relation to clinical practice, the findings suggest that

depression and HbA1c levels should be targeted concurrently by prevention and treatment efforts.

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## Supplemental Material to Chapter 6

## Supplemental Methods

### *Study selection*

All citations retrieved by the presented search strategy were imported into EndNote (Endnote version X9.2) to manage records and identify duplicates.

As one of the main outcomes, all types of depression (including depressive symptoms) were chosen since epidemiological studies based on general populations often do not use clinical diagnoses. Studies including individuals with prediabetes were excluded since a meta-analysis assessing persons with undiagnosed diabetes or impaired glucose metabolism showed to have a lower risk for depression than individuals with known T2DM and a similar risk compared to individuals with normal glucose metabolism or the general public.[1] Moreover, studies are often found to choose different cut-off values for HbA1c levels to distinguish suboptimal and optimal glycaemic control.[2] Therefore, only studies treating HbA1c as a continuous measure were included.

Efforts were made to find the respective published articles for the abstracts identified by the search strategy. However, none were found that also fulfilled the relevant inclusion criteria.

For one article, the analysis was conducted with the effect measure in the adequate format for this meta-analysis but was not reported.[3] The authors were contacted for their results, but no response was received until submission of this manuscript.

### *Quality assessment*

### ADJUSTED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE - COHORT STUDIES AND RATIONALE FOR ADJUSTMENTS[4]

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of three stars can be given for Comparability. Please find the adjusted items written in italics.

#### Selection

1) Representativeness of the exposed cohort

a) truly representative of the average person with diabetes in the community *
b) somewhat representative of the average person with diabetes in the community *
c) selected group of users e.g., nurses, volunteers
d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) secure record (e.g., surgical records) *
b) structured interview *
c) validated self-report measurement instrument *
d) no description

4) Demonstration that outcome of interest was not present at start of study

a) individuals with depression at baseline excluded *
b) adjustment for baseline HbA1c values *
c) no exclusion or adjustment

**Comparability**

1) Adjustment for main confounding factors

a) study controls for sex and age *
b) study additionally controls for
    Antidepressant medication *
    BMI *
c) study does not control for oversampling variable -1 *

**Outcome**

1) Assessment of outcome

a) independent blind assessment *
b) record linkage *
c) validated self-report measurement instrument *
c) self-report (for HbA1c)
d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (12 weeks for HbA1c, 6 months for depression/depressive symptoms) *
b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - description provided of those lost *
c) No description of those lost or no statement

Thresholds for converting the Newcastle-Ottawa scales to Agency for Healthcare Research and Quality standards (good, fair, and poor):

**Good quality:** 3 or 4 stars in selection domain AND 0.5 - 3 stars in comparability domain AND 1.5 - 3 stars in outcome/exposure domain
**Fair quality:** 2 stars in selection domain AND 0.5 - 3 stars in comparability domain AND 1.5 - 3 stars in outcome/exposure domain
**Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

For the domain *representativeness of the exposed cohort*, a star was awarded, when the study was conducted within the general population of individuals with diabetes rather than in a selected population, for instance only in volunteers.

Item 3c was changed from *written self-report* to *validated self-report measurement instrument.* Whereas for the original item no star would have been awarded, the adapted item is considered to fulfil the requirements for a star. Undoubtedly, a structured clinical interview is the gold standard for assessing depression. However, observational studies often use self-report questionnaires instead of clinical diagnosis to identify individuals with depression. Moreover, self-report tools such as the Patient Health Questionnaire-9 (PHQ-9), the Center for Epidemiological Studies Depression Scale (CES-D) or the Hospital Anxiety and Depression Scale (HADS) have demonstrated high specificity and sensitivity when it comes to identifying depression. A meta-analysis of individual patient data identified a sensitivity of 0.88 (95% CI 0.83-0.92) and a specificity of 0.85 (95% CI 0.82-0.88) for the PHQ-9.[5] The CES-D demonstrated a sensitivity of 0.87 (95% CI 0.82-0.92) and a specificity of 0.70 (95% CI 0.65-0.75) in a meta-analysis including studies conducted in the general population.[6] In a literature review, the HADS was found to perform well in psychiatric or primary care patients and in the general population to assess depressive symptoms severity and caseness of depression.[7]

For the category *demonstration outcome of interest is not present*, analyses had to be adjusted for baseline values of HbA1c or depressive symptoms or exclude individuals with depression at baseline.

For the domain comparability, a star was given if the study adjusted for sex and age as female sex and younger age are identified risk factors for individuals with diabetes and

depression.[8] Another star was awarded if the authors additionally controlled for antidepressant medication since some types of antidepressants have been shown to negatively impact control and are associated with an increased risk of incident diabetes.[2] Moreover, adjustment for BMI as major confounder was also awarded a star. It was further taken into account, if a study that oversampled a specific population group also statistically corrected for that.

One domain of the NOS assesses if the follow-up period in the study was long enough for the outcome to occur. For HbA1c a period of twelve weeks was chosen since it reflects changes in blood glucose over a four to twelve-months period.[9] A meta-analysis on lifestyle intervention studies on depressive symptoms in individuals at-risk or suffering from type 2 diabetes found a mean follow-up period of six months across the included studies. A significant reduction effect of the interventions on depressive symptoms could already be shown in studies lasting ≤ six months. Accordingly, a conservative follow-up period of six months was chosen as adequate.[10]

Studies that assessed the reciprocal association were awarded half a star if they, for instance, use a valid measure to ascertain exposure for one variable, and a complete star if they did that for both exposures.

## Supplemental Tables

### Table S6.1 Final search per database including limits

| PubMed | PsycINFO and CINAHL | EMBASE |
|---|---|---|
| ((((((((((((((((Glycem*[Title/Abstract]) OR Glycaem*[Title/Abstract]) OR Dysglycem*[Title/Abstract]) OR Dysglycaem*[Title/Abstract]) OR hypoglycemia[MeSH Terms]) OR hyperglycemia[MeSH Terms]) OR Glycated Haemoglobin[Title/Abstract]) OR Glycated Hemoglobin[Title/Abstract]) OR HbA1c[Title/Abstract]) OR glycated hemoglobins[MeSH Terms]) OR Glycated Hemoglobin A[MeSH Terms])) OR Hemoglobin A*[Title/Abstract]) OR Haemoglobin A*[Title/Abstract] NOT glycosylated[Title/Abstract])) AND ((((depression[MeSH Terms]) OR depressive disorder[MeSH Terms]) OR major depressive disorder[Title/Abstract]) OR depression[Title/Abstract] OR depressive symptom*[Title/Abstract] OR dysthymic disorder[MeSH Terms])) AND (((((((((longitudinal[Title/Abstract]) OR panel stud*[Title/Abstract]) OR repeated observation*[Title/Abstract]) OR cohort*[Title/Abstract]) OR cohort studies[MeSH Terms]) OR follow-up studies[MeSH Terms])) OR prospective studies[MeSH Terms] OR prospective stud*[Title/Abstract] OR randomized controlled trial[Publication Type] OR randomized controlled trials as topic[MeSH Terms]) Filters: Publication date from 2000/01/01 to 2020/12/31 | ( TI (glyc#emi* OR dysglyc#mi* OR Hyp*glyc#emia OR glycated h#moglobin OR h#moglobin A OR HbA1c OR glycate h#moglobin A) OR AB( glyc#emi* OR dysglyc#mi* OR Hyp*glyc#emia OR glycated h#moglobin OR h#moglobin A OR HbA1c OR glycate h#moglobin A) OR MM "Hyperglycemia" OR MM “Hypoglycemia" OR MM “Glycemic Control” ) AND ( TI (depression* OR depressive symptom* OR depressive disorder OR depressive syndrome OR depressive personality disorder OR depressive illness OR depressive disease OR major depressive disorder) OR (AB (depression* OR depressive symptom* OR depressive disorder OR depressive syndrome OR depressive personality disorder OR depressive illness OR depressive disease OR major depressive disorder)) OR MM "Major Depression" OR MM "Anaclitic Depression" OR MM "Dysthymic Disorder" OR MM "Endogenous Depression" OR MM "Late Life Depression" OR MM "Postpartum Depression" OR MM "Reactive Depression" OR MM "Recurrent Depression" OR MM "Treatment Resistant Depression"exp OR MM "Depression+" ) AND ( TI(Longitudinal OR panel stud* OR repeated observation* OR cohort* OR cohort stud* OR follow-up stud*) OR (AB((Longitudinal OR panel stud* OR repeated observation* OR cohort* OR cohort stud* OR follow-up stud*)) OR MM “Longitudinal Studies” OR MM “Prospective Studies” OR MM “Randomized Controlled Trials” OR MM “Randomized Clinical Trials” OR MM “Repeated Measures” OR MM “Prospective Studies+” OR MM “Clinical Trials+” )<br><br>Limiters - Published Date: 20000101-20201231 | 6<br>(glyc?emic or glycem* or glycaem* or dysglyc?emia or hypoglycaemia).mp. or exp hyperglycemia/ or exp hemoglobin A1c/ [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]<br><br>7<br>limit 6 to yr="2000 - 2020"<br><br>8<br>exp depression/ or exp major depression/<br><br>9<br>limit 8 to yr="2000 - 2020"<br><br>10<br>(longitudinal study or panel study or repeated observation* or cohort* or cohort stud* or follow up or prospective study).ti,ab.<br><br>11<br>limit 10 to yr="2000 - 2020"<br><br>12<br>6 and 7 and 8 and 9 and 10 and 11 |

**Table S6.2 Overview of the study characteristics**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| *$HbA_{1c}$ as outcome variable* | | | | | | | |
| *Meta-analysis and systematic review* | | | | | | | |
| Aikens et al., 2009 [11a] | US | Urban healthcare system users with type 2 diabetes; Ø diabetes duration > 10 years; mild Ø baseline depressive symptom severity 5.5 ±4.7; Ø $HbA_{1c}$ at baseline 7.6 ±1.6%<br><br>Ø age: 57.3 ±8.3<br>50.0% women | 253 | PHQ-9 (Q) | Capillary blood samples analysed with DCA 2000 through a monoclonal antibody method | 6 months<br>2 time points | Race/ethnicity, diabetes duration, baseline depressive symptoms |
| Chiu & Du, 2019 [12a] | US | Community-dwelling individuals with type 2 diabetes; oversampling of Hispanics and African Americans; Ø $HbA_{1c}$ at baseline 7.2% (4.8-15.5%)<br><br>Ø age: 67.9[b]<br>55.5% women | 398 | CES-D 8-item version (Q) | Blood spot assays returned to Flexsite Diagnostics | 36 months (3 years)<br>2 time points | - |
| Chiu et al., 2010 [13] | US | Community-dwelling individuals with type 2 diabetes; Ø diabetes duration > 12 years; 23% of participants had depressive symptoms at baseline; Ø $HbA_{1c}$ at baseline 7.2 ±1.4%<br><br>Ø age: 65.2 ±8.1<br>47.9% women | 998 | CES-D (Q)<br><br>CIDI-SF for MDD (D) | Blood spot assays returned to Flexsite Diagnostics | 60 months (5 years)<br>3 time points | Baseline health behaviours |

**Table S6.2 (Continued)**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| Ismail et al., 2017 [14] | UK | Individuals from GPs in the inner-city boroughs in South London; recent diagnosis of type 2 diabetes (< 6 months); 14.1% of participants had depressive symptoms at baseline; Ø $HbA_{1c}$ at baseline 53 ± 11 mmol/mol (7.0 ±1.4%)<br><br>Ø age: 56.2 ±11.1<br>44.9% women | $HbA_{1c}$ at year 1: 1,421<br><br>$HbA_{1c}$ at year 2: 1,234 | PHQ-9 (Q) | Blood samples assessed with affinity chromatography | 24 months<br>3 time points | Age, sex, non-white ethnicity, prescription of hypoglycaemic medications and prescription of insulin, baseline $HbA_{1c}$ |
| Stahl-Pehe et al., 2019 [15] | Germany | Young adults with type 1 diabetes onset occurred from 0 to 4 years of age during 1993–2002 from a nationwide cohort; Ø HbA1c at baseline 63-65 mmol/mol (7.9 – 8.1%)<br><br>Ø age: 22.4[e]<br>58.4 % women | 112 | PHQ-9 (Q) | Medical records (n = 55), Self-report | 36 months (3 years)<br>2 time points | Age, sex, socioeconomic status index, and baseline HbA1c |
| Tully et al., 2016 [16] | Australia | Men aged 35-80 years, living in North West regions of Adelaide; 16.3% developed incident type 2 diabetes; Ø $HbA_{1c}$ at baseline ranged between 5.47-5.52 depending on chronicity group<br><br>Ø age: 52.8[b]<br>0.0% women | 688 | BDI-I (Q) | High-performance liquid chromatography using a spherical cation exchange gel | 60 months (5 years)<br>2 time points | Propensity score calculated from follow-up data (18 covariates) |

**Table S6.2 (Continued)**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| *Systematic Review* | | | | | | | |
| Ascher-Svanum et al., 2015 [17] | Greece, Portugal, Romania, Sweden, Turkey | Insulin-naive individuals with type 2 diabetes<br><br>Ø age: 60.4 ±10.8<br>47.2% women | Depressive symptoms: 971<br><br>Depression diagnosis: 985 | EuroQol (EQ)-5D item (Q)<br><br>History of diagnosis of depression (D) | Not reported | 24 months<br>6 time points | Age, sex, BMI, education, duration of diabetes, initiated insulin type, microvascular and macrovascular complications |
| Bayliss et al., 2011 [18] | US | Individuals with type 2 diabetes from diabetes registry; sub-cohort with new-onset depression<br><br>Ø age: 62.0 ± 12.5<br>56.4% women | 2,739 | ICD-9 diagnosis of depression from a mental health provider (D) | Electronic medical records | 60 months (5 years)<br>6 time points | Male, black, Hispanic, other race, unknown race, age (decade), BMI, number of conditions, continuity of care, PC visits, specialist visits |
| Fisher et al., 2010 [19] | US | Individuals with type 2 diabetes from urban community-based medical groups and diabetes education settings<br><br>Ø age: 57.8 ±9.8<br>57.0% women | 506 | CES-D (Q)<br><br>CIDI for MDD (D) | Not reported | 18 months<br>3 time points | Insulin intake, BMI, Number of complications, comorbidities and stressful events, diet, exercise, MDD, diabetes distress, sex, race, age, education, time since diagnosis |

**Table S6.2 (Continued)**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| Graco et al., 2012 [3] | Australia | Individuals from the Northern Health Diabetes HARP service<br>Type 1 diabetes (7.0%), Type 2 diabetes (91.9%)<br><br>Ø age: 58.8 ±14.0<br>48.8% women | 86 | HADS (Q) | Service or GP medical records | 12 months<br>2 time points | Diabetes duration |
| Hessler et al., 2017 [20] | US, Canada | Individuals from diabetes clinics with type 1 diabetes for at least 12 months<br><br>Ø age: 43.0 ±15.2<br>56.3% women | DS: 224<br><br>SCID: 212 | PHQ-8 (Q)<br><br>SCID (D) | Clinic-reported $HbA_{1c}$ | 9 months<br>2 time points | - |
| Kampling et al., 2018 [21a] | Germany | Individuals from 12 German hospitals with newly diagnosed type 1 diabetes included in the German Multicenter Diabetes Cohort (GMDC) study<br><br>Ø age: 28.2[b]<br>39.0% women | 290 | DIMD short version for MDD (D)<br><br>SCL-90-R subscale depression for depression severity (Q) | Medical record | 60 months (5 years)<br>5/6 time points | Not reported |
| Kampling et al., 2017 [22] | Germany | Individuals from 12 German hospitals with newly diagnosed type 1 diabetes included in the German Multicenter Diabetes Cohort (GMDC) study<br><br>Ø age: 28.2 ±6.3<br>38.0% women | 291 | DIMD short version for MDD (D)<br><br>SCL-90-R subscale depression for depression severity (Q) | Record from treating physician | 60 months (5 years)<br>5 time points | Age, sex |

**Table S6.2 (Continued)**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| Nazu et al., 2020 [23] | Finland | Patients with type 2 regional electronic health records of North Karelia, Finland, from 2011 to 2016 (retrospective cohort)<br><br>Ø age: 67.41[b]<br>47.3% women | 6,070 | ICD-10 diagnosis for major depressive disorder, single or recurrent episode, mild from electronic health record (D) | Blood samples analysed by the turbidimetric inhibition immunoanalysis method | 72 moths (6 years)<br>2 time points | Age, sex |
| Rassart et al., 2015 [24a] | Belgium | Individuals with type 1 diabetes from the Belgium Diabetes Registry<br><br>Ø age: 23.5 ±3.7<br>57.0% women | For cross-lagged analyses: 164 | CES-D (Q) | Laboratory assessment | 60 months (5 years)<br>2 time points | Age, sex, illness duration |
| Schmitz et al., 2016 [25a] | UK | Community-dwelling participants of the English Longitudinal Study of Ageing with type 2 diabetes<br><br>Ø age: 62.9 ±7.2<br>55.6% women | 2,886 | CES-D (Q) | Blood samples analysed at the Royal Victoria Infirmary | 96 months (8 years)<br>3 time points | Age, sex, education at baseline |
| Speerforck et al. 2019 [26] | Germany | Participants of the German National Interview and Examination Study (GHS) with type 1 or type 2 diabetes; stratified random sample from 130 sampling units<br><br>Ø age: 54.8 ±8.5<br>30.1% women | 85 | CIDI for lifetime MDD (D) | Assessment at central epidemiology laboratory unit at the Robert Koch Institute (Berlin) using Architect® ci8200 | 144 months (12 years)<br>2 time points | Baseline $HbA_{1c}$, age, sex, years of schooling, alcohol consumption, smoking |

**Table S6.2 (Continued)**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| Trief et al., 2019 [27] | US | Individuals with clinical diagnosis of presumed autoimmune type 1 diabetes and islet cell antibodies present or insulin must have been started at or shortly after diagnosis<br><br>Ø age: 42 ±16<br>57.0% women | 2,744 | PHQ-8 (Q)<br><br>Behavioural Risk Factor Surveillance Survey for depression status (Q) | Medical records | 60 months (5 years)<br>2 time points | Age (at baseline), sex, race/ethnicity, duration of diabetes (at baseline), CGM status (from baseline to FU), pump status (from baseline to FU), insurance status (at baseline and FU), annual income (at baseline and FU), and clinic site, $HbA_{1c}$ at baseline |
| Whitworth et al., 2017 [28] | Australia | Individuals with clinically diagnosed type 2 diabetes living in a postcode-defined, geographic area surrounding the city of Fremantle in the state of Western Australia<br><br>Ø age: 65.3 ±10.9<br>46.0% women | 1,201 | PHQ-9 (Q) and advice from GP for depressive symptoms<br><br>Brief Lifetime Depression Scale for lifetime MDD at baseline (Q) | Laboratory assessment | 48 months (4 years)<br>3 time points | Age, disease duration, sex, marital status |

**Table S6.2 (Continued)**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| *Depression outcome variable* | | | | | | | |
| *Meta-analysis and systematic review* | | | | | | | |
| Akimoto et al., 2019 [29] | Japan | Patients with type 2 diabetes for at least 30 days registered in the Nihon University School of Medicine (NUSM) Clinical Data Warehouse (CDW) clinical database between 2004 and 2018 (retrospective cohort)<br><br>Ø age: 60.7[b]<br>41.2% women | 40,214 | ICD-10 diagnosis for major depressive disorder, single episode, mild or unspecified or other depressive episodes from medical doctor (D) | Medical record | Duration (Ø FU period 3.08 years)<br>>2 time points not reported | Age, sex, use of oral hypoglycaemic agent, duration of type 2 diabetes, hospital, and medical history before the onset date of depression |
| Hamer et al., 2011 [30] | UK | Participants from the population-based English Longitudinal Study of Ageing; diabetes type is not specified; 6.6% reported diabetes at baseline; 12.7% of participants had elevated depressive symptoms at baseline<br><br>Ø age: 62.9[b]<br>54.8% women | 4,338 | CES-D (Q) | Blood samples analysed at the Royal Victoria Infirmary | 24 months<br>2 time points | Age, baseline CES-D score, smoking, alcohol intake, PA, social status, C-reactive protein, cholesterol, BMI, self-reported diabetes |
| Naranjo et al., 2011 [31] | US | Individuals from primary care facilities with type 2 diabetes for at least 12 months, without MDD at study start who subsequently met DSM-IV criteria for MDD<br><br>Ø age: 58.0 ±9.9<br>56.4% women | 338 | CIDI for current and prior MDD (D) | Not reported | 18 months<br>3 time points | BMI, Number of comorbidities, Number of diabetes complications, *(additionally, all demographic characteristics were adjusted for in the combined model)* |

**Table S6.2 (Continued)**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| Pibernik-Okanovic et al., 2008 [32] | Croatia | Randomly selected individuals with depression from outpatient facilities with type 2 diabetes; CES-D score ≥ 16<br><br>Ø age: 55.9[b]<br>66.8% women | 79 | CES-D (Q)<br><br>SCID (D) | Automated immunoturbidimetric method using Bayer reagents on Olympus AU600 analyser | 12 months<br>2 time points | Sex, age, education, SES, insulin therapy, BMI, concomitant disease, baseline severity of depression, role physical (SF-12), social functioning (SF-12) |
| Yagi et al., 2011 [33] | Japan | Participants of the Shiga Prospective Observational Follow-up Study for Diabetic Complications with type 2 diabetes; Ø diabetes duration > 18 years; Ø $HbA_{1c}$ at baseline 7.4 ±0.8%<br><br>Ø age: 65.8 ±10.0<br>78.5% women | 141 | Zung Self-Rating Depression Scale (Q) | Not reported | 6-12 months (Ø FU period 7.3 months)<br>2 time points | Age, sex, BMI, insulin therapy, neuropathy, nephropathy, and retinopathy |
| *Systematic review* | | | | | | | |
| Geraets et al., 2020 [34] | The Netherlands | Participants from The Maastricht Study (population-based cohort oversampled with individuals with type 2 diabetes)<br><br>Ø age: 59.9 ±8.1<br>48.2% women | 2710 | PHQ-9 (Q) | Determined in fasting venous blood samples by ion-exchange high performance liquid chromatography | Duration (Ø FU period 3.8 ± 1.0 years)<br>2-5 time points | Age, sex, educational level, waist circumference, office systolic blood pressure, antihypertensive medication, total-to-HDL-cholesterol ratio, lipid-modifying medication, history of cardiovascular disease, smoking behaviour, and alcohol use |

**Table S6.2 (Continued)**

| Authors & Year | Country | Study population | Sample size[c] | Depression measurement[d] | $HbA_{1c}$ assessment | Duration and number of follow-up measurements | Confounders |
|---|---|---|---|---|---|---|---|
| Li et al., 2019 [35] | China | Participants of the China Health and Retirement Longitudinal Study; diabetes type is not specified<br><br>Ø age: 58.9[b]<br>53.6% women | 9,804 | CES-D (Q) | Boronate affinity high-performance liquid chromatography | 60 months (5 years)<br>3 time points | Demographics, health behaviours, baseline health conditions, cardiac marker, antidepressant use, cognition scores |

[a] Studies that used both HbA1c and depression as outcome variables. [b] Average age calculated by reviewers. [c] Size of the analysed sample. [d] (Q) for questionnaire, (D) for diagnostic interview. [e] Average age and % women of total cohort (n=303). Abbreviations: BDI-I = Beck Depression Inventory-I, CES-D = Center for Epidemiologic Studies Depression, CIDI(-SF) = Composite International Diagnostic Interview (-Short Form), DIMD = Diagnostic Interview for Mental Disorders, DS = Depressive symptoms, HADS = Hospital Anxiety and Depression, ICD-9 = International Classification of Diseases 9th revision, ICD-10 = International Classification of Diseases 10th revision, MDD = Major Depressive Disorder, PHQ-8 = Patient Health Questionnaire-8 (suicide item omitted), PHQ-9 = Patient Health Questionnaire-9, SCID = Structured Clinic Interview for the DSM, SCL-90-R = Die Symptom-Checkliste von Derogatis.

**Table S6.3 Quality assessment of all included studies (n=26) based on the Newcastle-Ottawa-Scale**

| Author & Year | Selection | Comparability | Outcome | Overall Rating |
|---|---|---|---|---|
| Aikens et al., 2009 | ★★★★ | ★ | ★★★ | Fair |
| Akimoto et al., 2019 | ★★★ | ★ | ★★★ | Good |
| Ascher-Svanum et al., 2015 | ★★★ | ★★ | ★★ | Good |
| Bayliss et al., 2011 | ★★★★ | ★★ | ★★ | Good |
| Chiu & Du, 2019 | ★★★ | | ★★ | Fair |
| Chiu et al., 2010 | ★★★ | ★ | ★★ | Poor |
| Fisher et al., 2010 | ★★★★ | ★★★ | ★ | Poor |
| Geraets et al., 2020 | ★★★★ | ★★★ | ★★★ | Good |
| Graco et al., 2012 | ★★★ | - | ★★ | Poor |
| Hamer et al., 2011 | ★★★ | ★ | ★★★ | Good |
| Hessler et al., 2017 | ★★★★ | ★ | ★★★ | Good |
| Ismail et al., 2017 | ★★★★ | ★ | ★★★ | Good |
| Kampling et al., 2018 | ★★★ | - | ★★ | Poor |
| Kampling et al., 2017 | ★★★ | ★ | ★★ | Good |
| Li et al., 2019 | ★★★ | ★★★ | ★★ | Good |
| Naranjo et al., 2011 | ★★★ | ★★ | ★★ | Good |
| Nazu et al., 2020 | ★★★ | ★ | ★★★ | Good |
| Pibernik-Okanovic et al., 2008 | ★★★★ | ★★ | ★★★ | Good |
| Rassart et al., 2015 | ★★★ | ★ | ★★ | Good |
| Schmitz et al., 2016 | ★★★ | ★ | ★★ | Good |
| Speerforck et al., 2019 | ★★★★ | ★ | ★★ | Good |
| Stahl-Pehe et al., 2019 | ★★★★ | ★ | ★ ★ | Good |
| Trief et al., 2019 | ★★★★ | ★ | ★★ | Good |
| Tully et al., 2016 | ★★★ | ★★★ | ★★ | Good |
| Whitworth et al., 2017 | ★★★ | ★ | ★★ | Good |
| Yagi et al., 2011 | ★ | ★★ | ★ | Poor |

Domain “Selection”: Maximum of 4 stars.
Domain “Comparability”: Maximum of 3 stars.
Domain “Outcome”: Maximum of 3 stars.

Good quality: 3 or 4 stars in selection domain AND 0.5 - 3 stars in comparability domain AND 1.5 - 3 stars in outcome/exposure domain.
Fair quality: 2 stars in selection domain AND 0.5 - 3 stars in comparability domain AND 1.5 - 3 stars in outcome/exposure domain.
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

**Table S6.4 Results of studies only included in systematic review with $HbA_{1c}$ as outcome**

| Author & Year | Effect measure | Reason for exclusion from meta-analysis | Effect size | p-value/SE/95% CI |
|---|---|---|---|---|
| Ascher-Svanum et al., 2015 | Mean difference $HbA_{1c}$ (%) –<br>Depressed mood vs. no depressed mood | No formula available for transformation into partial correlation coefficient | Baseline: 0.14<br>3 months: 0.40<br>6 months: 0.24<br>12 months: 0.26<br>18 months: 0.28<br>24 months: 0.34 | < 0.001<br>< 0.001<br>0.010<br>0.002<br>0.001<br>0.001 |
| Bayliss et al., 2011 | Change in mean $HbA_{1c}$ (over time, in months) | No formula available for transformation into partial correlation coefficient | -24 – -6: 8.1<br>-6 – 0: 8.0<br>0 – 6: 7.8<br>6 – 12: 8.0<br>12 – 24: 8.1<br>24 – 60: 8.1 | -24 – -6: SE 0.03<br>-6 – 0: SE 0.04<br>0 – 6: SE 0.04<br>6 – 12: SE 0.04<br>12 – 24: SE 0.03<br>24 – 60: SE 0.04 |
| Fisher et al., 2010 | Unstandardized beta | Regression coefficients only reported in unstandardized format | 0.001 | 0.18 |
| Graco et al., 2012 | Beta coefficient | Effect size not reported | Not reported | Not reported |
| Hessler et al., 2017 | Unstandardized beta | Regression coefficients only reported in unstandardized format | -0.01 | 0.71 |
| Kampling et al., 2018 | Unstandardized beta | Effect size not reported | Not reported | Not reported |
| Kampling et al., 2017 | F ratio | Trajectories of depression used that could not be combined | 4.81 | 0.009 |
| Nazu et al., 2020 | Change in mean | Depression as independent variable measured in binary format | Type 2 diabetes[a]: 0.30<br>Type 2 diabetes + Depression: 0.31 | 0.115 |
| Rassart et al., 2015 | Cross-lagged coefficient | Effect size not reported | Not reported | Not reported |
| Schmitz et al., 2016 | (Standardized) regression coefficient | Depression as independent variable measured in binary format | 0.129 (0.051[b]) | 95% CI 0.080 – 0.178 |
| Speerforck et al., 2019 | Beta coefficient | Depression as independent variable measured in binary format | 0.3 | 0.14 |
| Trief et al., 2019 | Change in mean | Results presented for different subgroups (elevated depressive symptoms (EDS), resolved EDS, new-onset EDS and not depressed) that did not allow for combination | Persistent EDS: 0.6<br>Resolved EDS: 0.3<br>New-onset EDS: 0.6<br>Not depressed: 0.4 | 0.001 |
| Whitworth et al., 2017 | Slope on predictor mean | Depression as independent variable measured in binary format | 0.04 | Not reported |

[a] reference group. [b] standardized regression coefficient.

**Table S6.5 Results of studies only included in systematic review with depression as outcome**

| Author & Year | Effect measure | Reason for exclusion from meta-analysis | Effect size | p-value or 95% CI |
|---|---|---|---|---|
| Aikens et al., 2009 | Standardized regression coefficient | Transformation into OR not possible as dependent variable is continuous | 0.04 | 0.361 |
| Chiu & Du, 2019 | Standardized regression coefficient | Transformation into OR not possible as dependent variable is continuous | 0.02 | 0.52[a] |
| Geraets et al., 2020 | Hazard ratio | Transformation of HR into OR not possible | 1.22 | 95% CI 1.09 – 1.37 |
| Kampling et al., 2018 | F ratio | Trajectories of $HbA_{1c}$ used that could not be combined | 0.43 | 0.72 |
| Li et al., 2019 | Risk ratios | Results were presented for quintiles of $HbA_{1c}$ or per level of $HbA_{1c}$ | Decreasing symptoms | Decreasing symptoms, 95% CI |
| | | | Quintile 1: 1.00 | Reference |
| | | | Quintile 2: 0.89 | Quintile 2: (0.73-1.08) |
| | | | Quintile 3: 1.02 | Quintile 3: (0.85-1.23) |
| | | | Quintile 4: 0.89 | Quintile 4: (0.74-1.07) |
| | | | Quintile 5: 1.01 | Quintile 5: (0.82-1.25) |
| | | | Increasing symptoms | Increasing symptoms, 95% CI |
| | | | Quintile 1: 1.00 | Reference |
| | | | Quintile 2: 1.05 | Quintile 2: (0.87-1.27) |
| | | | Quintile 3: 0.99 | Quintile 3: (0.82-1.20) |
| | | | Quintile 4: 1.21 | Quintile 4: (1.01-1.44) |
| | | | Quintile 5: 1.12 | Quintile 5: (0.92-1.36) |
| Rassart et al., 2015 | Cross-lagged coefficient | Effect size not reported | Not reported | Not reported |
| Schmitz et al., 2016 | (Standardized) regression coefficient | Transformation into OR not possible as dependent variable is continuous | 0.020 (0.051[b]) | 95% CI 0.012 – 0.033 |

[a] p-value calculated based on reported z-score. [b] standardized regression coefficient.

Quintiles in publication from Li et al. (2019): Quintile 1 (≤ 4.8%), 2 (4.9 - 5.0%), 3 (5.1 - 5.2%), 4 (5.3 - 5.5%), and 5 (≥ 5.6%).

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# Chapter 7

## General Discussion

7

Depression is a common mental health problem. The number of individuals with depression is rising, which reflects both the overall growth and the proportionate increase of the elderly population at which depression is more prevalent [1]. Late-life depression (LLD) is highly comorbid [2-5] and more often persistent compared to depression earlier in life [6]. Furthermore, it has been shown that half of the individuals with LLD fail to remit with first line antidepressant medication [7,8]. The aetiology underlying depression remains unclear, possibly due to the heterogeneous nature of depression, including marked differences across age groups [9]. Previous studies have shown that vascular dysfunction [10], neurodegeneration [11], and hyperglycaemia [12] may be involved in the pathophysiology of LLD. However, evidence for the temporality of these associations was limited. To highlight new targets for the prevention and treatment of LLD, it is imperative to further understand the contribution of these mechanisms in the pathophysiology of LLD.

The general aim of this dissertation was to investigate, in a population-based setting, the associations of vascular dysfunction, neurodegeneration, and hyperglycaemia with the prevalence, incidence and course of LLD over time. In addition, we investigated whether the association between LLD and cognitive functioning could be explained by structural brain abnormalities. This chapter will discuss the key findings of this dissertation. In addition, we will propose a pathophysiological model that links these findings. Methodological considerations and clinical implications will be addressed. Finally, recommendations for future research are provided.

## Key findings

### *1. Are markers of cerebral small vessel disease and brain atrophy associated with incidence and course of depressive symptoms in late-life?*

In chapter 2 of this dissertation, we observed that white matter hyperintensity (WMH) volume was associated with incidence of depressive symptoms in individuals above 60 years of age, independent of major demographical, cardiovascular and lifestyle risk factors. This association, was similar in women and men, and in participants with and without type 2 diabetes mellitus (T2DM). No association was found between overall cerebral small vessel disease (CSVD) burden and incidence of depressive symptoms. In addition, we found that WMH volume was associated with persistence of depressive symptoms in individuals above 60 years, while overall CSVD burden was associated with persistence of depressive symptoms irrespective of age.

In chapter 2, we also studied the associations between global brain atrophy with the incidence and persistence of depressive symptoms. Results suggested that there were no associations between markers of global brain atrophy and incidence or persistence of depressive symptoms.

***2. Are markers of microvascular dysfunction measured in the retina, skin, and plasma associated with prevalent and incident depressive symptoms in late-life?***

In chapter 3, we extended the findings of chapter 2 to the microcirculation outside of the brain. We observed that functional markers of the microcirculation in the retina and plasma markers of endothelial dysfunction were associated with prevalent and incident depressive symptoms, independently of demographic, cardiovascular and lifestyle risk factors. The associations with incident depressive symptoms were similar in women and men, and in participants with and without T2DM. No association was found between the skin hyperemic response and prevalent or incident depressive symptoms after adjustment for cardiovascular risk factors.

***3. Is MDD associated with structural brain abnormalities and cognitive function in late-life? And if so, do structural brain abnormalities mediate the association between MDD and cognitive functioning in late-life?***

In chapter 4, we found that major depressive disorder (MDD) was associated with cognitive impairment, and more impaired performance in information processing speed and executive functioning & attention, but not memory. These associations were independent of demographic, cardiovascular, and lifestyle-related risk factors, and were similar in women and men, and in participants with and without T2DM.

Contrary to our expectations, MDD was not associated with overall CSVD burden or markers of global brain atrophy. However, MDD was associated with overall CSVD burden in participants without T2DM.

Despite above associations, neither CSVD nor markers of global brain atrophy explained the worse cognitive profile of individuals with MDD or among those with MDD without T2DM.

***4. Are markers of hyperglycaemia and insulin resistance associated with incident depressive symptoms in late-life?***

In chapter 5, we observed that fasting plasma glucose, 2 h post-load glucose and HbA1c were associated with incident depressive symptoms, with an increased risk of ~20% per SD higher level of hyperglycaemia markers. These associations were independent of demographical, cardiovascular and lifestyle-related risk factors, and were similar in women and men. We found no association between skin autofluorescence (SAF) and incident depressive symptoms.

In addition, we examined in chapter 5 if insulin resistance was associated with LLD. Results suggested that the association of insulin resistance with incident depressive symptoms could be explained by cardiovascular risk factors, in particular central obesity.

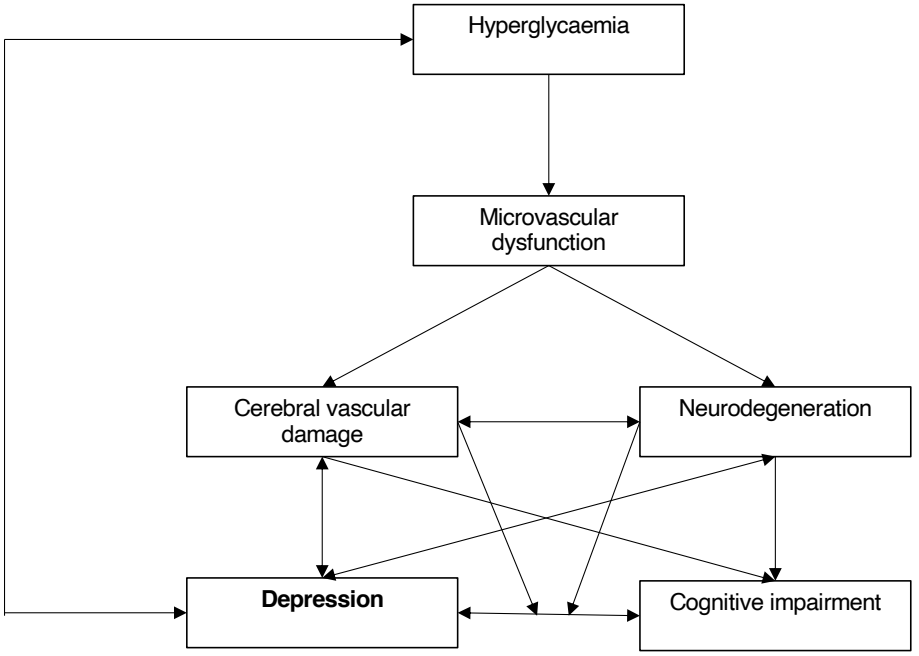
***5. Is there a bidirectional longitudinal association between hyperglycaemia and depression in late-life?***

In chapter 6, we extensively and systematically assessed the longitudinal association between depression and HbA1c levels, and between HbA1c levels and depression in a systematic review and meta-analysis. We found a significant bidirectional association, despite the relatively small number of studies that could be included in the meta-analysis.

**Towards a pathophysiological model of late-life depression**

The key findings of this dissertation can be summarized into a pathophysiological model (Figure 7.1).

**Figure 7.1 Pathophysiological model for the role of hyperglycaemia, microvascular dysfunction, cerebral vascular damage, neurodegeneration, and cognitive impairment in late-life depression**




### *The association of cerebral vascular damage with late-life depression*

In chapter 2 we observed an association between WMH volume with incidence and persistence of depressive symptoms in individuals above 60 years of age. WMH become more apparent at later age [13], which may explain the absence of this association in younger individuals. Overall CSVD burden was only associated with persistence of depressive symptoms irrespective of age. Several explanations can be found for the absence of an association between overall CSVD burden and incident depression. Lack of a significant contribution of lacunar infarcts and cerebral microbleeds might have diluted the association. Furthermore, overall CSVD burden was assessed on a dichotomous scale, which may result in less power compared to the more precise continuous measures of semi-automatically generated WMH volume. Lastly, WMH were more common than lacunar infarcts and cerebral microbleeds, which may suggest that WMH are an earlier marker of CSVD and/or more accessible to assess in epidemiological studies [14].

These results generalize findings reported in clinical studies of more severely depressed patient to the general population. WMH burden predicts clinical outcome in LLD patients [9]. However, there are studies reporting no association between WMH and treatment outcome as well [9,15]. The two previous population-based studies that assessed the association of other markers of CSVD with a persistent course of depression yielded inconclusive results [16,17]. Observed differences could be explained by the variability in methodology and the inclusion of different subtypes of LLD [15]. The pathophysiology of these subtypes could be different and lead to mixed results.

Several mechanisms may explain the association between cerebral vascular damage and LLD. Cerebral vascular damage may lead to LLD via disruption of frontal-limbic systems involved in mood regulation or their modulating pathways by brain lesions in crucial white matter tracts [18-20]. Alternatively, LLD may represent an early manifestation of vascular dementia or a psychological response to subjective cognitive decline [21]. Lastly, endothelial dysfunction and low-grade inflammation can be the mechanisms underlying cerebral vascular damage and LLD [9,22,23].

***The association of neurodegeneration with late-life depression***

Although we did not find an association between markers of global brain atrophy and incidence or persistence of depressive symptoms in late-life, this association could not be excluded. Previous studies have related a lower brain volume to incident depressive symptoms [24-26]. Participants included in these studies were older on average. This difference in age may lead to other results, as it has been shown that the associations of frontal and temporal volume reductions on depression increases with age [27]. Furthermore, two studies investigated the associations of specific brain regions with incident LLD [25,26]. Results from cross-sectional studies have shown that LLD is related to smaller volumes in brain regions involved in affective processing and cognitive control in the response to internal and external stressors [28,29], especially the orbitofrontal cortex, anterior cingulate cortex, amygdala, basal ganglia, hippocampus, and parahippocampus [9]. Thus, LLD may be related to focal volume loss rather than generalized volume loss.

***The association of microvascular dysfunction and late-life depression***

In chapter 3 we extended the findings of chapter 2 to the microcirculation outside of the brain. The finding that functional markers of the microcirculation in the retina and plasma biomarkers of endothelial dysfunction were associated with

prevalent and incident depressive symptoms, supports the concept that early microvascular dysfunction plays a role in the pathophysiology of LLD. Markers of microvascular dysfunction may represent early deficits in the microcirculation because functional impairments in the pericyte, endothelial, and glycocalyx are likely to precede structural impairments [30].

The absence of an association between skin hyperemic response and depressive symptoms could be explained by a lack of power because the study population with skin data comprised only half the number of participants of the plasma marker study population. Alternatively, the association between the skin hyperemic response and depressive symptoms is mediated by cardiovascular risk factors. Furthermore, different mechanisms may be involved in skin hyperemic response as compared with dilatation in both the retinal arterioles and venules.

Several mechanisms may be involved in the association between microvascular dysfunction and LLD. The association between microvascular dysfunction and depression may be the result of chronic ischemia. Microvascular dysfunction induces chronic ischemia in brain tissue [22]. Chronic ischemia results from structural or functional occlusion may result in cognitive and behavioural problems [22]. Microvascular dysfunction may also lead to depression via low-grade inflammation, as it has been shown that the association between microvascular endothelial dysfunction and incident depression is to an important extent mediated by low grade inflammation [31].

### *The association between late-life depression and cognitive functioning*

In chapter 4, we observed an association of MDD with cognitive impairment, and more impaired performance in information processing speed and executive functioning & attention, but not memory. This finding corroborates previous evidence of a relation between depression and cognitive deficits [32], and are in line with studies that show that these cognitive deficits are often persistent [33] and can increase over time [34].

### *The association of late-life depression with structural brain abnormalities*

MDD was associated with overall CSVD burden in participants without T2DM, which mirrors previous findings [35]. The absence of this association in participants with T2DM might be explained by the high vascular burden in this subgroup [36], in which the presence of MDD might add little to the variation in the observed association with CSVD [37]. As mentioned earlier, the absence of an association

between MDD and markers of global brain atrophy could have been a result of difference in age of participants included in our study compared to previous studies [27] or an existing relation with focal volume loss rather than generalized volume loss [9]. Our finding that MDD is more strongly associated with information processing speed and executive functioning & attention as compared to memory is more in line with an underlying vascular mechanism than a neurodegenerative mechanism [38].

***The mediation of structural brain abnormalities on the association between late-life depression and cognitive functioning***

Neither CSVD nor markers of global brain atrophy explained the worse cognitive profile of individuals with MDD or among those with MDD without T2DM. It is possible that markers of CSVD and cognitive impairment are only related within a subgroup of depression (the so-called vascular depression subtype) [39], but such associations might be diluted at the population-average level. Alternatively, several other, not mutually exclusive mechanisms may explain the higher prevalence and risk of cognitive impairment in individuals with MDD. This includes neurobiological effects of depression such as chronically increased cortisol levels and glutamatergic neurotoxicity [40], and decreased in heartrate variability and an increase in platelet activation and pro-inflammatory factors [41]. On the other hand, CSVD and global brain atrophy might be a common etiological factor for both MDD and cognitive impairment. In that case, brain markers could be seen as a classical confounder for the association between MDD and cognitive impairment, though reported direct effects of MDD on cognition remained significant in models including the MRI markers. Next, lower grey matter volumes might be a marker of impeding dementia [42] and the association be due to reverse causation. The stronger association in older age groups between MDD and grey matter seems in line with this, though we would have expected to find associations with intracranial CSF volumes, as a proxy of generalized brain atrophy, in particular. Finally, cognitive impairments might be a state effect of a current depressive episode, known as the phenomenon of pseudodementia [43]. Yet, several studies suggest impairments are highly persistent or worsening in depression[44].

***The association between hyperglycaemia and late-life depression***

The prevalence of depression is nearly doubled in individuals with T2DM as compared with the general population [45]. Hyperglycaemia and insulin resistance are key features of T2DM, and have been proposed as underlying mechanisms

involved in the aetiology of depression [12]. The brain is particularly vulnerable to fluctuations in plasma glucose levels because neurons do not possess an active glucose transporter. As a consequence, high extracellular glucose levels lead to high intracellular glucose levels. The resulting biochemical changes may lead to neuronal damage, which eventually may lead to LLD [12].

In chapter 5, we found that hyperglycaemia is associated with LLD. This finding corroborates and further extends previous evidence of an association between T2DM and incident depression [46], and of an association between both diagnosed and undiagnosed diabetes and higher prevalence of depression [47]. In addition, this finding provides evidence that hyperglycaemia as such may be directly involved in the development of depression.

No association was found between SAF and LLD. SAF is thought to represent the accumulation of fluorescent advanced glycation end products (AGEs) in the skin, but may be a less specific measure of hyperglycaemia, as it also measures other fluorescent proteins in the skin and does not reflect non-fluorescent AGEs [48]. Nevertheless, there are currently no other prospective studies available that have assessed this association. Therefore, this finding warrants replication in other prospective population-based studies in order to draw firm conclusions.

Several mechanisms may be involved in the association between hyperglycaemia and LLD. Hyperglycaemia is associated with microvascular dysfunction [49], which may consequently lead to cerebral vascular damage and subsequent LLD [13]. Furthermore, hyperglycaemia may activate the polyol pathway, inducing an overgeneration of reactive oxygen species, and cause the generation of advanced glycation end products [12]. These processes induce oxidative stress which may lead to neuronal apoptosis. Neuronal apoptosis may subsequently lead to neurodegeneration which could eventually cause LLD [12,50]. Moreover, hyperglycaemia has been associated with low-grade inflammation [51], which in turn has been associated with cerebrovascular damage [22] and LLD as well [9,23].

***The association between insulin resistance and late-life depression***

In chapter 5, we also observed that the association of insulin resistance with incident depressive symptoms could be explained by cardiovascular risk factors, in particular central obesity. This is in contrast with results of the Whitehall II Study, the Caerphilly Study and the Pittsburgh Healthy Heart Project, which did not show an association between insulin resistance and incident depression after adjustment for age only [52-54]. However, these studies have important

methodological limitations, such as a single follow-up assessment of depression [52,54], inclusion of only men [53], or a small study population [54]. The Health in Men Study did show an association between insulin resistance and incident depression after adjustment for cardiovascular risk factors including central obesity [55]. Yet, this study only included older men aged 70–93 years, which hinders direct comparison with our younger population [55].

There are several explanations for the attenuation of the association between insulin resistance and incident depressive symptoms after adjustment for central obesity. First, central obesity may also play a causal role in the relation between insulin resistance and depression, which might have resulted in overadjustment. Second, the use of surrogate markers of insulin resistance may or may not coincide with cerebral insulin resistance [56]. Consequently, we cannot exclude the possibility that only cerebral insulin resistance is involved in the development of depression. Third, hyperglycaemia may be one of the mechanisms linking insulin resistance to depression. Obesity is associated with the development of insulin resistance, but only individuals who lack sufficient insulin secretion to match the degree of insulin resistance will develop T2DM [57].

***The existence of a bidirectional association between hyperglycaemia and late-life depression***

In chapter 6, we extensively and systematically assessed the longitudinal association between depression and HbA1c levels. Findings supported the temporality of both associations, further emphasising that both depression and HbA1c are important prevention and treatment targets in individuals with depression and in individuals with and without diabetes.

A previous meta-analysis which used glycaemic state as a categorical measure did not find an association of impaired glucose metabolism or newly diagnosed diabetes with incident depression [58]. The use of HbA1c as a continuous measure gave us more statistical power to detect differences. Besides, the size of our pooled effect estimate was within the range they reported. The small, but statistically significant association between depression and HbA1c extends previous cross-sectional research [59]. A possible explanation for the relatively small magnitude of the effect sizes could be that longitudinal studies are more often subject to attrition bias, with healthier and more compliant individuals less likely to drop-out, leading to an underestimation of the effect size.

The following pathways can link depression to the development of hyperglycaemia. Higher depressive symptoms have been associated with less

optimal diabetes self-management which has in turn been related to hyperglycaemia [60]. In addition, physical inactivity and an unhealthy diet may lead to weight gain which in turn negatively affects blood glucose levels [61,62]. Furthermore, pharmacological therapies for depression can also lead to weight gain [63]. In case of weight gain only individuals who lack sufficient insulin secretion to match the degree of insulin resistance will develop hyperglycaemia [57].

**Methodological considerations**

The findings of this dissertation need to be interpreted in light of various methodological considerations. Reported associations are based on observational data. Results of observational data may be influenced by confounding, plausibility bias, selection bias, information bias, analytic bias, inferential bias, publication bias, and over- or underadjustment [64]. In addition, depression is a complex multifactorial disease. As a result, small effects sizes are expected, which are in general difficult to distinguish from bias [65].

***Confounding***

Confounding occurs when a third extraneous variable accounts for some or all of the observed association between a given exposure and an outcome. In addition, a confounder should not be a consequence of the exposure, and must be causally related to the outcome without being an intermediate variable in the causal pathway between exposure and outcome [64]. To control for confounding, we extensive adjusted for potential confounders in multivariable analyses. Furthermore, we performed a range of sensitivity analyses to control for residual confounding. Nevertheless, we cannot exclude the possibility of residual confounding due to an unknown or unmeasured factor or due to measurement error in the confounder, e.g. a too broad definition of a confounder [64]. Confounding needs to be distinguished from effect modification, in which the effect of the exposure on the outcome differs depending on the level of a third variable. In case we expected effect modification, we tested for interaction and stratified our analyses to study the association in the different strata.

***Selection bias***

Selection bias occurs when a systematic error in the recruitment or retention of study participants results in a tendency towards distorting the measure expressing the association between exposure and outcome [64]. In cohort studies there might be a selective response depending on exposure at baseline and a selective response depending on exposure or outcome during follow-up.

Participants who were suffering from a depressive episode or with higher comorbidities may have been less likely to participate. The same holds for withdrawal during follow-up. In particular participants suffering from a depressive episode during follow-up may not participate in follow-up questionnaires. In addition, participants suffering from depression are less likely to complete all measurements. The performance of full-case analyses may have led to the exclusion of participants who were more depressed or with a more adverse cardiovascular risk profile. Subsequently, our study population may have been less depressed and healthier than the general population, which may have led to an underestimation of the observed findings [66]. To test for selection bias, we compared the crude association in the total study population to the crude association in the study population with available data on the confounder. In case these crude associations differed, we adjusted for this confounder in sensitivity analyses.

In chapter 4, we did not find an association between MDD and memory in our study sample with available MRI data, but the fact that this association was present in the larger study sample including participants without MRI data suggests that depressed participants with MDD and poor memory were less likely to undergo MRI, leading to selection bias. This likely also applies to other population-imaging studies [66]. Furthermore, participants in The Maastricht Study were in general well-treated with regard to cardiovascular risk factors, which may have led to less variations in the assessed exposure variables and suppressed associations.

***Information bias***

Information bias in epidemiologic studies results from imperfect definition of study variables or imperfect data collection procedures. These errors may result in misclassification of exposure and/or outcome for a significant proportion of the study population [64]. In cohort studies, the chance of exposure identification bias is reduced because exposure is usually measured before the outcome. As a result, measurement errors tend to be similar with regard to outcome status, which results in non-differential misclassification [64]. In addition, we performed several sensitivity analyses in which variables were replaced (e.g., body mass index for waist circumference) or other definition were used (e.g., to be defined as not depressed a maximum of two missing follow-up moments was allowed). Nevertheless, misclassification can still have resulted in under- or overestimation of the true effect.

Several points in this dissertation can be discussed in relation to information bias. First, during follow-up we measured depressive symptoms with the PHQ-9 questionnaire. The PHQ-9 questionnaire is a screening instrument to measure depressive symptoms that consists of the criteria upon which MDD is based [67]. A cut-off score of ≥10 is suggestive for clinically relevant depressive symptoms [68], but does not necessarily equate with MDD [69]. It could therefore be argued to what extent clinically relevant depressive symptoms assessed with a depression questionnaire could be generalized to the clinic. Psychiatric patients have searched for help related to their depression, while participants in a population-based study are not participating because of a need for psychological care. Second, depression during follow-up in a population-based setting may be under classified. In clinical studies, patients are closely monitored by their health care provider, and new episodes are readily detected. Within The Maastricht Study, measurements are only collected at baseline and annual follow-up. The chance of misclassification participants as 'not depressed' or 'remitted' could therefore not be excluded because the presence of depression is assessed at fixed intervals. Furthermore, there may be responder bias, in which participants are less likely to fill in the questionnaire at to moment they feel depressed [64]. To reduce the chance of misclassification, it is therefore desirable to link clinical data from health care providers to research data, but these data were not available to us. Third, the definition of course of depression in a population-based setting is a challenge. While data on chronic depression is available in clinical studies, data on chronic depression at population level are scarce. In The Maastricht Study, annual assessment of depressive symptoms enabled the definition of both incidence and course of depressive symptoms over time. However, there are no clear definitions about how to define course of depression in a population-based setting. We defined incident depressive symptoms as no depressive symptoms at baseline (PHQ-9 score <10) and presence of clinically relevant depressive symptoms on at least one follow-up moment (PHQ-9 score ≥10). Course of depressive symptoms was defined as (1) persistent depressive symptoms, i.e. clinically relevant depressive symptoms at baseline and on at least one follow-up moment (PHQ-9 score ≥10); (2) remitted depressive symptoms, i.e. clinically relevant depressive symptoms at baseline (PHQ-9 score ≥10) and no clinically relevant depressive symptoms during follow-up (PHQ-9 score <10); and (3) no depressive symptoms, i.e. no clinically relevant depressive symptoms at baseline and follow-up (no incident depressive symptoms; PHQ-9 score <10). Another population-based study with annual assessment of depressive symptoms defined persistent depressive symptoms as depression at least two consecutive assessments independent of baseline [17]. As a consequences rates of persistent

depression are highly heterogenic across studies [16,17]. Fourth, microvascular dysfunction was measured in the retina, skin, and plasma, in which different mechanisms may be involved compared to cerebral microvascular dysfunction. However, cerebral and retinal small vessels have similar vascular structure (end small arteries that have no anastomoses), and the blood-brain-barrier is structurally and functionally similar to the blood–retinal barrier [70]. In addition, several clinical studies have shown that retinal microvascular abnormalities are closely related to CSVD, suggesting that retinal microvascular abnormalities are an imaging marker for cerebral microvascular dysfunction [71]. Furthermore, impairments in both flicker light–induced retinal dilation and heat-induced skin hyperaemia have been shown to be partly nitric oxide-dependent [72,73], which suggest that the same mechanisms are involved as in the regulation of cerebral blood flow and cell viability and in the protection of nerve cells or fibres against pathogenic factors associated with cerebral ischemia, trauma, and haemorrhage [74]. Plasma biomarkers of endothelial dysfunction also reflect microvascular endothelial function because ≈98% of the endothelium is located in the microcirculation [75]. Although it is assumed that these markers of microvascular dysfunction reflect cerebral microvascular dysfunction, probably in conjunction with vascular smooth muscle cell dysfunction and/or neuronal dysfunction [76-78], this is not necessarily true.

***Analytic bias***

With regard to analytic bias, it is important to note that depressive symptoms do not follow a linear function over time. Depressive symptoms rather fluctuate over time which demands for appropriate statistical approaches. Change scores may not be appropriate to investigate whether someone has experienced clinically relevant depressive symptoms over a period with multiple follow-up moments; a combination of positive and negative change will end up in no change while this person could have experienced severe depressive symptoms at one time. Certain statistical analyses have been developed to investigate non-linear functions. Generalized estimating equation models can investigate correlated data with both linear and non-linear functions [79]. However, while scores are expected to fluctuate over time, these fluctuations are not expected to happen parallel with those of other participants. Consequently, the interpretation of the results is difficult, as it is unclear where someone starts in the function based on group level.

To get a better insight in the fluctuation of depression over time it is recommended to investigate different trajectories of depression by use of a data-

driven approach. Figure 7.2 provides an overview of different trajectories of depressive symptoms. Trajectories of depression in the general population are heterogeneous, with most individuals showing no symptoms (green line) but a notable minority experiencing persistent high symptom burden (red line) [80]. Because of this high heterogeneity, it is not informative to investigate mean scores as these mean scores are mainly driven by the large group without depressive symptoms. Trajectories of depression can be identified using growth mixture modelling (GMM) [81]. Rather than use an analytical technique which reports symptom means on group level, GMM provides information about individual symptom trajectories which can then be explored to identify whether people with particular characteristics are more or less likely to follow a particular trajectory [81]. This is useful for tailoring and optimising treatment [82]. A further advantage of GMM is that cases with missing data are still included in the analysis [81]. Several population-based studies have identified trajectories of depressive symptoms using the PHQ-9 questionnaire and have associated risk factors with a persistent course [83,84].

**Figure 7.2. Trajectories of depressive symptoms**


### *Overadjustment*

Overadjustment occurs when one adjusts for an intermediate variable on the causal path from exposure to outcome. Overadjustment in the estimation of total causal effects is not only unnecessary but likely harmful as it may result in an increase of bias or a decrease in precision of the investigated association without affecting bias [85]. Overadjustment in the estimation of direct causal effects are not valid when there are unmeasured shared causes of the exposure and outcome [85]. If you adjust for a collider (common effect of two variables in the causal model) you may induce an association between these two variables which in reality is not there. Because the pathophysiological pathways to depression are still unclear, we adjusted for several cardiovascular and lifestyle factors that might very well be on the causal pathway. This overadjustment might have resulted in the loss of significant associations in the more complex models. Because of this reason, we distinguished between possible confounders and intermediate variables in separate models. However, associations that remained significant after adjustment for these risk factors are relevant independent of these risk factors.

## Clinical implications

The findings of this dissertation have important clinical implications. Since LLD is often persistent in individuals with cerebrovascular damage (chapter 2) and T2DM [86], and is itself related to an increased risk to develop cardiovascular diseases (CVD), all-cause mortality [87,88], and suboptimal blood glucose levels [89], early recognition and treatment of LLD is important. Microvascular dysfunction and hyperglycaemia may identify those individuals at higher risk for LLD. However, more research is needed to investigate the effect of screening for LLD in primary care. Several guidelines related to CVD recommend screening for LLD using a depression questionnaire as the PHQ-9, e.g. the European Guidelines on CVD prevention in clinical practice [90], the European Society of Cardiology guidelines for the diagnosis and treatment of heart failure [91], and the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing [92]. However, one study has shown that only 3% of the cardiologists routinely screen for depression in their patients [93]. Most cardiologists believe that it is the responsibility of someone else such as a nurse, rehabilitation programme, or general practitioner [94]. Also in diabetes care, specific guidelines to identify and manage depression have been developed [95,96]. The implementation of these guidelines is highly recommended, as is screening for depression in vascular and diabetes care in non-western countries [97]. In addition to these guidelines, it is important to distinguish between need for treatment and a high score on a depression questionnaire; i.e. the absence of a mental disorder is not the same as a good well-being, and a score on a questionnaire indicative of a mental disorder does not equate to need for psychological care [98].

Microvascular dysfunction and hyperglycaemia may also provide potential targets for the prevention and treatment of LLD. However, more evidence is needed to evaluate the effect of microvascular dysfunction treatment and its causal effect on LLD incidence and prognosis. Therefore, it is not recommended to actively screen for microvascular dysfunction using expensive and time-consuming techniques as MRI and dynamic vessel analyses. CVD risk management, including treatment of hypertension, hypercholesteremia, hyperglycaemia, obesity, smoking behaviour, physical activity, nutrition, and stress-management, is often used in routine primary care to prevent CVD. In addition to prevention of CVD, CVD risk management may also be effective in the prevention of LLD. Consistent evidence has shown that LLD is both a risk factor, as well as a prognostic factor in CVD [99]. More recent evidence suggest a bidirectional association between CVD and LDD [99]. However, studies that investigate whether CVD risk management is effective in the reduction of LLD

are scare. In guidelines for psychiatric care, screening for CVD risk factors in patients with LLD is recommended [100]. To what extent this recommendation is implemented and which interventions strategies are effective for both clinical outcomes is subject for future research.

With regard to hyperglycaemia, integrated care approaches that treat LLD and hyperglycaemia jointly need to be implemented. Although research has shown a positive effect of simultaneously treat depression and hyperglycaemia [101], more studies are needed that elucidate the effectiveness of individual intervention components [101]. Optimising blood glucose levels is the most effective therapy to prevent the development of microvascular complications in T2DM, hospital admissions due to hyper- or hypoglycaemic episodes [102], and could potentially also contribute to preventing or slowing down the development of depressive symptoms. In addition, LLD and hyperglycaemia might share the same antecedents such as physical inactivity. Consequently, future research is requested to study the effect of prevention efforts aimed at targeting these antecedents to concurrently prevent LLD and hyperglycaemia.

**Conclusion and future directions**

In conclusion, this dissertation has shown that microvascular dysfunction and cerebral vascular damage are involved in the aetiology of LLD. In addition, cerebral vascular damage is associated with the persistence of LLD. No associations between markers of global brain atrophy with the incidence or persistence of LLD were found. Although we found an association between MDD and cognitive impairment, this association could not be explained by markers of cerebral vascular damage or neurodegeneration. Furthermore, this dissertation has shown that hyperglycaemia is involved in the aetiology of LLD, while the association between insulin resistance and incident depressive symptoms was explained by cardiovascular risk factors. We also found that the association between hyperglycaemia and depression is bidirectional based on meta-analytic data.

The above findings raise several new research questions. First, there is a need for studies that investigate both the effect of microvascular dysfunction treatment as well as microvascular dysfunction treatment effects on LLD. Second, more research is needed to elucidate the effectiveness of individual intervention components in simultaneous treatment of LLD and diabetes [101], whether optimising blood glucose levels contributes to preventing or slowing down the development of depressive symptoms in individuals without diabetes, and

whether prevention efforts aimed at targeting shared antecedents, as physical inactivity, contribute to the prevention of both LLD and hyperglycaemia. Third, differences in previous studies that asses biological causes of LLD could be explained by the existence of pathophysiological distinct subtypes within the LLD concept [15]. Studies that identify and characterize these subtypes of LLD are recommended to better understand heterogeneity in its etiology and provide suitable treatment. Previous studies have identified a vascular depression subtype [39] and a depression-executive dysfunction syndrome [103]. In view of the findings of this dissertation, it would be recommended to investigate the existence of a metabolic depression subtype [104]. Fourth, cerebral vascular damage and neurodegeneration are irreversible and appear to be more pronounce in older adults, as most studies who found these effects included participants above the age of 60 years. Research into more subtle reversible markers of brain changes, like brain connectivity measures, is therefore recommended for younger populations and prevention purposes. In line with the more consistent evidence for an association between smaller volumes in specific brain regions and LLD [105], it is also recommended to investigate associations with regional brain volumes, like hippocampus volume. Fifth, there is a lack of population-based studies that assess course of depression using multiple follow-up moments. Self-report questionnaires can be easily filled in online during an annual follow-up assessment, which will provide important insight into the course of depression in the general population. Lastly, as microvascular dysfunction has widespread consequences [49] and may provide a potential target for public health prevention strategies, more population-based studies should implement state-of-the-art measurements of the microcirculation.

In summary, identification and treatment of new potential risk factors for LLD is expected to reduce the high clinical, societal, and economical burden of depression on patient, their environment, and society. This dissertation suggest that microvascular dysfunction and hyperglycaemia are promising targets for the prevention and treatment of LLD. More research is needed to evaluate which interventions may be effective in clinical practice and for who.

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# Chapter 8

**Summary**
**Nederlandstalige samenvatting**
**Impact paragraph**
**Dankwoord (Acknowledgements)**
**Publications**
**Thesis defences from MHeNs and CARIM**
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# Summary

Depression is a global mental health problem. The aetiology underlying depression remains unclear, possibly due to the heterogeneous nature of depression, including marked differences across age groups. Vascular dysfunction, neurodegeneration, and hyperglycaemia may be involved in the pathophysiology of late-life depression (LLD). To highlight new targets for the prevention and treatment of LLD it is imperative to further understand the contribution of these mechanisms in the pathophysiology of depression.

The general aim of this dissertation was to investigate, in a population-based setting, the associations of vascular dysfunction, neurodegeneration, and hyperglycaemia with the prevalence, incidence and course of LLD over time. In addition, we investigated whether the association between LLD and cognitive functioning could be explained by structural brain abnormalities. A general introduction including an overview of the investigated biological mechanisms, a description of the cohort study used in the present thesis, a thesis outline, and research questions is provided in **Chapter 1**.

In **Chapter 2,** we observed that white matter hyperintensity (WMH) volume was associated with incidence of depressive symptoms in individuals above 60 years of age, independent of major demographical, cardiovascular, and lifestyle risk factors. This association was similar in women and men, and in participants with and without type 2 diabetes mellitus (T2DM). No association was found between overall cerebral small vessel disease (CSVD) burden and incidence of depressive symptoms. In addition, WMH volume was associated with persistence of depressive symptoms in individuals above 60 years, while overall cerebral small vessel disease (CSVD) burden was associated with persistence of depressive symptoms irrespective of age. Contrary to our expectations, no associations of markers of global brain atrophy with incidence or persistence of depressive symptoms were found.

In **Chapter 3,** we extended the findings of Chapter 2 to the microcirculation outside of the brain. We observed that functional markers of the microcirculation in the retina and plasma markers of endothelial dysfunction were associated with prevalent and incident depressive symptoms, independently of demographic, cardiovascular and lifestyle risk factors. The associations with incident depressive symptoms were similar in women and men, and in participants with

and without T2DM. No association was found between the skin hyperaemic response and prevalent or incident depressive symptoms after adjustment for cardiovascular risk factors.

In **Chapter 4,** we found that major depressive disorder (MDD) was associated with cognitive impairment, and more impaired performance in information processing speed and executive functioning & attention, but not memory. These associations were independent of demographic, cardiovascular, and lifestyle-related risk factors, and were similar in women and men, and in participants with and without T2DM. Contrary to our expectations, MDD was not associated with overall CSVD burden or markers of global brain atrophy. However, MDD was associated with overall CSVD in participants without T2DM, but this relation could not explain the associations between MDD and cognitive functioning.

In **Chapter 5,** we observed that fasting plasma glucose, 2 h post-load glucose and HbA1c were associated with incident depressive symptoms, with an increased risk of ~20% per SD higher level of hyperglycaemia markers. These associations were independent of demographical, cardiovascular and lifestyle-related risk factors, and were similar in women and men. We found no association between skin autofluorescence (SAF) and incident depressive symptoms. The association of insulin resistance with incident depressive symptoms could be explained by cardiovascular risk factors, in particular central obesity.

In **Chapter 6,** we conducted a systematic review and meta-analysis to evaluate whether there is a bidirectional longitudinal association between depressive symptoms and HbA1c levels. Results supported a bidirectional longitudinal association, despite the relatively small number of studies that could be included in the meta-analysis.

Finally, in **Chapter 7,** we discussed the key findings of this dissertation and provided a pathophysiological model of LLD. In addition, methodological considerations, clinical implications and directions for future research were addressed.

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# Nederlandstalige samenvatting

Depressie is een wereldwijd gezondheidsprobleem. De oorzaak van depressie blijft echter onduidelijk, mede door de heterogeniteit van de aandoening, waaronder verschillen tussen leeftijdscategorieën. Vasculaire dysfunctie, neurodegeneratie en hyperglycemie zouden een rol kunnen spelen bij het ontstaan van depressie op latere leeftijd. Voor het ontwikkelen van nieuwe preventie- en behandelstrategieën voor depressie op latere leeftijd, is het van belang een beter inzicht te krijgen in de rol van deze mechanismen bij de ontwikkeling en persistentie van depressie op latere leeftijd.

Het doel van deze dissertatie was om de associaties van vasculaire dysfunctie, neurodegeneratie en hyperglycaemie met prevalente, incidente en persisterende symptomen van depressie over tijd te onderzoeken in de algemene bevolking. Tevens werd in deze dissertatie onderzocht of de associatie tussen depressie en cognitief functioneren verklaard kan worden door structurele breinabnormaliteiten. Een algemene introductie, inclusief een overzicht van de onderzochte biologische mechanismen, een beschrijving van het cohort welke gebruikt is in deze thesis, een thesis overzicht en de onderzoeksvragen zijn opgenomen in **Hoofdstuk 1**.

In **Hoofdstuk 2** hebben we geobserveerd dat witte stof laesie volume geassocieerd is met de incidentie van depressieve symptomen in individuen boven de leeftijd van 60 jaar, onafhankelijk van belangrijke demografische, cardiovasculaire en leefstijl-gerelateerde risicofactoren. De associatie was hetzelfde voor vrouwen en mannen en voor individuen met en zonder type 2-diabetes mellitus (T2DM). We vonden geen associatie tussen *cerebral small vessel disease* (CSVD) en incidentie van depressieve symptomen. Tevens vonden we dat witte stof laesie volume geassocieerd is met de persistentie van depressieve symptomen in individuen boven de leeftijd van 60 jaar, terwijl CSVD geassocieerd is met de persistentie van depressieve symptomen onafhankelijk van leeftijdscategorie. In tegenstelling tot onze verwachtingen, vonden we geen associaties tussen markers van breinatrofie met de incidentie of persistentie van depressieve symptomen.

In **Hoofdstuk 3** trokken we de bevindingen van Hoofdstuk 2 door naar de microcirculatie buiten het brein. We zagen dat functionele markers van de microcirculatie in de retina en plasma markers van endotheel dysfunctie geassocieerd waren met prevalente en incidente depressieve symptomen,

onafhankelijk van demografische, cardiovasculaire en leefstijl-gerelateerde risicofactoren. De associaties met incident depressieve symptomen waren vergelijkbaar tussen vrouwen en mannen en voor deelnemers met en zonder T2DM. We vonden geen associatie tussen hyperemische reactie van de huid met prevalente of incidente depressieve symptomen na correctie voor cardiovasculair risico factoren.

In **Hoofdstuk 4** vonden we dat een depressieve stoornis geassocieerd was met een verminderd cognitief functioneren, met verminderde prestaties in informatieverwerkingssnelheid en met executief functioneren en aandacht, maar niet met geheugen. Deze associaties waren onafhankelijk van demografische, cardiovasculaire en leefstijl-gerelateerde risicofactoren, en vergelijkbaar voor vrouwen en mannen en voor deelnemers met en zonder T2DM. In tegenstelling tot onze verwachtingen was een depressieve stoornis niet geassocieerd met CSVD of markers van breinatrofie. Een depressieve stoornis was wel geassocieerd met CSVD bij deelnemers zonder T2DM, maar deze relatie kon de associaties tussen een depressieve stoornis en cognitief functioneren niet verklaren.

In **Hoofdstuk 5** observeerden we dat nuchter plasma glucose, 2-h post-load glucose en HbA1c levels geassocieerd waren met incidente depressieve symptomen, met een verhoogd risico van ~20% per SD hogere hyperglykemie marker. Deze associaties waren onafhankelijk van demografische, cardiovasculaire en leefstijl-gerelateerde risicofactoren, en waren vergelijkbaar bij vrouwen en mannen. We vonden geen associatie tussen huid autofluorescentie en incidente depressieve symptomen. Het verband tussen insulineresistentie en incidentie van depressieve symptomen werd verklaard door cardiovasculaire risicofactoren, in het bijzonder centrale obesitas.

In **Hoofdstuk 6** hebben wij een systematische review en meta-analyse uitgevoerd om te evalueren of er een bidirectionele longitudinale associatie bestaat tussen depressieve symptomen en HbA1c levels. De resultaten ondersteunden een bidirectionele longitudinale associatie, ondanks het relatief kleine aantal studies dat in de meta-analyse kon worden opgenomen.

Ten slotte presenteerden we in **Hoofdstuk 7** de belangrijkste bevindingen van deze dissertatie en gaven we een pathofysiologisch model van depressie op latere leeftijd. Daarnaast werden methodologische overwegingen, klinische implicaties en suggesties voor toekomstig onderzoek besproken.

# Impact paragraph

The goal of scientific research is to describe, predict, and explain observed events. Furthermore, scientific research wants to apply the generated knowledge to the society. This paragraph reflects about the scientific impact of the results of this dissertation and the expected impact on the society.

**Aim and key findings**

Depression is a common mental health problem. Currently, up to 350 million individuals world-wide suffer from depression and this number continues to increase [1]. Individuals with late-life depression (LLD; in this dissertation defined as depression above the age of 40 years) have an increased risk for other mental and physical diseases, including cognitive impairment [2-4]. However, the mechanisms underlying LLD are still unclear despite decades of research. The aim of this dissertation was to investigate vascular and metabolic mechanisms which may be important in the development and prognosis of LLD. In addition, we investigated whether the association between LLD and cognitive functioning could be explained by brain damage.

We found that damage of the small blood vessels, measured in the brain and eye, and with blood biomarkers, is involved in the development of LLD. Results also suggested that damage of the small blood vessels in the brain is associated with the persistence of LLD. No relation between shrinkage of the brain and the development or persistence of LLD was found. Although findings support an association between LLD and cognitive functioning, this relation could not be explained by brain damage. Furthermore, this dissertation provides evidence for the contribution of high blood sugar level to the development of LLD. Based on a large literature study, in which results of previous studies were systematically reviewed and analysed, we found that this association exists in both directions; presence of depression is also related to the development of high blood sugar levels.

**Relevance**

The knowledge gained from this dissertation is of high relevance. Results of this dissertation support the vascular depression hypothesis, which assumes that damage of the small blood vessels in the brain contributes to the development and persistence of LLD [5]. The small blood vessels play an important role in the supply of oxygen and nutrients to body tissue and the removal of waste products

out of body tissue. Damage of the small blood vessels may lead to disturbances of these processes, especially in organs which are highly dependent of a good blood supply like the brain. In addition, damage of the small blood vessels in the brain is likely to be irreversible, which may provide a good explanation for the worse response to depression treatment among elderly [6,7]. Therefore, our results may lead to new prevention and treatment targets for LLD. In addition, results of this dissertation are relevant for individuals with LLD and type 2 diabetes. The existence of an association between high blood sugar levels and depression in both directions provides support for a collaborative treatment of LLD in diabetes care.

**Target groups**

The results of this dissertation are of relevance for various target groups. First, the results of this dissertation raise several new research questions. These research questions could directly be implemented in new studies. Second, health care providers may benefit from the increased insight in the mechanisms underlying LLD. Damage of the small blood vessels and high blood sugar levels may identify patients at risk for LLD. Based on the patient's health profile, modifiable risk factors associated with these factors as obesity, high blood pressure, high blood sugar levels, high levels of cholesterol, smoking, diet, and physical activity, could be identified. Personalized treatment aimed to improve these modifiable risk factors may contribute to the functioning of the small blood vessels and the optimisation of blood sugar levels, and may consequently prevent LLD. In addition, early treatment of LLD in these patients may prevent treatment non-adherence, development of complications, and mortality [8-10]. Third, policy makers might use the results of this dissertation to improve clinical guidelines. Although guidelines in vascular and diabetes care recommend screening for depression [11-14], the implementation of these guidelines can be improved. Fourth, results of this dissertation might benefit the general public. Depression has an increasing high societal [15] and economic [16] impact on the society. In late-life, depression is often persistent [17,18] and half of the elderly have a poor response to depression treatment [6,7]. Support for the vascular depression hypothesis and the existence of a bidirectional association between high blood sugar levels and LLD may provide new prevention and treatment strategies.

**Activities**

Researchers and health care providers could be involved and informed about the results of this dissertation via scientific publications and scientific conferences.

Findings of this dissertation are published in peer-reviewed scientific journals, in which the quality of the study is evaluated by experts in the field. Furthermore, results are presented and discussed on national and international conference of several disciplines.

Policy makers could be involved and informed via expert groups that contribute to the development of policies. For instance, chapter 6 is the result of a collaboration of experts in the field of depression in diabetes, the European Depression in Diabetes (EDID) Research Consortium. The EDID Research Consortium identifies and implements research activities required to explore and resolve issues in the assessment, treatment and management of depression in diabetes, to help optimise clinical outcomes for patients and quality of life. As a result, consensus is made on important topics amongst leading psychologists, diabetologists, and other health care providers associated with the treatment of diabetes patients.

The general public might be informed via several activities. The Maastricht Study actively participates in the translation of research results to participants. Results of this dissertation are shared on the website and presented during the annual conference of The Maastricht Study, which is organized for participants and freely accessible. Furthermore, results of this dissertation can be shared with the general public via several media channels, as the television, radio, internet, and information leaflets. Moreover, key findings of this dissertation have been published in several regional newspapers as *De Limburger* and *1Limburg,* and are reported on the regional news *RTV Maastricht.*

**Conclusion**

The results of this dissertation support the concept that damage of the small blood vessels and high blood sugar levels are involved in the development of LLD. Improved insight in the mechanisms underlying LLD is important for the development of new prevention and treatment strategies focused on the small blood vessels in the brain. In addition, optimization of blood sugar levels and collaborative treatment of LLD in diabetes care is recommended.

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# Publications

## This dissertation

**Geraets AFJ**, van Agtmaal MJM, Stehouwer CDA, et al. Association of Markers of Microvascular Dysfunction With Prevalent and Incident Depressive Symptoms: The Maastricht Study. *Hypertension.* 2020;76(2):342-349.

**Geraets AFJ**, Köhler S, Muzambi R, et al. The association of hyperglycaemia and insulin resistance with incident depressive symptoms over 4 years of follow-up: The Maastricht Study. *Diabetologia*. 2020;63(11): 2315-2328.

**Geraets AFJ**, Schram MT, Jansen JFA, et al. The relation of depression with structural brain abnormalities and cognitive functioning: the Maastricht study. *Psychological Medicine*. 2021:1-10.

**Geraets AFJ**, Köhler S, Jansen JFA, et al. The Association of Markers of Cerebral Small Vessel Disease and Brain Atrophy with Incidence and Course of Depressive Symptoms - The Maastricht Study. *Journal of Affective Disorders*. 2021.

Beran M, **Geraets AFJ**, Muzambi R, et al. The bidirectional longitudinal association between depressive symptoms and HbA1c: a systematic review and meta-analysis. *Submitted.*

## Other

**Geraets AFJ**, van der Velden PG. Low-cost non-professional interventions for victims of sexual violence: A systematic review. *Aggression and Violent Behavior*: 2020;53.

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. *Submitted.*

van der Heide FCT, Steens ILM, **Geraets AFJ**, et al. Lower retinal nerve fiber layer thickness, an index of neurodegeneration, is associated with incident depressive symptoms – The Maastricht Study. *Submitted.*

Schmitt A, Beran M, **Geraets AFJ**, et al. Impact of HbA1c improvement on comorbid depressive symptoms in diabetes: A systematic review of intervention studies. *In preparation.*

**Geraets AFJ**, Schram MT, Jansen JFA, et al. Internal validity and prognosis of the metabolic depression subtype: The Maastricht Study. *In preparation.*

**Geraets AFJ**, Köhler S, Vergoossen LWM, et al. The association of structural white matter connectivity with prevalence, incidence, and course of depressive symptoms - The Maastricht Study. *In preparation.*

**Geraets AFJ**, Köhler S, Schram MT. Risk factors of late-life depression. *In preparation.*

**Geraets AFJ**, Leist A, Schram MT, et al. The influence of lifestyle factors on the association between depression and incident dementia. *In preparation.*

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# Thesis defences from the School for Mental Health and Neuroscience and School for Cardiovascular Diseases



**School for Mental Health and Neurosciences**

**2021**

Laura Vergoossen, **Brain Network Alterations due to Cardiometabolic Risk Factors; Insights from Population Magnetic Resonance Imaging**. Supervisors: Prof. W.H. Backes, Dr. J.F.A. Jansen; Co-supervisor: Dr. M.T. Schram

Sophie Leijdesdorff, **Ain't no mountain high enough - How to improve access to youth mental health care.** Supervisors: Prof. T.A.M.J. van Amelsvoort, Prof. A. Popma, AMC**;** Co-supervisor: Dr. R.M.C. Klaassen, AMC

Johannes de Munter, **The patient's own bone marrow-derived stromal cells: disease modifiers in (neuro) degenerative disorders.** Supervisors: Prof. B.W.W. Kramer, Prof. E.CH.Wolters; Co-supervisors: Dr. T. Strekalowa, Dr. J. Mey

Ranjana J. Jairam, **Sacral nerve stimulation for lower urinary tract dysfunctions: towards better outcome.** Supervisors: Prof. Ph.E.V.A. Van Kerrebroeck, Prof. G.A. van Koeveringe; Co-supervisor: Dr. D.M.J. Vrijens

Luiz Kae Sales Kanazawa, **The antimanic-like effects of an-Dr.ographolide and quercetin.** Supervisors: Prof. J. Prickaerts; Co-supervisor: Dr. Roberto Andreatini, Paraná, Brasil

Maria Ferrarac, **Early Intervention in Psychosis A data-Dr.iven population health approach to reduce the duration of untreated psychosis.** Supervisors: Dr. S. Guloksuz, Prof. J.J. van Os; Co-supervisor: Prof. V.H. Srihari (Yale University, USA)

Talakad Narasappa Sathyaprabha, **Cardiovascular autonomic regulation in health and neurological disorders.** Supervisors: Prof. B.W.W. Kramer, Prof. H.W.M. Steinbusch; Co-supervisors: Dr. T.R. Raju, Bangalore

Raoul Stevens, **Unboxing the Brain; Development of Technologies for Non-Invasive Assessment of Cerebral Pathologies.** Supervisor: Prof. T. Delhaas, Prof. W.H. Mess; Co-supervisors: Dr. W. Huberts

Clara Snijders, **Post-traumatic stress disorder epigenetic signatures of differential susceptibility to combat trauma.** Supervisor: Prof. B.P.F. Rutten; Co-supervisors: Dr. L. de Nijs, Dr. G. Kenis

**2020**

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Suat Kucukgoncu, **Metabolic Disturbances in Mental Illness.** Supervisor: Prof. B.P.F. Rutten; Co-supervisor: Dr. S. Gölöksüz

Lotta-Katrin Pries, **The interplay between the genome and the exposome in psychosis spectrum.** Supervisors: Prof. B.P.F. Rutten, Prof. J. van Os; Co-supervisor: Dr. S. Guloksuz

Suzanne van Bronswijk, **Personalized treatment strategies for depression.** Supervisors: Prof. F.P.M.L. Peeters, Prof. M.J.H. Huibers, VU Amsterdam; Co-supervisor: Dr. L.H.J.M. Lemmens

Jan Wouter Brunings, **Concerning Assumptions in Laryngology.** Supervisor: Prof. B. Kremer; Co-supervisors: Dr. L.W.J. Baijens, Dr. A.E.W. Hamaekers

Jonas Weijers, **Mentalization and psychosis Trying to understand the "un-understandable".** Supervisors: Prof. J.P.C.J. Selten, Prof. E.H.M. Eurelings-Bontekoe, Universiteit Leiden; Co-supervisor: Dr. W. Viechtbauer

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Glenn Franken, **Neuromodulation of the Dorsal Root Ganglion in Experimental Chronic Neuropathic Pain: Efficacy and Mechanisms of Action.** Supervisors: Prof. E.A.J. Joosten, Prof. J.H.M. van Zundert; Co-supervisors: Dr. A.L. Liem, MC Jan van Goyen, Amsterdam

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Ricky Kamps, **Resolving the Role of Genetic Defects and mtDNA Copy Number in MitochonDr.ial Disease and Development.** Supervisor: Prof. H.J.M. Smeets; Co-supervisor: Dr. F.H.J. van Tienen

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Daniël Verberne, **Psychosocial outcome after stroke and traumatic brain injury - Longitudinal perspectives and recommendations for aftercare.** Supervisors: Prof. C.M. van Heugten, Prof. R.W.H.M. Ponds; Co-supervisor: Dr. M.E.A.L. Kroese

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Ekaterina Veniaminova, **The impact of the 'Western Diet' on Emotional, Social and Cognitive Behaviours as revealed by a study on conventional and serotonin Transporter-Deficient Mice.** Supervisor: Prof. K. Lesch, Universitätsklinikum Würzburg; Co-supervisors: Dr. T. Strekalova, Prof. D.C. Anthony, Oxford

Anna Gorlova, **Understanding the Molecular Mechanisms of Aggression in BALB/C and TPH2-Deficient Mice.** Supervisor: Prof. K. Lesch, Universitätsklinikum Würzburg; Co-supervisors: Dr. T. Strekalova, Prof. L. Bettendorff, University of Liège

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Joost Riphagen, **Vascular matters in aging and dementia.** Supervisor: Prof. F.R.J. Verhey; Co-supervisor: Dr. H.I.L. Jacobs

Johan Haumann, **Prevalence and pharmacological treatment of pain in patients with cancer; The role of opioids with and without NMDA receptor affinity.** Supervisor: Prof. E.A. Joosten; Co-supervisors: Prof. M.H.J. van den Beuken-van Everdingen, Dr. S.M.J. Van Kuijk

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**2020**

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Tan Lai Zhou, **Blood Pressure Variability: causes and consequences.** Supervisors: Prof. C.D.A. Stehouwer, Prof. A.A. Kroon; Co-supervisor: Dr. R.M.A. Henry

Ilvy Geraets, **Metabolic phenotyping of the pressure-overloaded Heart - Focus on model development.** Supervisor: Prof. J.F.C. Glatz; Co-supervisors: Dr. M. Nabben, Dr. J.J.F.P. Luiken

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Margaux Fontaine, **The MacroScreen Platform – Capturing Cardiovascular Disease Inflammation In Vitro.** Supervisor: Prof. E.A.L. Biessen; Co-supervisors: Dr. J.C. Sluimer, Dr. L. Temmerman

Daniëlle Beurskens, **Extracellular histone H3: biomarker and therapeutic target for the prevention of tissue damage.** Supervisor: Prof. C. Reutelingsperger; Co-supervisor: Dr. G. Nicolaes

Frank Stifft, **Novel Insights for Improvement of Tacrolimus Therapy.** Supervisor: Prof. J. van Hooff; Co-supervisor: Dr. C. Christiaans

Rick van Gorp, **Oral anticoagulants as double-edged sword: balancing between coagulation and calcification**. Supervisors: Prof. L. Schurgers, Prof. C. Reutelingsperger

Lisa van der Vorm, **Unravelling von Willebrand Factor: Active VWF in conditions of (un)balanced haemostasis.** Supervisor: Prof. H. ten Cate; Co-supervisors: Dr. B. de Laat, Dr. J. Remijn

Mahmoud Elbatrik, **Network pharmacology for mechanistically redefined comorbidities.** Supervisor: Prof. H.H.H.W. Schmidt; Co-supervisor: Dr. A.I. Casas Guijarro

Tatjana Josefs, **Diabetes-related factors and atherosclerosis regression**. Supervisors: Prof. C.G. Schalkwijk, Prof. E.A. Fisher (NYU School of Medicine); Co-supervisor: Dr. K. Wouters

Dominique van Dongen, **Pre-hospital risk stratification in suspected Non ST-elevation acute coronary synDr.ome.** Supervisor: Prof. A.W.J. van 't Hof; Co-supervisors: Dr. J.P. Ottervanger, Dr. R.J. Slingerland (Isala, Zwolle)

Martijn Smulders, **Diagnostic evaluation of chest pain. The role of non-invasive cardiac imaging.** Supervisors: Prof. H.J.G.M. Crijns, Prof. J.E. Wildberger; Co-supervisors: Dr. S. Bekkers, Dr. B. Kietselaer (Zuyderland Medisch Centrum)

Robert-Jan Goldhoorn, **Endovascular treatment of acute ischemic stroke in clinical practice.** Supervisors: Prof. R.J. van Oostenbrugge, Prof. W.H. van Zwam

Aomin Sun, **Role for phosphatidylinositol 4-kinase IIIß in cardiac metabolic diseases.** Supervisor: Prof. J.F.C. Glatz; Co-supervisors: Dr. J.J.F.P. Luiken, Dr. D. Neumann

Shujin Wang, **Vacuolar H+-ATPase as target to restore cardiac function in the diabetic heart.** Supervisor: Prof. J.F.C. Glatz; Co-supervisors: Dr. J.J.F.P. Luiken, Dr. M. Nabben

Wim Vroemen, **Cardiac Troponin T; It's all in the shape of you.** Supervisor: Prof. O. Bekers; Co-supervisors: Dr. D. de Boer, Dr. W. Wodzig

Michael Wolf, **Evolution and technological advances in ablation of complex atrial and ventricular arrhythmias.** Supervisors: Prof. H.J.G.M. Crijns, Prof. M. Duytschaever (AZ Sint-Jan, Brugge)

Armand Jaminon, **Key role for VSMCs in vascular remodeling and calcification.** Supervisors: Prof. L.J. Schurgers, Prof. C.P. Reutelingsperger

Selena Prisco, **The role of Aldosterone and PTH in Human Primary Aldosteronism and Vascular Calcification.** Supervisors: Prof. L.J. Schurgers, Prof. T. Hackeng, Prof. G.P. Rossi (Padua)

Wenjie Li, **Microvascular dysfunction, physical activity, and cardiometabolic disease.** Supervisor: Prof. C.D.A. Stehouwer; Co-supervisors: Dr. A.J.H.M. Houben, Dr. M.T. Schram

Ilona Cuijpers, **A novel paradigm for heart failure with preserved ejection fraction. Working towards understanding the pathology of HFpEF**. Supervisors: Prof. S. Heymans, Prof. E.A. Jones (KU Leuven)

Sytze Rensma, **Causes and consequences of microvascular dysfunction Focus on the brain**. Supervisor: Prof. C.D.A. Stehouwer; Co-supervisor: Dr. T.T. van Sloten

Ploingarm Petsohonsakul, **Role of vascular Remodeling in Atherosclerosis and Aortic Aneurysm; Vascular calcification as a hallmark of increased vascular smooth muscle cell oxidative stress.** Supervisors: Prof. L.J. Schurgers, Prof. C.P.M. Reutelingsperger; Co-supervisor: Dr. B.M.E. Mees

Kanchi Muralidhar, **Renal protection off pump coronary artery bypass grafting.** Supervisors: Prof. J.G. Maessen, Prof. L. Vincent (Narayana Health City, Bangalore); Co-supervisor: Dr. Y. Ganushchak

Yaqui Sang, **Innovation and standarization of near-patient platelet function assays.** Supervisor: Prof. H. ten Cate; Co-supervisors: Dr. B. de Laat, Dr. M. Roest

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Indira Vonhögen, **Bridging the gaps of microRNAs in Obesity.** Supervisors: Prof. L.J. de Windt, Prof. P. da Costa Martins, Prof. M.E.A. Spaanderman;

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Pascale Notten, **Ultrasound-accelarated catheter-directed thrombolysis for the prevention of postthrombotic synDr.ome**. Supervisors: Prof. H. ten Cate, Prof. M.J.H.M. Jacobs; Co-supervisor: Dr. A.J. ten Cate-Hoek

Attila Krasznai, **Optimizing the perioperative period in the treatment of varicose veins.** Supervisor: Prof. C.H.A. Wittens; Co-supervisor: Dr. L.H. Bouwman

Maurio Gaudino, **The Radial Artery for Coronary Artery Bypass Grafting.** Supervisors: Prof. R. Lorusso, Prof. J. G. Maessen; Co-supervisors: Dr. M.C.G. van de Poll

Patrick Schönleitner, **Dynamic Regulation of Subcellular Calcium Handling in the Atria; Modifying Effects of Stretch and ADr.energic Stimulation.** Supervisors: Prof. U. Schotten, Prof. H.J.G.M. Crijn; Co-supervisor: Dr. G. Antoons

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**2021**

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Job Verdonschot, **CAUSES AND CONSEQUENCES OF DILATED CARDIOMYOPATHY. Integrating genotype and phenotype to redefine disease diagnostics and therapeutics**. Supervisors: Prof. S.R.B. Heymans, Prof. H.G. Brunner; Co-supervisors: Dr. I.P.C. Krapels, Dr. M.R. Hazebroek

Frank van Rosmalen, **New items in the electrophysiologist's toolbox. Future improvements for electrophysiological AF treatment.** Supervisors: Prof. T. Delhaas, Prof. U. Schotten; Co-supervisor: Dr. S. Zeemering

Svenja Petersohn, **Health technology assessment of treatment for peripheral arterial disease.** Supervisor: Prof. M.A. Joore; Co-supervisors: Dr. A.J. ten Cate-Hoek, Dr. B.L.T. Ramaekers

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Emilia Ruggiero, **MEDITERRANEAN DIET AND BEYOND: AN ITALIAN PERSPECTIVE.** Supervisors: Prof. H. ten Cate, Prof. G. de Gaetano, Pozzilli, Italy; Co-supervisors: Dr. L. Iacoviello, Pozzilli and Varese-Como Italy, Dr. M. Bonnaccio, Pozzilli Italy

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# Curriculum Vitae

Anouk Geraets was born on March 16th, 1989, in Brunssum, The Netherlands. She graduated from secondary school in 2007 (Sintermeerten College, Heerlen), and started to study psychology at the Erasmus University Rotterdam. During her studies, Anouk worked as a tutor within the Erasmus University Rotterdam and as a research assistant for the Generation R Study within the department of Child Psychiatry of the Erasmus Medical Centre. In 2010, she received her Bachelor's degree in Clinical Psychology and subsequently started pursuing her Master's degree. Anouk performed her research internship within the Erasmus University Rotterdam and a clinical internship within Stichting Centrum'45 in Oegstgeest. She graduated Cum Laude in Clinical Psychology in 2012. Thereafter, Anouk worked as a psychologist in The Hague and continued to work for the Generation R Study as a research coordinator within the Radiology department of the Erasmus Medical Centre. In 2015, she moved to Nairobi, Kenya, to work as a researcher in the field of sexual violence under supervision of Prof. P.G. van der Velden (INTERVICT department, Tilburg University). Anouk started her PhD project in 2017 at the department of Psychiatry and Neuropsychology and the department of Internal Medicine of the Maastricht University Medical Centre+. The research, as presented in this dissertation, was performed under supervision of dr. Miranda T. Schram, Prof. dr. F.R.J. Verhey, and dr. S. Köhler. During her PhD, Anouk presented her work at national and international conferences, and received several awards and grants. Currently, Anouk works as a postdoctoral researcher at the department of Psychiatry and Neuropsychology at Maastricht University and Alzheimer Centre Limburg.