Chapter 10

Summary
Nederlandse samenvatting
Dankwoord
About the author
List of publications
Chapter 1

The aim of this thesis was to develop, validate and update prediction models and to identify potential etiological factors in epidemiological cohort studies in the field of type 2 diabetes and in the field of pneumonia in nursing home residents with dementia. The focus of this thesis was on the methodological issues that were encountered in the application of existing methods for prediction modelling and for etiological modelling to these two fields. The first chapter is a general introduction to the types of epidemiological models that were used in this thesis, the disease fields that this thesis focuses on, and the cohort studies that were used.

Two types of epidemiological models were applied to data from cohort studies: etiological models and prediction models. Etiological models—or, association models—aim to estimate a causal relationship between a determinant and an outcome. This way, etiological models can help to identify the causes of a disease or a complication or to understand the underlying mechanisms that contribute to these causes. Subsequently, interventions can help to eliminate these causes and thus, to prevent the development of a disease or a complication. Prediction models aim to predict an outcome as accurately as possible. This way, prediction models inform on the risk of developing a disease in the future, in order to plan lifestyle or therapeutic interventions. Also, prediction models can be used to inform physicians, patients and patients’ families on disease prognosis, in order to aid decision-making on treatment. Of note is that etiological factors can be predictive of a disease outcome, but that not all prediction models need to contain etiological factors in order to predict a disease accurately.

This thesis focuses on two disease fields: type 2 diabetes and pneumonia in nursing home residents with dementia. Type 2 diabetes is a chronic metabolic disorder characterized by high blood glucose levels, which can lead to several diabetes-related complications. Type 2 diabetes can be prevented or delayed by early interventions. These interventions are most successful when targeted to individuals at high risk of developing the disease, instead of randomly targeting the general population. Therefore, chapters 2 and 3 focus on prediction models that can help to identify those individuals at high risk. Further, chapters 6, 7 and 8 focus on etiological research questions that might help to understand the mechanisms of developing type 2 diabetes or developing diabetes-related complications.

Dementia is a syndrome characterized by a progressive decline in cognitive functions, and is associated with a reduced life expectancy. Pneumonia is a highly prevalent and burdensome disease for people with dementia: it is associated with discomfort and it is an important cause of death. Especially in people with advanced dementia, it may sometimes be questioned whether or not treatment of pneumonia with antibiotics is desirable. Palliative care is often seen as appropriate for people with advanced dementia, which means that the focus is on improving comfort while preventing overtreatment with possibly non-beneficial and burdensome treatment. It is not clear whether antibiotics
actually improve comfort for these people. In addition, patients’ wishes regarding treatment are often unclear. Therefore, chapter 4 and 5 focus on prediction models that can inform on prognosis with and without treatment with antibiotics. This way, these models can support physicians and patients’ families in decision-making.

Finally, this first chapter describes the 16 cohort studies that are used in this thesis, including 8 population-based cohorts, arrived at by inviting a random sample of all residents of a specific city or region for research. Further, these cohort studies include 6 nursing home cohorts that were set up to study pneumonia (or lower respiratory infections) or end-of-life care. In addition, these cohort studies include two cohorts of people with type 2 diabetes that comprise data that were collected as part of routine clinical care.

Chapter 2
With regard to prediction modelling in the field of type 2 diabetes, in this chapter, we developed and externally validated the DIRECT-DETECT prediction model. For this model, data from three population-based cohort studies (The Hoorn Study, the Inter99 Study, and the Cooperative Health Research in the Region of Augsburg) were combined to predict glycated haemoglobin (HbA1c) levels in the general population after six years of follow-up. HbA1c levels reflect average blood glucose levels over the last 2-3 months. Data from a fourth population-based cohort study (the Metabolic Syndrome in Men Study) were used for the external validation of the model. The model is stratified for gender and includes the following non-invasive predictors that have previously shown to be able to predict type 2 diabetes: age, body mass index (BMI), waist circumference, use of anti-hypertensives, smoking, and parental history of diabetes. We were the first to show that these predictors can also be used to predict HbA1c levels. However, the performance of the model was moderate. The model systematically overestimated HbA1c levels at follow-up in two out of the three cohorts that were used to develop the model, and it systematically underestimated HbA1c levels in the third development cohort as well as in the cohort that was used to externally validate the model. In addition, the explained variance and discrimination of this model were moderate, limiting its use as a screening tool in clinical practice.

Chapter 3
In this chapter, we externally validated a second prediction model in the field of type 2 diabetes. This was a non-invasive risk prediction model that was previously developed in three Dutch population-based cohort studies (The Hoorn Study, The Rotterdam Study, and The Prevention of Renal and Vascular End-stage Disease study) for predicting the combined 7-year risk for chronic cardiometabolic diseases. Chronic cardiometabolic diseases, including type 2 diabetes, cardiovascular disease, and chronic kidney disease, share many modifiable risk factors and can be prevented using combined prevention
programs. In this study, data from an Australian population-based cohort study (The Australian Diabetes, Obesity and Lifestyle Study) were used to externally validate the previously developed model that is stratified for gender and that includes the predictors age, BMI, waist circumference, use of antihypertensives, smoking, and family history of diabetes. This model showed good performance in the development study, as well as in our external validation study, which showed acceptable discrimination of the model and adequate calibration after updating the model intercept. Thus, the model can be a useful tool in large-scale prevention programs, as a first step in screening to identify individuals who are at increased risk for the development of chronic cardiometabolic diseases. In a second step, these high-risk individuals should further be screened for risk factors, including standard blood tests.

Chapter 4
In the field of pneumonia in nursing home residents with dementia, we evaluated whether a previously developed model for predicting 14-day mortality in nursing home residents with dementia and pneumonia treated with antibiotics could be applied to residents who were not treated with antibiotics. These untreated residents were generally sicker than the treated residents who were included in the development of the model. This model included the predictors gender, respiratory rate, respiratory difficulty, pulse rate, decreased alertness, insufficient fluid intake, eating dependency, and pressure sore. We assessed the external validation of the model in three steps: first, the model was applied to untreated residents of the same nursing home cohort that was used to develop the model for the treated residents: The Dutch Pneumonia Study. Second, we updated the model for these untreated residents. Third, we externally validated this updated model in untreated residents of four other nursing home cohorts: the Missouri Lower Respiratory Infection Study, The ‘Dutch 2006-2007’ study, The ‘Bedford US’ study, and the Dutch End of Life in Dementia study. We observed that the discriminative ability of the model was good in different populations of untreated residents. In addition, calibration of the model was adequate after a simple update of the model intercept. Thus, the same predictors that were relevant to predict short-term mortality for nursing home residents with dementia and pneumonia treated with antibiotics, could also adequately predict short-term mortality for untreated residents, despite large differences in characteristics between treated and untreated residents. The updated model can therefore be a useful tool to predict short-term mortality risk in nursing home residents with dementia and pneumonia not treated with antibiotics.

Chapter 5
In this chapter, we evaluated the performance of the same prediction model for treated residents –developed in a cohort from the 1990s– in a more recent nursing home cohort (around 20 years later): the PneuMonitor study. In addition, we evaluated if model
performance improved by revising or adding variables that are related to changes in care for older people and changes in resident characteristics in that time-period, including nutritional and hydration status, cardiovascular risk and overall health condition of nursing home residents. We found that the model for treated residents was still valid after 20 years, but the performance of the model in the more recent nursing home cohort improved after extension of the model with the predictors dehydration, bowel incontinence, increase in eating dependency and cardiovascular history, while removing the predictor pressure sores. This extended model performed similarly to the original model in the old cohort. Based on this chapter and the previous chapter, we conclude that the two models—one for treated and one for untreated residents—can be used in clinical practice to inform physicians, residents and their families on prognosis and may this way support decision-making.

Chapter 6
With regard to identifying etiological factors in the field of type 2 diabetes, we evaluated the association between social jetlag, cardiometabolic risk factors and type 2 diabetes in cross-sectional data from a population-based cohort: the New Hoorn Study. Social jetlag was defined as the difference in midpoint sleep—that is, the midpoint between bedtime and wake time—between weekdays and weekend days. Age was evaluated as a possible effect modifier, and the models were adjusted for gender, employment status, education, smoking, physical activity, sleep duration, and BMI. We indeed observed effect modification by age. We found that in older people (≥61 years), no significant associations were found between social jetlag, cardiometabolic risk factors and diabetes/prediabetes. This might be explained by the lower prevalence of social jetlag in this group, possibly due to the absence of work obligations in higher age. As a result, the ‘no social jetlag’ group might actually be a mix of people who never had social jetlag and people who had social jetlag for more than 40 years. In younger people, however, a larger social jetlag was associated with a higher prevalence of cardiometabolic risk factors and diabetes/prediabetes, compared to no social jetlag.

Chapter 7
A second potentially etiological relation that was assessed in this thesis, is the association between self-reported hypoglycaemia and mortality in a cohort of people with type 2 diabetes that consists of data that were collected as part of routine clinical practice in the Hoorn Diabetes Care System Cohort. Hypoglycaemia was self-reported in an interview by a medical assistant, by asking about hypoglycaemia in the past year, distinguishing between events requiring medical assistance, events requiring help from others, or events not requiring help. Surprisingly, we found that people who reported hypoglycaemia not requiring medical assistance did not have an increased risk of short-term mortality, compared to people who reported no hypoglycaemia. We hypothesize that these results
might be explained by the concept of impaired awareness of hypoglycaemia: people who reported no hypoglycaemia might in fact have an impaired awareness of hypoglycaemia, which could prevent them from taking actions to resolve their hypoglycaemic events. Unfortunately, we did not have measures of hypoglycaemia awareness and therefore more research is needed to verify this possible mechanism. Overall, our results suggest that hypoglycaemic sensations that do not require medical assistance are not an indicator of increased short-term mortality risk in people with type 2 diabetes.

Chapter 8

A third potentially etiological relation that was evaluated in this thesis, is the association between individual and partner’s level of occupation with HbA1c levels in people with type 2 diabetes in cross-sectional data from a cohort that consists of data that were partly collected as part of routine clinical practice in the Diabetes Pearl cohort. Occupational level was classified according to International Standard Classification of Occupations (ISCO)-08 skill levels. Gender was evaluated as a possible effect modifier, and the models were adjusted for age, recruitment centre and diabetes medication. We indeed observed effect modification by gender. Women seemed to benefit from a partner with a higher level of occupation, while men seemed to benefit from a partner with a lower level of occupation. Underlying pathways of the association between partner socio-economic status and health outcomes are not yet clear and could not be evaluated in our study. However, the fact that partner’s socio-economic status was associated with HbA1c levels in people with type 2 diabetes suggests that physicians or nurse practitioners should not only consider the socio-economic status of a person with type 2 diabetes when assessing the risk of poor glycaemic control, but also the socio-economic status of the partner.

Chapter 9

The final chapter puts the main findings of this thesis into the context of the literature. In addition, this chapter discusses the methodological issues that were encountered in this thesis, and it provides implications and recommendations for clinical practice, research practice and future research. First, when combining individual patient data from different cohort studies, sensitivity analyses are needed to evaluate the impact of differences in variable definitions between cohorts. Second, confounding does not only play a role in etiological models, but also when developing prediction models in a combined dataset of different cohorts, even though causality is not the focus in prediction modelling. Confounding by cohort source should be considered and evaluated when a prediction model is developed in a combined dataset of different cohorts. Third, using routinely collected data for research purposes might better reflect the clinical care setting compared to using data from an experimental research setting. However, researchers should be aware that cleaning this type of data and checking the quality of the data are very time-consuming. Further, sensitivity analyses can help to understand and further
explore observed associations and the role of (residual) confounding. Fourth, a simple method for recalibration sufficed to make two existing prediction models applicable to different populations, even when the external validation population was treated differently. These findings support recommendations from previous research: existing prediction models should be validated and –if necessary– updated, instead of developing new models for each population. Fifth, when clinicians want to use a prediction model in clinical practice, they should consider whether patient characteristics and outcome prevalence in this population are expected to be comparable to the population that was used to develop or validate the model. For example, can the population characteristics related to illness severity be expected to be comparable? Has the treatment of risk factors changed substantially since the development of the model? The model intercept should be recalibrated before applying a model to a population that is expected to differ from the development population in prevalence of the outcome.

In conclusion, next to answering research questions that are relevant for the field of type 2 diabetes and the field of pneumonia in nursing home residents with dementia, we focused on the application of existing methods for prediction modelling and for etiological modelling, and on the methodological issues that were encountered when applying these methods. We conclude that this focus on the application of existing methods and on methodological issues encountered can have an added value for future research in comparable situations. Researchers and clinicians should consider the topics discussed in this thesis when applying and interpreting prediction models and etiological models to their specific disease fields or to clinical practice.