Dementia and depression

Chapter 10

Impact paragraph

Dementia and depression are devastating disorders that are common among older individuals. These disorders not only pose an enormous burden to patients and their families, but also a significant economic burden to society. These burdens are expected to increase dramatically in the next decades,[1,2] driven in part by the projected rise in the number of individuals living with these disorders[1,3] and the lack of curative solutions to treat them. New targets for prevention are therefore needed. Such new preventive targets are particularly important for those with cardiovascular disease[4,5] or type 2 diabetes[6,7] who are at an up to twofold increased risk of developing dementia, depression, or both. A better understanding of the mechanisms underlying dementia and depression is required so that these preventive targets can be identified. In this thesis, I investigated these mechanisms, and I had three main findings:

I. A higher number of risk factors meeting guideline-recommended levels was associated with a lower excess risk of dementia and depression in cardiovascular disease and type 2 diabetes.
II. Cardiovascular disease in midlife, rather than in late-life, was associated with a higher risk of dementia.
III. Measures of cerebral microvascular mechanisms were associated with a higher risk of clinically relevant depressive symptoms.

In this chapter, I discuss how these three findings guide further scientific research and clinical practice, and how they might impact on society as a whole.

Finding I: Risk factors as targets for prevention of dementia and depression in cardiovascular disease and type 2 diabetes

In this thesis, we show that the excess risk of dementia and depression in cardiovascular disease and type 2 diabetes decreased stepwise for a higher number of risk factors meeting guideline-recommended levels (i.e. glycated hemoglobin, blood pressure, body mass index, smoking, albuminuria, physical activity and dietary habits). This suggests that multifactorial risk factor modification may be a potential target for prevention of dementia and depression in cardiovascular disease and type 2 diabetes. This approach is part of the current guidelines regarding the management of individuals with cardiovascular disease[8,9] and type 2 diabetes[10,11] and is known to improve quality of life and life expectancy through reduction of cardiovascular disease and microvascular complications.[9,11] This thesis adds dementia and depression to that list.

Using our findings, we can speculate on the exact risk reduction (i.e. the effect size) that can be achieved by multifactorial risk factor modification. Based on our data, I can extrapolate that, among individuals with cardiovascular disease, every additional lifestyle factor meeting guideline-recommended levels is expected to result in a 27% reduction of dementia risk (*chapter 2*). Similarly, among individuals with type 2 diabetes, every additional risk factor meeting guideline-recommended levels is expected to result in a 29% reduction of dementia risk (*chapter 3*) and a 13% reduction of depression risk (*chapter 4*). These findings highlight the importance of risk factor modification strategies in individuals with cardiovascular disease and type 2 diabetes, and underline the important public health implications they carry. However, these numbers are based on observational data and therefore not directly translatable to those obtained by interventional studies. In observational studies, risk factors can already be at recommended levels prior to any treatment, and effect sizes are dependent on the distribution of the risk factor levels and confounders in the investigated populations.[12] Trials testing the effect of multifactorial risk factor modification on risk of dementia and depression in individuals with cardiovascular disease or type 2 diabetes have not been performed. Such trials will, most likely, no longer be initiated due to several reasons, including ethical concerns and financial constraints.

Despite the availability of evidence-based guidelines, optimal control of risk factors in cardiovascular disease or type 2 diabetes is difficult to achieve.[13] For example, in *chapters 3 and 4* we had to combine individuals with type 2 diabetes who had 5, 6 or 7 risk factors meeting guideline-recommended levels into one category in order to include groups that were sufficiently large. This indicates that in the majority of participants with type 2 diabetes, control of their risk factors was not optimal. This finding is supported by previous studies,[13-15] and the treatment gap may be more pronounced among individuals of lower socioeconomic classes.[13] Similarly, an unhealthy lifestyle is common in the general population. Among individuals living in the Netherlands, 50.2% has a body mass index ≥25 kg/m^2 and only 44% meets WHO-recommended levels of physical activity (i.e. ≥150 minutes/week of moderate-to-vigorous physical activity).[16,17] In addition, studies show that lifestyle interventions are often unsuccessful. For example, a meta-analysis of clinical trials testing lifestyle-based weight loss interventions among participants with type 2 diabetes showed, on average, only modest reductions in body weight.[18] Future research is needed to determine which components are needed to make lifestyle interventions effective, in order to improve risk factor control and, in the long term, reduce the global burden of dementia and depression.

Finding II: Primary prevention of cardiovascular disease in midlife to mitigate dementia risk

Previously, it had been observed that individuals with type 2 diabetes in midlife rather than in late-life are at greater risk of dementia.[19] We now show that age at onset of cardiovascular disease affects risk of dementia in a similar manner. In particular those with cardiovascular disease or type 2 diabetes in midlife seem to be at risk of developing dementia. These findings support public health policies for prevention and management of cardiovascular disease and type 2 diabetes in midlife, or earlier, to mitigate risk of dementia at older age.

Finding III: cerebral microvascular dysfunction as a target for treatment and prevention of dementia and depression

In this thesis, we show that various measures of cerebral microvascular mechanisms were associated with an increased risk of clinically relevant depressive symptoms. These results thereby add to growing evidence suggesting that cerebral microvascular mechanisms could be important targets for treatment and prevention of dementia and depression. However, further research is necessary before any of these findings can be translated into public health policies, treatment strategies and prediction models. In this section, I will give directions for further research, highlight potential interventions for cerebral microvascular dysfunction and discuss the group of individuals that will likely benefit most from these interventions.

Finding III: Directions for further research

While the research presented in this thesis has led to important new insights, some questions about the role of cerebral microvascular mechanisms in the development of dementia and depression remain unresolved. For example, it remains unclear to what extent impairment in different functions of the cerebral microvasculature contribute to dementia or depression. Blood-brain barrier permeability, cerebrovascular reactivity and cerebral microvascular perfusion can now be measured using advanced neuroimaging techniques.[2] These measures may provide important information about the role of cerebral microvascular mechanisms in dementia and depression. We investigated the association between microvascular mechanisms and brain connectivity to explore if brain connectivity could be a potential mechanism in the pathway of cerebral microvascular mechanisms leading to dementia and depression. Using urinary

albumin excretion, retinal microvascular measures and plasma biomarkers of endothelial dysfunction, there were no consistent associations between microvascular mechanisms and brain connectivity. The direct measurement of different functions of the cerebral microvasculature enables further study of the association between cerebral microvascular mechanisms and brain connectivity. In addition, future research can explore whether cerebral microvascular mechanisms lead to dementia and depression through mechanisms other than brain connectivity. We also found that the association between plasma neurofilament light (NfL) and incident dementia was, in part, explained by MRI-determined features of cerebral small vessel disease. However, the explained effect by cerebral small vessel disease was rather small, and therefore the clinical implications of this plasma biomarker as a marker of cerebral microvascular mechanisms remain uncertain. Advanced neuroimaging techniques may provide further insights into the extent to which plasma NfL, and other biomarkers, reflect impairments in different functions of the cerebral microvasculature in dementia.

Finding III: Potential interventions

Several ways through which cerebral microvascular function could be improved are under investigation. Lifestyle interventions and drugs used to treat diseases other than dementia and depression may improve cerebral microvascular function and may also have beneficial effects on cognitive function or depressive symptoms.

Lifestyle interventions

As obesity is an important driver of microvascular dysfunction, lifestyle interventions that achieve body weight loss and increase physical activity are likely to be a successful approach.[20] Indeed, trials show that exercise and weight loss interventions have a beneficial effect on cognitive function[19] and depressive symptoms.[22,23] To what extent these beneficial effects are mediated by improved microvascular function has not yet been investigated.

Glucose-lowering drugs

Some glucose-lowering drugs, including metformin and incretin-based therapies (i.e. glucagon-like peptide 1 (GLP-1) receptor agonist and dipeptidyl peptidase 4 (DPP-4) inhibitors) might improve cerebral microvascular function and have beneficial effects on cognitive function and depressive symptoms.[2,24,25] Most of the trials investigating these drugs did not find evidence for a beneficial effect on cognitive function.[26,27] One trial found a beneficial effect of linagliptin (i.e. a GLP-1 receptor agonist) on cognitive function among individuals with Alzheimer's disease dementia.[28] In addition, various

trials that assess the effect of these drugs on cognitive function and depressive symptoms are currently ongoing.[2,29]

Other drugs

Other drugs that might favourably influence the cerebral microvasculature are nitric oxide donors (e.g. isosorbide mononitrate) and phosphodiesterase 3 inhibitors (e.g. cilostazol).[30] At the International Stroke Conference 2023, the results of the Lacunar Intervention Trial 2 (LACI-2) were presented. In this trial among 360 patients with clinical lacunar stroke, treatment with a combination of isosorbide mononitrate and cilostazol for 1 year compared to administration of neither of the two drugs was shown to reduce progression of cognitive impairment. Further research will now be done to investigate whether these findings can be confirmed in a larger, phase III trial (LACI-3). Other trials testing the effect of some of these drugs on cognitive function and depression are currently ongoing.[2,29]

Finding III: Target group

Accurate risk prediction of dementia and depression will be crucial to identify individuals who will most likely respond to targeted interventions. This thesis contributes to an advanced understanding of the role of the retinal microvasculature in dementia and depression and may present the retina as a clinical tool to improve risk prediction models. Retinal microvascular measures capture cerebral microvascular dysfunction at an early disease stage, which is essential for effective prediction.[31] In addition, retinal microvascular measures can easily be implemented in prediction models, because they are readily accessible and already commonly used in clinical practice, for example, for eye screening in diabetes. The findings of *chapters 5 and 6* show that the interpretation of individual values of retinal microvascular measures can be complex. Future studies are needed to assess whether retinal microvascular measures are good indicators of individual dementia and depression risk. In addition, further defining vascular depression as a subtype of depression may be an alternative way through which individuals can be selected for targeted interventions. Emerging evidence suggests that vascular depression is a specific subtype of depression that is more common among older individuals and individuals with cardiovascular disease or type 2 diabetes.[2] Vascular depression may be characterized by a specific clinical presentation and a lower response to current antidepressant medication.[32] However, much is still unclear about vascular depression. Future studies are needed to evaluate whether cerebral microvascular mechanisms are associated with specific comorbidities, specific depressive symptoms or specific trajectories of depressive symptoms across the life course.

Conclusion

The findings described in this thesis advance our understanding of the mechanisms underlying dementia and depression, and highlight the role of risk factors and the cerebral microvasculature herein. Our findings provide evidence for multifactorial risk factor modification as an important approach to prevent dementia and depression among those with cardiovascular disease and type 2 diabetes. In addition, our findings on microvascular mechanisms identify cerebral microvascular dysfunction as a potential target for prevention and treatment of depression. This thesis provides directions for future research to further characterize the contribution of cerebral microvascular mechanisms to dementia and depression, establish adequate interventions for microvascular dysfunction and define the subset of individuals that might benefit most from such interventions.

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