VALORISATION ADDENDUM
Valorisation addendum

Creating knowledge through research seems pointless when this new knowledge does not reach those who might benefit from it. Knowledge valorisation, ie, translation of research into practice, is an essential step in making research worthwhile. Here we discuss how the results of this thesis may impact society. To make it more lively, we start by introducing Mrs. Janssen.

Mrs. Janssen is a 65-year-old woman, slightly overweight and mild hypertensive, who visits her general practitioner for her annual diabetes check-up. She was diagnosed with type 2 diabetes 10 years ago and her glycaemic control has been adequate, though not perfect, ever since. Normally, she would not be nervous to visit her general practitioner, but today she is. She recently participated in The Maastricht Study where she was subjected, among many other things, to a cognitive test battery. When she asked the examiner who conducted the cognitive assessment why this test battery was administered, the friendly PhD student told her that people with type 2 diabetes have an increased risk of developing dementia and other cognitive problems. Although Mrs. Jansen knew that she had been free from diabetic complications, she was afraid that the diabetes might have affected her brain. She frequently forgot names and had to keep a diary to remind herself of the appointments she made. She asked herself: “do these complaints indicate that I am suffering from diabetes-associated cognitive problems?”, “how can I prevent myself from developing diabetes-associated cognitive problems?”, and “are there any treatment options available for diabetes-associated cognitive problems?”. With these questions in mind, she asked her husband, a 63-year-old obese man with prediabetes, to join her to the general practitioner.

Awareness

Many people with type 2 diabetes do not know that their disease puts them at increased risk of cognitive problems. If this thesis succeeds in raising this awareness, especially among patients and caregivers, it would already be of societal value. After all, awareness is the first step towards early detection, treatment and perhaps even prevention of diabetes-associated cognitive problems. One might, however, argue that increasing this awareness is somewhat unethical as it might scare people while there is, at least at present, no treatment available that can alter the course of cognitive impairment. Moreover, it is difficult to establish to what extent the subtle cognitive decrements often seen in people with diabetes will impact their daily lives and well-being. Yet, it has been shown that individuals with type 2 diabetes with undiagnosed cognitive impairment do suffer from more depressive symptoms and have a lower health status. In addition, cognitive problems clearly impact diabetes self-care, which results in worse glycaemic
control and a higher likelihood of hypoglycaemia.

Novel insights
To understand diabetes-associated cognitive problems, one must know the factors that contribute to their onset and severity. This thesis is an effort to identify such factors and suggests that diabetes-associated cognitive problems should be considered as a glucose-mediated complication of type 2 diabetes, since the differences in cognitive performance between individuals with and without diabetes were largely explained by hyperglycaemia. The effects of long-term exposure to elevated blood pressure should, however, not be overlooked as they may also, to a lesser extent, contribute to the cognitive sequelae of diabetes, and could exacerbate the negative cognitive effects of hyperglycaemia. Importantly, however, none of the metabolic and vascular factors we explored explained a large amount of the variance in cognitive performance among individuals with type 2 diabetes. Abnormalities in glucose metabolism and vascular function are thus less likely to explain why only a subset of individuals with type 2 diabetes experience cognitive problems.

Prevention targets
Based on the findings of this thesis, we believe that early glycaemic and blood pressure control might be promising targets for the primary prevention of diabetes-associated cognitive problems. At present, individuals with prediabetes are encouraged to change their lifestyle in order to lose weight and hopefully return to normal glucose metabolism.\(^2\) Guidelines also recommend the identification, and if appropriate, treatment of other vascular risk factors, including hypertension. There, are, however no strict targets for glycaemic control and individuals with prediabetes are seldom prescribed glucose-lowering medication to prevent deterioration in glycaemic control.\(^2\) Our work indicates that intensified glycaemic and blood pressure control in those without diabetes may be necessary to prevent diabetes-associated cognitive problems. This adds fuel to the debate as to whether individuals with prediabetes should be treated with glucose-lowering treatment. The prevention of cognitive problems may be just another reason to consider targets for glycaemic control in people without diabetes. This view is supported by results of the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, which found that insulin therapy in prediabetes to normalise blood glucose levels tends to reduce the decline in some aspects of cognitive performance.\(^4\)

People who already have diabetes do not benefit from primary prevention. For them, secondary prevention of diabetes-associated cognitive problems is necessary, that is, amelioration of cognitive problems among individuals with type 2 diabetes. Unfortunately, our thesis provides little guidance on how to target secondary prevention
as we showed that hyperglycaemia, carotid arterial stiffness, and traditional vascular risk factors explain only marginal amounts of variance in cognitive performance in diabetes. Although this may be why randomised controlled trials on intensified glucose-lowering, blood pressure-lowering, or lipid-lowering treatment in people with type 2 diabetes have failed to show improvement in cognitive performance, it does not foreclose the possibility that improving the metabolic and vascular risk profile of individuals with diabetes may have some beneficial effects. Indeed, positive effects on cognitive performance were observed in both treatment groups in most randomised trials on intensified glucose-lowering treatment, suggesting that improving glycaemic control does have beneficial effects on brain function.

Back to Mrs. Janssen. Luckily for her, her general practitioner recently received a copy of this thesis and he even found some time to read it. He decides to refer her to a neuropsychologist for detailed neuropsychological assessment, which might help to differentiate between (diabetes-associated) cognitive problems and normal cognitive functioning. He also increases her dose of glucose-lowering and antihypertensive medication, although he knows, and warns Mrs. Janssen, that this is likely to have little or no effect on (the progression of) her cognitive complaints. Then he turns to the 63-year-old obese Mr. Janssen with prediabetes, who has failed every diet over the last 5 years, and starts to wonder whether he should start glucose-lowering treatment.
References