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Biological risk factors and sleep-related risk factors of type 2 diabetes mellitus

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SUMMARY

Part 1: Non-modifiable biological factors

Currently, we can identify those with an increased risk of developing Type 2 Diabetes Mellitus (T2DM) reasonably accurately based on risk models for T2DM. However, this group of individuals at risk is still very large, only a small proportion actually progresses to T2DM and those who do have a highly variable phenotype. Hence, information on the different mechanisms that play a role in T2DM is essential for personalized T2DM prevention strategies and underlines the need to refine the characterization of T2DM development. Therefore, the first aim of this thesis was to examine the value of non-modifiable biological factors that could play a role in the development of T2DM and could contribute to the refined characterization of people at risk of developing T2DM.

In the first part of this thesis, the incretin hormones, glucagon and GAD65 antibodies were examined as non-modifiable biological factors that may contribute to elucidating the heterogeneity in the pathophysiological processes to incident T2DM and could refine the characterization of people who develop T2DM. Individuals studied in chapter 2 and 3 were from the Hoorn Meal Study, a prospective general population cohort. **In chapter 2**, we examined the association between incretin responses to an oral glucose tolerance test (OGTT) and mixed meal test (MMT) at baseline and changes in fasting glucose levels 7 years later, in 121 individuals without T2DM at baseline. We showed that a low GLP-1 response to an OGTT was prospectively associated with a steeper increase in fasting glucose levels. Adjusting for possible confounders or mediating variables, including indicators of insulin sensitivity, beta cell function or overweight, did not explain the observed associations. No such association was observed for GIP and neither for the GLP-1 response following a MMT. Although this is the first prospective study on this association, these results suggest that a reduced GLP-1 response precedes glucose deterioration and may play a role in the development of T2DM.

In addition to the role of incretin hormones, we examined in **chapter 3** the association between glucagon responses at baseline and fasting glucose levels 7 years later, in the same 121 individuals from the Hoorn Meal Study. The early glucagon response following the MMT was associated with an increase in fasting glucose levels of 0.18 mmol/l (95%CI: 0.04-0.31, $p=0.01$), per unit increase in the incremental area under the curve of glucagon. Results were adjusted for possible confounders such as fasting glucagon and fasting glucose levels at baseline, BMI at baseline and at follow-up, fasting GIP and GLP-1 levels and indicators of insulin sensitivity and beta cell function. No significant associations were observed for the late response after the MMT or for the responses to the OGTT. These results suggested that a relative lack of glucagon suppression early after a meal precedes deterioration of glycemic control and may play a role in the development of T2DM.

Finally, **in chapter 4** we conducted a systematic review and meta-analysis to assess the association between GAD65 antibody positivity and incident T2DM in a non-diabetic adult population. Our meta-analysis of seven studies showed that diabetes autoimmunity,

as reflected by GAD65 antibody positivity, was associated with incident T2DM with a pooled risk estimate of 3.36 (95%CI: 1.9-5.9). This result was robust to a range of sensitivity analyses. However, the included studies were characterized by heterogeneity due to different risk estimates, study populations and study designs. Nevertheless, our meta-analysis showed that overall, the presence of GAD65 antibodies increases the risk of developing T2DM.

Part 2: Sleep as a novel and modifiable lifestyle factor

While physical inactivity and an unhealthy diet are established lifestyle related risk factors for T2DM, impaired sleep is a relatively novel lifestyle risk factor for T2DM. In the second part of this thesis, we aimed to examine sleep as a possible novel modifiable lifestyle factor associated with T2DM development and progression.

With regard to examining sleep as a novel modifiable lifestyle factor for T2DM development, we evaluated the association between social jetlag and the metabolic syndrome and pre(T2DM) in **chapter 5**. We used cross-sectional data of 1585 participants from the New Hoorn Study. Social jetlag was defined as the difference in midpoint sleep (the midpoint between bedtime and wake time), between weekdays and weekend days. We observed effect modification by age such that only in younger people (<61 years) social jetlag was associated with a higher prevalence of the metabolic syndrome and (pre)T2DM, compared to no social jetlag. For (pre)T2DM, prevalence ratios of 1.39 (95%CI: 1.1-1.9) for participants with 1-2h social jetlag and 1.75 (95%CI 1.2-2.5) for participants with >2h social jetlag were observed, compared to participants with <1h social jetlag. These results confirm that even small changes of circadian misalignment are associated with adverse health outcomes, such as (pre)T2DM.

In addition to this less-known form of disturbed circadian rhythm, in **chapter 6** we examined the individual and conjoint effect of sleep duration, napping, insomnia and use of sleep medication in relation to the metabolic syndrome. In cross-sectional data of 1679 participants from the New Hoorn study, napping compared to no napping was associated with a 1.7 (95% CI: 1.4-2.2) higher prevalence ratio for the metabolic syndrome for those who napped >30 minutes. In addition, a graded association was observed, such that ≥ 2 sleep-related characteristics, compared to no none, were associated with a 40% higher chance of having the metabolic syndrome. Chapter 5 and 6 showed that waist circumference and fasting glucose levels were significantly increased in the participants with larger social jetlag and napping time. In order to confirm any causal associations, prospective studies are needed, but overall, chapter 5 and 6 suggest that the association of social jetlag and napping with the metabolic syndrome and (pre)T2DM was driven by visceral obesity and glucose homeostasis.

With regard to T2DM progression, it is still unclear whether people with T2DM also have an increased risk of insomnia. Therefore, we conducted in **chapter 7** a systematic review and meta-analysis to determine the prevalence of insomnia and its association with metabolic parameters and glycemic control in people with T2DM. Pooled data of 78 studies

showed that the prevalence of (symptoms) of insomnia was 39% (95%CI: 34-45%) in the T2DM population and appeared to be associated with deleterious glycemic control. However, the results of this meta-analysis were limited by the high heterogeneity between the studies and the low methodological quality of the studies examining the association of insomnia with metabolic parameters and glycemic control. Overall, our findings from the second part of this thesis suggested that impaired sleep may be an important modifiable factor related to T2DM development and progression.