Low-grade inflammation and endothelial dysfunction predict four-year risk and course of depressive symptoms: The Maastricht study

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ABSTRACT

Background: Low-grade inflammation (LGI) and endothelial dysfunction (ED) might play a key role in the development of depression. We investigated the associations and mediation of LGI and ED with four-year incidence and course of depressive symptoms (remitted, recurrent or persistent).

Design, setting, participants, measurements: In this prospective cohort study (mean age 59.6 ± 8.2 years, 48.9% women, 26.6% diabetes by design), Cox and multinomial regression analyses, adjusted for age, sex, educational level and diabetes status were used to investigate the associations of LGI and ED with onset and course of depressive symptoms as assessed by the PHQ-9 questionnaire.

Results: During 10,847 person-years of follow-up, 264 participants developed incident depression. Higher levels of LGI (OR [95%CI] per SD 1.32[1.16–1.49], p < 0.001) and ED (1.26[1.11–1.43], p < 0.001) were associated with incident depressive symptoms. In mediation analysis, 60% of the total effect of ED with incident depressive symptoms could be attributed to LGI. 76 out of 2637 participants had a persistent course of depressive symptoms. Higher levels of LGI (1.75[1.40–2.19], p < 0.001) and ED (1.33[1.04–1.71], p = 0.021) were associated with a persistent course of depressive symptoms. Higher ED was more strongly associated with persistent depressive symptoms (1.33[1.04–1.71], p = 0.021), while LGI was associated with remission of depressive symptoms. Conclusions: LGI and ED were both associated with incident depressive symptoms, where the latter association was substantially mediated by LGI. ED was further associated with a persistent course of depressive symptoms, while LGI was not. These results suggest a temporal, vascular contribution of both LGI and ED to the etiology and chronicity of depressive symptoms.

1. Introduction

Depression is the leading cause of disability globally and the largest contributor to disease burden (World Health Organization, 2017). It is of importance to enhance our understanding of the mechanisms underlying late-life depression (Valkanova et al., 2013; van Agtmaal et al., 2017) in order to provide novel targets for intervention and personalized therapy for depression in an aging population. Depression is a complex disorder with a multi-faceted etiology, variable disease course and inconsistent treatment response (Valkanova et al., 2013; van Dooren et al., 2016). As age increases, depression is associated with treatment resistance and recurrent episodes (van Dooren et al., 2016).

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Low-grade inflammation (LGI) and endothelial dysfunction (ED) have a bidirectional relation (Schram and Stehouwer, 2005) and are assumed to play a key role in the development and course of depression (van Agtmaal et al., 2017; Tomfohr et al., 2008). A proinflammatory process has been demonstrated in depressive disorders (Howren et al., 2009; Miller et al., 2009) and may contribute to the biological mechanisms associated with its onset and evolution (Milaneschi et al., 2009; Pasco et al., 2010; Dinan, 2008; Haapakoski et al., 2015; Bonaccorso et al., 2001; Schippers et al., 2005; Lesperance et al., 2004; Strawbridge et al., 2015). Furthermore, a recent meta-analysis showed that treatment responders had lower levels of pro-inflammatory markers (e.g. TNF-α) than non-responders, whereas treatment resistance in depression was associated with persistently elevated inflammation markers (Strawbridge et al., 2015).

With regard to ED, associations have been reported with both prevalent and incident depression (van Agtmaal et al., 2017). ED 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 (van Agtmaal et al., 2017). Indeed, a few small studies observed cross-sectional associations between ED and depression (van Dooren et al., 2016; Sherwood et al., 2005; Do et al., 2010; Thomas et al., 2007; van Sloten et al., 2014). Like LGI, ED appears to be more pronounced in treatment-resistant depression (Taylor et al., 2013).

Taken together, an etiological link between both LGI and ED and incident depression may be present. So far, LGI and ED have been studied independently, although it is more likely that their associations are interrelated. Yet, longitudinal studies on their joint effects are missing. A better understanding of the relation between LGI, ED and depression would establish better understanding of the biological mechanisms of this prevalent psychiatric disorder and may lead to the identification of highly needed markers for prediction of depression onset and course and could open the way for the development of new therapeutic targets.

Hence, we investigated the associations of LGI and ED with i) incidence and ii) the course of depressive symptoms (remitted, recurrent and resistant), in a large population-based cohort study with four years of follow-up. In addition, we investigated whether the association of ED and incident depressive symptoms was independent and/or mediated by LGI and vice versa.

2. Methods

2.1. Study population

The current study is part of The Maastricht Study, a population-based prospective cohort study. The rationale and methodology have been described previously (Schram et al., 2014). The study focuses on the etiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus (T2DM) and is characterized by an extensive phenotyping approach. All individuals aged 40–75 years and living in the southern part of the Netherlands were eligible for participation. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status for reasons of efficiency, with an oversampling of individuals with T2DM. The present report includes data from the 3451 participants, who completed the baseline survey between November 2010 and September 2013. The baseline examinations of each participant were performed within a time window of three months. Follow-up questionnaire data were collected annually after baseline assessments. Response rates were 95% (n = 2,695), 89% (n = 2,514), 83% (n = 2,347) and 75% (n = 2,111) from 1 to 4 years of follow-up, respectively. Supplemental Fig. S1 shows the flowchart of the study population. From the initial 3,451 participants, sum scores of LGI and ED and PHQ-9 data were available in 3,102 participants at baseline (Supplemental Fig. S1). Of the remaining 3102 participants, a PHQ-9 score ≥ 10 at baseline was present in 138 (4.5%) participants, 137 participants had no follow-up PHQ-9 data, resulting in a study population for longitudinal analyses of n = 2827, with an average follow-up duration of 3.8 ± 1.0 years, 10,847 person-years of follow-up, and a person-time rate of 24 cases per 1000 person-years.

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, on the basis of the Health Council’s opinion (Permit 131088-105234-PG). All participants gave written informed consent.

2.2. Markers of LGI and ED

Plasma biomarkers of LGI, i.e. high sensitivity CRP, serum amyloid A (SAA), sICAM-1, IL-6, IL-8 and TNF-α, and plasma biomarkers of ED, i.e. sVCAM-1, sICAM-1, sE-selectin and vWF, were used in this study. A sum score of the LGI and ED markers was calculated according to predefined clusters of conceptually related biomarkers (de Jager et al., 2006; Yudkin et al., 1999); for each individual biomarker, a z-score was calculated using the total sample’s mean and standard deviation. Markers were log-transformed first. The resulting individual biomarker z-scores were averaged and standardized again to yield an overall standardized sum score for LGI and ED separately. Additional information is available in Supplementary Methods.

2.3. Assessment of depressive symptoms

Depressive symptoms were assessed with the Patient Health Questionnaire-9 (PHQ-9), a self-administered questionnaire based on the DSM-IV criteria for a major depressive disorder at baseline and annually during four years of follow-up (Kroenke et al., 2001). It comprises nine items rated on a four-point scale, ranging from 0 (not at all) to 3 (nearly every day), which are summed up to calculate a total-score ranging from 0 to 27. We used a pre-defined cut-off score of ≥ 10 to define clinically relevant depressive symptoms (Kroenke et al., 2001). Incident depressive symptoms were defined as a PHQ-9 < 10 at baseline and a PHQ-9 ≥ 10 on at least one follow-up moment. ‘No depressive symptoms’ was defined as a PHQ-9 < 10 both at baseline and during follow-up. Remitted depressive symptoms were defined as PHQ-9 ≥ 10 at baseline and no depressive symptoms at follow-up (PHQ-9 < 10), and persistent depressive symptoms were defined as a PHQ-9 ≥ 10 both at baseline and on at least one follow-up moment. In addition, at baseline only, current or lifetime diagnosis of major depressive disorder (MDD) was assessed by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

2.4. Possible confounders

Education status (low, middle, high), partner status, history of cardiovascular disorder, smoking, physical activity (measured through CHAMPS (Resnicow et al., 2003) and medication use were assessed by questionnaires. Estimated glomerular filtration rate (eGFR), HbA1c, body mass index (BMI) and office blood pressure were assessed as previously described (Schram et al., 2014). Diabetes status was assessed by 75 gr oral glucose tolerance test after an overnight fast according to World Health Organization criteria (Organization, 2006).

2.5. Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics version 25.0 (IBM Statistics for Windows, Armonk, New York) and Mplus8 (Muthen & Muthen, Los Angeles). We used Cox proportional hazard regression analyses to assess the association of LGI and ED sum scores with incident depressive symptoms (PHQ-9 ≥ 10), with time-in-study as time axis. The proportional hazard assumption was checked by
inspection of the Kaplan-Meier curves. Multinomial logistic regression analyses were used to investigate the association of LGI and ED sum scores with course of depression (no, remitted, persistent depressive symptoms) in the total sample. Model 1 was adjusted for age, sex, and educational level; model 2 was additionally adjusted for type 2 diabetes status. Observations with missing data on possible confounders were excluded from the analysis. Structural equation modelling for continuous-time survival analysis was used to investigate potential mediation of LGI and ED on incident depression by decomposing total effects into direct and indirect paths calculating the proportion of the total effects that is mediated by the indirect path. Continuous variables with a skewed distribution were log-transformed before regression analyses. Sensitivity analysis were performed on additional adjustment for antidepressant use, cardiovascular risk factors (such as waist circumference, office systolic blood pressure, use of statins, estimated glomerular filtration rate, history of cardiovascular disease, and smoking behavior), physical activity, Mediterranean diet score and alcohol use. For all analysis, a p-value of 0.05 was considered statistically significant in two-sided test.

3. Results

3.1. Demographical and clinical characteristics

During 10,847 person-years of follow-up, 264 (9.3%) participants developed clinically relevant depressive symptoms (PHQ-9 ≥ 10), which yields an incidence rate of 24 cases per 1,000 person-years. Participants not included in the analyses (n = 624) had a lower level of education, less often a partner, higher sum scores of LGI and ED, and a worse cardiometabolic risk profile than participants included in the analyses (data not shown).

Table 1 shows general characteristics by baseline depression status. Individuals with depressive symptoms were younger, had a lower educational level, and higher PHQ-9 scores throughout follow-up, higher BMI and waist circumference, more often a history of cardiovascular disease, T2DM, higher HbA1c levels, were more often current smokers, consumed less alcohol, and more often used medication compared to the group without depression.

Both LGI and ED were cross-sectionally associated with depressive symptoms, after adjustment of demographics the association was strengthened, but after adjustment for T2DM the association of both LGI and ED were attenuated yet remained statistically significant (Supplementary Table S1).

3.2. Longitudinal associations of LGI and ED with incident depression

Of the 2964 individuals without depression at baseline, 2688 (90%) had data on baseline LGI and ED and at least one PHQ-9 assessment during follow-up. Table 2 shows the associations between the LGI and ED sum score with incident depression when tested separately. Higher levels of LGI and ED were both associated with incident depression in crude analyses. As expected, adjustment for age, sex and educational level (model 1) and additionally for T2DM (model 2) resulted in attenuated but still statistically significant associations.

3.3. Mediation analyses

Mediation analyses of model 2 was then used to decompose the total effect of ED into a direct (independent of LGI) and indirect effect (mediation by LGI). This showed that the total effect (HR [95%CI] 1.23 [1.15; 1.32]) of ED on incident depressive symptoms was mediated by LGI (indirect effect ED via LGI: 1.13 [1.03; 1.24]; Fig. 1). In contrast, the remaining direct path of ED on incident depressive symptoms that was independent of LGI was not statistically significant (direct effect ED: 1.09 [0.92; 1.29]). LGI itself had a direct effect on incident depression in the presence of ED (mediation by LGI). This showed that the total effect of LGI on incident depressive symptoms (1.30 [1.15; 1.47]) was not mediated by ED.
adjustment for cardiovascular risk factors, physical activity, Mediterranean diet score, or alcohol use (Supplemental Table S2). Due to the oversampling of participants with T2DM, we tested for interaction between T2DM and LGI or ED to study differential associations with incident depressive symptoms by diabetes status. We also tested whether there was an interaction with sex. None of these interactions were statistically significant (data not shown).

### 3.6. Missing data

To address potential selection bias by missing data, we compared participants with missing data to participants included in the final analyses and found no indications that the validity of the results is undermined (Supplementary Results, Missing Data).

### 4. Discussion

In this prospective cohort study, higher levels of LGI and ED were consistently associated with incidence and course of depressive symptoms. The association of ED with incident depression was substantially mediated by LGI. Together, ED and LGI were able to discriminate between a single depressive episode with a remitting course versus a persistent course: ED was associated with a persistent course, while LGI was not, and LGI was associated with a single depressive episode, while ED was not. Our findings suggest a pathway from ED through LGI to incident depression, where the continuing activation of LGI by ED may further predispose to persistent depressive symptoms.

To our knowledge, no other study evaluated the relation of LGI and ED in relation to different courses of depression. The longitudinal association of LGI and ED with depression has been studied previously, but associations were inconclusive because these attenuated or remained after adjustment for confounders (Valkanova et al., 2013; Copeland et al., 2012; Chocano-Bedoya et al., 2014; Baune et al., 2012; Wiium-Andersen et al., 2013; Zalli et al., 2016; van den Biggelaar et al., 2007; Stewart et al., 2009). We adjusted our analyses for demographics and T2DM, and our results show that high baseline ED marks a group with persistent depressive symptoms. In contrast, LGI was associated with both single as well as persistent and incident depressive symptoms. Thus, high LGI might be considered a state-marker of ‘being depressed’, while high ED appears to more specifically flag those at risk for a persistent course. ED and LGI were jointly able to discriminate between single versus persistent depressive symptoms, which is promising for clinical application, although this finding needs replication in independent cohorts.

Our study suggests that LGI is an important determinant of depression and a central mechanism in the putative causal pathway. With regard to inflammation, our results extend the findings from the longitudinal meta-analysis by Valkanova et al. (2013), who found an association of CRP and IL-6 with incident depression. There is evidence suggesting that a strong association between inflammation and depression is especially found in older adults because of more peripheral immune activation and a chronic neuro-inflammation in ageing (Valkanova et al., 2013). For instance, LGI can lead to alterations in the tryptophan-kynurenine pathway and in the hypothalamus-pituitary-adrenal axis, which in turn have been linked to depression (Miller et al., 2009; Carvalho et al., 2014; Penninx, 2017) and ED (Wardlaw et al., 2013).

Our results seem to fit well with a bidirectional association between ED and LGI (Penninx, 2017; van Sloten et al., 2016). Indeed, studies have shown that damage to the endothelium can also lead to activation of the immune system, blood-brain-barrier dysfunction, cerebral small vessel disease and subsequent chronic depression (Wardlaw et al., 2013). Meta-analyses on the association of MRI detected cerebral small vessel disease with depression suggest that depression may then be due to strategic infarcts in fronto-subcortical pathways involved in mood regulation (van Agtmaal et al., 2017; Krishnan et al., 1997; Aizenstein et al., 2016). Our findings hence lend further support to the vascular depression hypothesis (Krishnan et al., 1997; Aizenstein et al., 2016; Alexopoulos, 2006).

Changes in ED plasma markers may provide an earlier indicator of cerebral small vessel disease than these MRI markers, as the latter represent mainly irreversible cerebrovascular damage.

In daily clinical practice, there is a need for markers that predict the course of depressive symptoms. Depression is known for its recurrence (Anderson et al., 2001). Response to treatment, i.e. pharmacotherapy...
and psychotherapy, varies between 30 and 60% of the initial therapy, possibly due to different underlying pathophysiological mechanisms, and because of this, switching and combining therapies for patients with depression is common (Pinquart et al., 2006; Casacalenda et al., 2002; Mottram et al., 2006). In addition, a depression of vascular origin may not respond to currently available therapies. Plasma samples are easily obtained and biomarkers can be measured with standardized procedures and at relatively low cost. A profile of low LGI and ED scores might indicate protection against the development of a new depressive episode and can therefore help identifying patients with high and low risk of chronic depressive symptoms. Studying whether these biomarkers can also predict the course of the disorder and response to treatment in advance may give clinicians new direction for interventions.

This study has several strengths, most notably the population-based longitudinal design with repeated measures of depression onset and course, its sample size, the biomarker profiles for the representation of LGI and ED, and the adjustment for multiple confounding factors. State-of-the-art and validated measures were used to assess depressive symptoms, LGI and ED. From a biological view, LGI and ED are closely linked and therefore hard to disentangle (van Sloten et al., 2014). We used appropriate multivariate statistics to model their interrelation.

Certain limitations should be acknowledged as well. The recruitment strategy and follow-up could have led to selection bias: individuals with more severe depressive symptoms or with greater comorbidity may have been less likely to participate. The prevalence of depression and severity of depressive symptoms might therefore be underestimated and may be
higher in an unselected population. However, the prevalence of depressive symptoms in our study is comparable with previously published data (Kessler and Bromet, 2013). Despite the large sample size for the cross-sectional and incidence analyses, the part of course of depression was limited in relatively small numbers among the depressed course-types, which withheld us from studying recurrent and chronic depression separately (both were considered ‘persistent depression’). With regard to follow-up, high scores on the PHQ-9 are suggestive for depressive symptoms, but do not necessarily equate with a major depressive disorder and therefore use of the PHQ-9 could have led to slight under- or over-reporting of depression. Nevertheless, with a sensitivity and specificity of 88% for the detection of depression with the PHQ-9 compared to a structured psychiatric interview (Kroenke et al., 2001); the under- or over-reporting of depression in this study is expected to be minimal.

This prospective cohort study indicates that LGI and ED may play an important role in the pathophysiology of LGI and ED were both associated with incident depression. The association of ED and incident depression is to an important extent mediated by LGI. ED was able to discriminate between outcome groups with a single episode versus persistent depressive symptoms. Our findings may suggest a strong vascular contribution to the etiology and chronicity of depressive symptoms.

5. Disclosures

5.1. Sponsor’s role

There was no sponsor involvement in data collection, analysis, interpretation, or manuscript preparation.

Author contributions

Janssen: study concept and design, analysis, interpretation, and writing of manuscript. Köehler and Schram: data acquisition, conceptualization, study concept and design, analysis, interpretation and writing of the paper. Gerards: analysis, interpretation and writing of manuscript. Stehouwer, Schaper, Sep, Henry, van der Kallen, Schalkwijk, Koster and Verhey: data acquisition, conceptualization, data interpretation. All authors: creation and revision of manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.06.013.

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