

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

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## 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 <sup>1</sup>. 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 <sup>2-4</sup>. 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 <sup>5</sup>. 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<sup>6,7</sup>. 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<sup>8-10</sup>. 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<sup>11-14</sup>, the implementation of these guidelines can be improved. Fourth, results of this dissertation might benefit the general public. Depression has an increasing high societal<sup>15</sup> and economic<sup>16</sup> impact on the society. In late-life, depression is often persistent<sup>17,18</sup> and half of the elderly have a poor response to depression treatment<sup>6,7</sup>. 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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