Cognitive decline in late-life: biological markers and early identification of persons at risk for dementia

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Tessa Nicole van den Kommer

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Cognitive decline in late-life: biological markers and early identification of persons at risk for dementia

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Tessa Nicole van den Kommer

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	dr. H.C. Comijs

“ ... It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair ...”

Charles Dickens, A Tale of Two Cities
English novelist (1812 - 1870)

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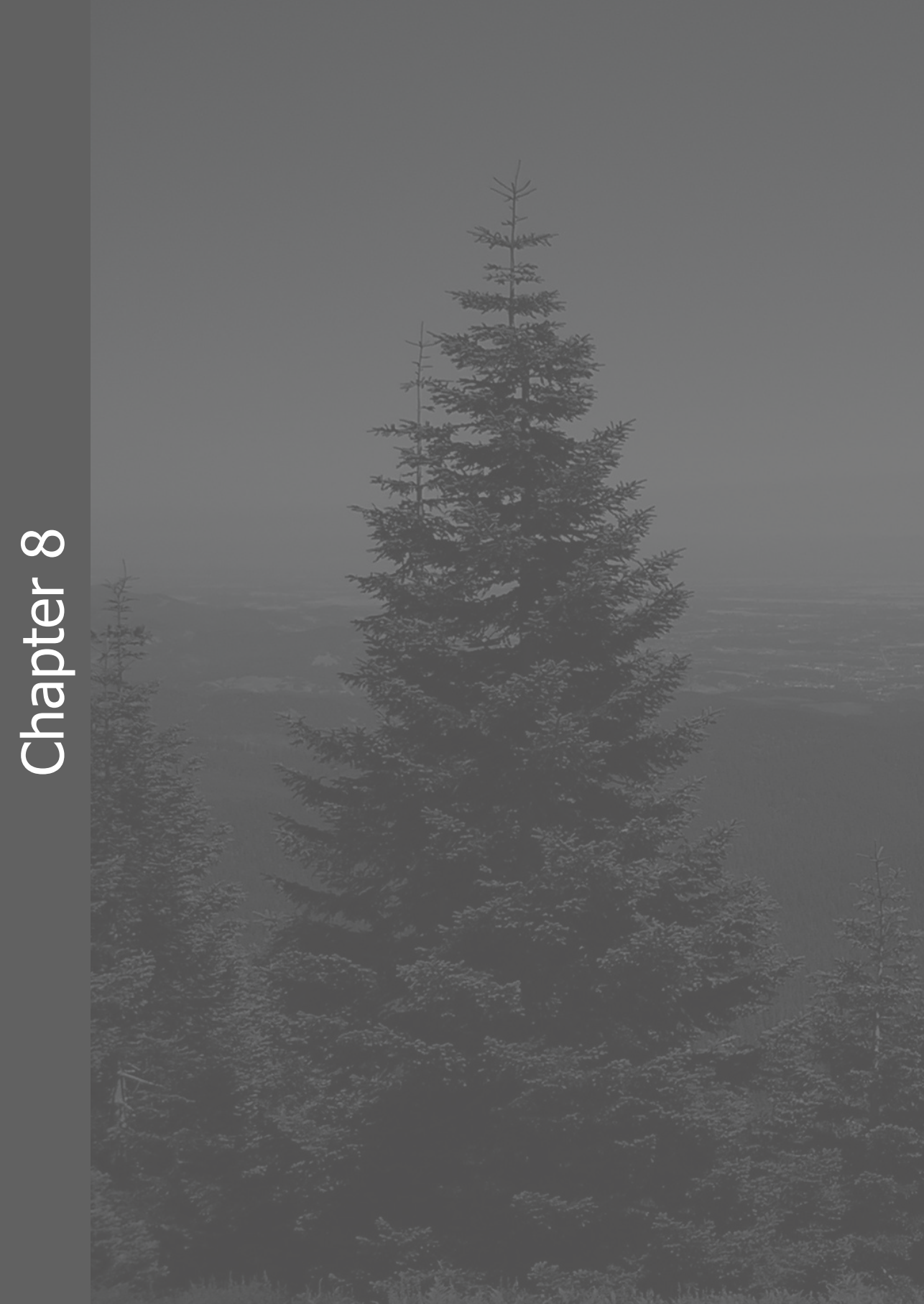
Chapter 8

General Discussion

The first main objective of the present thesis was the development and further evaluation of classification models for early identification of persons at risk for persistent cognitive decline and dementia (Chapters 2 and 3). The second main objective was to study the associations between several biological predictors, namely markers for cholesterol homeostasis, lipoprotein carriers of cholesterol, triglycerides and homocysteine, and the trajectory of cognitive functioning in older persons. In addition, the modifying role of Apolipoprotein E (ApoE) e4 status on the associations between markers for cholesterol homeostasis and cognitive decline was studied (Chapters 4 and 5). With respect to the associations between homocysteine and cognitive decline, and lipoproteins, triglycerides and cognitive decline, the modifying role of inflammation was studied (Chapters 6 and 7).

Summary of findings

Classification models

The study presented in Chapter 2 describes the development of two classification models (basic and extended) for early identification of persons at risk for future persistent cognitive decline for use in primary care. For the development of the basic model a set of predictors was used comprising variables already known to the general practitioner or otherwise easily enquired in an interview (basic set). The extended model was developed using the basic set and an extended set of predictors including variables that require further assessment such as laboratory tests. In the basic model, persons over 75 years old, with memory complaints, low education and Mini-Mental State Examination (MMSE) score of 24 or lower were at the highest risk of developing persistent cognitive decline, resulting in a substantial increase in positive predictive value from an initial 4.0% to a final 43.5% rate of cases identified with persistent cognitive decline after three years of follow-up. In the extended model, persons over 75 years old, with low cholesterol levels (below 5.0 mmol/L) and MMSE score of 24 or lower were at the highest risk of developing persistent cognitive decline, resulting in an increase in positive predictive value from 4.0% to 30.0%. Furthermore, both models mostly identified a different subsample. In Chapter 3, these models were reconstructed in another independent longitudinal population-based study of persons 80 years and older in which longitudinal data on dementia diagnosis based on formal criteria were available, in order to test whether congruent models would develop. The results as presented in Chapter 3 show a fairly similar combination of predictors. In the basic model, the initial two-year rate of 6.9% new dementia cases, increased to a final 28.8%, while the cumulative positive predictive value for dementia over the course of the study increased from 17.9% to a final 52.6% in persons reporting memory complaints and MMSE score of 25 or lower. In the extended model, persons with low cholesterol and MMSE of 24 or lower were at the highest risk of future dementia. The cumulative positive predictive value over the course of the study increased from 15.0% to 45.8% newly identified dementia cases. Again, both models identified mostly different persons at risk

for dementia, i.e. showing low overlap. In conclusion, fairly congruent models for early detection of persons at risk for dementia were developed in two independent longitudinal population-based studies.

Biological predictors of cognitive functioning and decline

In Chapter 4, the associations between total cholesterol and the oxysterols 27-hydroxy (OH) and 24S-OH cholesterol, and level of cognitive functioning and rate of decline were studied. In addition, the modifying effect of ApoE e4 on these associations was examined. It was shown that a lower level of total cholesterol was an independent predictor of a relatively worse level of general cognitive performance and lower information processing speed over six years of follow-up in persons over 65 years of age. In addition, only in carriers of the ApoE e4 allele, a lower level of total cholesterol was predictive of a faster rate of decline in information processing speed. Furthermore, a higher ratio of 27-OH cholesterol to cholesterol, which may be indicative of cholesterol breakdown, was an independent predictor of a worse level of general cognitive performance and memory performance, only in ApoE e4 carriers. The ratio of oxysterol 24S-OH cholesterol to cholesterol, indicative of brain cholesterol metabolism, was not significantly related to the trajectory of cognitive functioning in persons over 65 years old.

In Chapter 5, the effect of cholesterol precursors lanosterol and lathosterol, and plant sterols campesterol and sitosterol, all extracerebral markers of cholesterol homeostasis, was studied on the trajectory of cognitive functioning in older persons. In addition, the modifying effect of ApoE e4 status on these associations was studied. The results show a significant non-linear association between a higher ratio of lanosterol to cholesterol, indicative of a higher rate of cholesterol synthesis, and lower general cognitive performance in the total study sample, after adjustment for relevant confounders. Further analysis in the total sample shows that this association was significant up to a ratio of 205 ng/mg. Higher ratios of lanosterol to cholesterol were not significantly associated with cognitive functioning. In addition, a modifying effect of ApoE e4 was found. It was shown that this association was significant in ApoE e4 non-carriers (up to a ratio of 189.96 ng/mg), not in ApoE e4 carriers. Furthermore, a lower ratio of the plant sterols to cholesterol, indicative of a lower rate of cholesterol absorption, was significantly associated with lower information processing speed, only in ApoE e4 non-carriers. In addition, a higher rate of cholesterol synthesis relative to absorption was significantly predictive of lower information processing speed, only in ApoE e4 non-carriers. Finally, the presence of cardiovascular disease could not explain the associations found.

The results from the study described in Chapter 6 show that a lower level of high-density lipoprotein (HDL) cholesterol was significantly associated with a lower level of memory performance in older persons. In addition, a lower level of low-density lipoprotein (LDL) cholesterol was an independent predictor of a lower level of general cognitive performance and information processing speed and a faster rate of decline in information processing speed. These associations were non-linear, and were significant up to respectively 4.2 mmol/L and 3.8 mmol/L LDL

cholesterol. Above these levels, the associations with cognitive functioning and decline were no longer significant. Furthermore, it was shown that persons with both low levels of LDL cholesterol and high levels of inflammation as indicated by C-reactive protein (CRP) or α1-antichymotrypsin (ACT) had the lowest level of general cognitive performance and memory performance. In addition, it was shown that a high level of triglycerides was associated with a prolonged lower level of memory performance in persons with high inflammation as indicated by levels of CRP or ACT. Finally, sensitivity analyses showed that the presence of cardiovascular disease could not explain the associations found.

Finally, in Chapter 7 the associations between total homocysteine (tHcy) levels and level of cognitive functioning and rate of decline were studied over six years of follow-up in persons over 65 years old. In addition, we examined whether inflammation was a potential effect modifier of these associations. It was found that a higher level of tHcy was a significant independent predictor of a lower level of general cognitive performance and memory performance, and a faster rate of decline in information processing speed and fluid intelligence. In addition, a modifying role of inflammation was found, although not consistently. In some instances, inflammation enhanced the negative effect of higher levels of tHcy on cognitive functioning over six years of follow-up.

Methodological considerations

Use of cohort studies

In the present thesis data were used from two cohort studies, the Longitudinal Aging Study Amsterdam (LASA) (Chapters 2, 4-7) and Origins of Variance in the Old-Old: Octogenarian Twins (OCTO-Twin) Study (Chapter 3). The use of cohort studies has major strengths, but unfortunately is also accompanied by a number of weaknesses. Both will be discussed below.

A major strength of the use of a longitudinal population-based study design is that we were able to study the trajectory of cognitive functioning in a representative older sample. An important strength of focusing on the trajectory of cognitive functioning is that level of functioning as well as rate of decline over time can be studied, and thus inter- and intra-individual differences in the course of cognitive decline could be identified. With repeated measurements over time of the outcome measures (performance on several cognitive tests) and confounding factors (i.e. other risk factors of cognitive decline and dementia) the influence of biological parameters of our interest with respect to these inter-individual differences could be studied (Chapters 4-7). Data on performance on several cognitive tests measuring different cognitive domains were used on three occasions over six years of follow-up.

In addition, we were able to study the prognostic value of multiple (biological) predictors with respect to the incidence of the condition in which we were interested, i.e. persistent cognitive decline and dementia, in a population that was initially free from this condition. Both cohorts were large enough to exclude persons already showing persistent cognitive decline and persons diagnosed with dementia (Chapters 2 and 3) at the time of measurement of potential

predictors and risk factors. This made it possible to identify the 'at-risk group' in an early phase, several years before persons showed persistent cognitive decline or were diagnosed with dementia.

However, studying predictors and risk factors of diseases, especially those with a long preclinical phase such as dementia by means of a cohort study is accompanied by difficulties. Since the clinical diagnosis of dementia is often preceded by a long period of cognitive decline, there is a need for a long follow-up period starting many years prior to the point at which persons developing dementia meet the formal criteria of a dementia diagnosis. The samples used in the present thesis, drawn from the LASA and OCTO-Twin Study comprise persons aged 65 and 80 years and older, respectively. Although, as commented on above, an important strength of using these longitudinal studies is that we were able to study potential predictors and risk factors measured several years before the identification of persistent cognitive decline and diagnosis of dementia (Chapter 2 and 3), the parameters to predict future dementia risk were used from only one measurement occasion. In the present thesis we did not study the predictive value of intra-individual changes in these parameters with respect to future dementia risk. In the studies described in Chapters 4 to 7, data were used from the second, third and fourth data collection of the LASA study. The biomarkers studied in the present thesis were only measured once, during the second data collection. At the following data collections no new blood samples were drawn. Therefore, we were unable to study whether an intra-individual change in these biomarkers significantly influenced the trajectory of cognitive functioning in our study sample (Chapters 4-7). In addition, the impact of these biomarkers (and confounding factors) prior to our first measurement of cognition in persons 65 years and older is unknown. Since dementia pathology may have presented earlier in life, before the age of 65, conclusions with respect to causality can not be drawn. Deterioration in dietary intake as a consequence of becoming demented and dementia pathology might lead to a change in certain biological markers, e.g. an increase in inflammatory markers and tHcy and a decrease in total cholesterol (Schmidt et al., 2002; Stewart et al., 2007; Van der Flier and Scheltens, 2005). A cohort study in which persons are followed from for example midlife well into late-life and repeated assessments of dependent and independent variables would be helpful in reducing these limitations. However, an experimental design is needed for definitive answers with respect to cause and effect.

Attrition

Another important issue with respect to the use of longitudinal studies that should be commented on is attrition. As has been described in the previous Chapters, loss to follow-up in both the LASA and OCTO-Twin studies was mainly due to mortality, a much smaller percentage was no longer eligible or refused to participate during follow-up. Previously, a study by Deeg et al. (2002) focused on modifiable causes of attrition and the effect of differential exposure to study characteristics. They showed that attrition through refusal was not selective. Persons who refused to participate did not differ in socio-demographic characteristics, physical and mental

health indicators from persons who were willing to participate. However, the risk of attrition through ineligibility was increased by poorer self-rated health, more cognitive impairment, the female sex and higher age (Deeg et al., 2002). With respect to the study samples used in the present thesis, it was shown that persons who were lost to follow-up in the LASA study were significantly older, were more likely to be men and performed worse on cognitive tests at the prior assessment compared to those who stayed in the study. Persons who dropped out of the OCTO-Twin Study were also older and had a lower cognitive status than those persons who did not drop out. Furthermore, on the whole, looking at differences with respect to our main biological predictors, persons who were lost to follow-up had lower levels of total cholesterol, plant sterols and LDL cholesterol, a lower ratio of lathosterol to cholesterol, and higher levels of inflammation and tHcy compared to those who remained in the study. Also, it was shown that persons who agreed to participate in the blood drawing procedure were younger and had a better cognitive status compared to those who refused to give blood. Thus, the most frail persons dropped out of the study samples used in the present thesis. Therefore, it may be hypothesized that inter- and intra-individual differences in the trajectory of functioning were underestimated, and this may have led to an underestimation of the strength of the associations between the biological markers studied in this thesis and cognitive functioning over time and risk of persistent cognitive decline and dementia. However, the results of a study that estimated the impact of potential selective attrition on cognitive change in a longitudinal study, suggest that the effect of attrition on cognitive change is small (Van Beijsterveldt et al., 2002). Still, the authors conclude that cognitive change may be underestimated if a select group of persons is lost to follow-up (Van Beijsterveldt et al., 2002). Also, another study focusing on the impact of attrition at follow-up on the outcome, concluded that attrition is not always a serious problem when associations between variables are studied (Kempen et al., 2002), as was the case in the present thesis.

With respect to the potential problem of missing data, a major strength of the studies described in the present thesis is that we predominantly made use of sophisticated methods for longitudinal data analyses. In Chapters 3, 4 and 7, Generalized Estimating Equations (GEE) were used, while Linear Mixed Models were used in Chapters 5 and 6. Using these more sophisticated methods, subjects with incomplete data are not excluded from analyses, making it probably less urgent to estimate missing data (Twisk and De Vente, 2002). Twisk and De Vente (2002) examined the consequences of missing data in longitudinal studies on the results of longitudinal statistical analyses. They conclude that when applying GEE analysis, imputation methods are not necessary. Thus, the use of sophisticated methods in the present thesis reduces the risk of underestimation of the associations studied.

Outcome measures

In the present thesis several different outcome measures were used, namely ‘trajectory of cognitive functioning over six years of follow-up’ as indicated by performance on various cognitive tests (Chapters 4-7), ‘persistent cognitive decline’ (Chapter 2), and ‘dementia’ (Chapter 3).

Cognitive functioning

In Chapters 4-7, predictors and effect modifiers of the trajectory of cognitive functioning over six years of follow-up were studied using data from LASA. An important strength of the studies described in this thesis is that we were able to use data from several cognitive tests, measuring cognition on different domains, i.e. global cognitive functioning (MMSE (Folstein et al., 1975)), memory (Auditory Verbal Learning Test (Rey, 1964)), information processing speed (Alphabet Coding task-15 (Piccinin and Rabbitt, 1999)) and fluid intelligence (Raven's Coloured Progressive Matrices (Raven, 1984)). Although performance on various cognitive domains was measured, a test of executive functioning was not available in LASA. It has been shown that executive functioning is a cognitive domain that is sensitive to (early) cognitive decline and rapid decline in AD has been linked to disproportionally impaired executive functioning (Coen et al., 1996; Mann et al., 1992). It may be suggested that by not studying the influence of the various biomarkers on the course of executive functioning as an outcome measure, we may have missed some significant and relevant associations. However, previous studies have suggested that information processing speed, which was one of the outcome measures in this thesis, appears to be the cognitive function most sensitive to aging (Salthouse, 1996) and decline in information processing speed may be an even earlier indicator of AD than memory decline (Dik et al., 2000).

Persistent cognitive decline

In Chapter 2 of this thesis we used data from the LASA study, in which a formal dementia diagnosis is not available. In the study described in Chapter 2, we identified persons showing persistent cognitive decline using a strict definition, i.e. clinically significant cognitive decline over three years of follow-up as indicated by more than two standard deviations decline on the MMSE below the average cognitive decline observed in the total study sample, and continued decline in the subsequent years. If repeated measures of the MMSE were not available, either obtained during a face-to-face interview or during a telephone interview in which an abbreviated version of the MMSE was administered, a short version of the IQCODE was administered to determine the clinical significance of the reported cognitive decline. In order to study predictors of incident persistent cognitive decline (at T_3) and identify the 'at-risk group', persons showing significant cognitive decline between the previous measurements (T_1 and T_2) were excluded, as well as persons with an MMSE below 19 at the time of measurement of predictors (T_2). The use of these strict criteria for persistent cognitive decline may have led to misclassification of persistent cognitive decliners (false negatives), and consequently an underestimation of the relative risk of identified predictors. However, a strict definition was considered necessary to ensure that persons who were classified as persistent cognitive decliners were in fact suffering from dementia or at risk of developing dementia (true positives), and thus to prevent inclusion of false positives, which would have led to dilution bias.

Furthermore, use of the present definition of persistent cognitive decline, based on repeated measures on the MMSE, most likely identified persons who were (at risk of) developing AD or

VaD, the two most common subtypes of dementia (Wancata et al., 2003). Persons with other subtypes of dementia, such as (early) fronto-temporal dementia or dementia caused by Lewy-bodies (LBD) were probably not identified using this definition based on the MMSE, given their symptom profile. However, in a population-based cohort such as used in the study described in Chapter 2, the number of persons with dementia caused by underlying diseases other than AD or VaD will be low. A previous collaborative study of population-based cohorts showed that between 0.2-2.5% of prevalence rates of all types of dementia over the different age bands (65-94 year olds) are accounted for by dementia subtypes other than AD and VaD (Lobo et al., 2000).

Dementia

In the OCTO-Twin Study dementia diagnosis was based on formal criteria (DSM-III-R). Although a strict and formal procedure was used during all waves to determine who had become demented, and a calculated 'best guess' was made in retrospect during a consensus meeting to determine the age of dementia onset, it is unfortunately impossible to ensure that age of dementia onset is a precise measure. In the study described in Chapter 3, time to event was the outcome measure in Cox survival analyses. In Cox survival analyses, subjects who did not experience the event (i.e. dementia) with a shorter time in study than the first subject experiencing the event are excluded from the analysis, as are persons with missing data on predictors. Due to the fact that age of dementia onset, and thus time to event, is not an exact measure, persons may have been needlessly excluded. This may have lowered power to detect significant predictors of incident dementia.

Also, we did not differentiate between different subtypes of dementia, e.g. AD, VaD, Parkinson's dementia (PD), and LBD. Although information on major subtypes of dementia was available in the OCTO-Twin Study, the numbers were too low to perform reliable data analyses. However, the clinical presentation of these various causes of dementia is different, and predictors and risk factors may differ as well.

Comparison of developed classification models

In Chapters 2 and 3 of this thesis fairly congruent classification models for early identification of persons at risk for persistent cognitive decline and dementia were developed using data from the LASA (Chapter 2) and OCTO-Twin Study (Chapter 3), with outcome measures persistent cognitive decline and dementia, respectively. A comparison of the used methods by which the strongest and most important predictors in these classification models were assessed in the LASA and OCTO-Twin Study will be made below, and validity of these measures will be discussed.

In the (basic) classification model which was developed using a basic set of predictors, which are already known to the general practitioner or otherwise easily assessed, the strongest predictor of future dementia was - in addition to age - memory complaints. In LASA this variable was measured by a simple question: "Do you have problems with your memory", with response categories 'yes' and 'no'. In OCTO-Twin this variable was also measured by

self-report, by asking: "Do you think that you have any problems with your memory which make daily living more difficult?". Response categories were 'no, not at all', 'no, hardly', 'hard to take a stand on', 'yes, to a certain degree' and 'yes, definitely'. Since this question puts emphasis on the difficulties that potential memory problems cause in daily life, instead of just having memory problems, we have recoded response category 'hard to take a stand on' to 'yes'. 'Yes, to a certain degree' and 'yes, definitely' were also recoded to 'yes'. Categories 'no, not at all' and 'no, hardly' were recoded to 'no'. Although inquired in a somewhat different manner, in both studies memory complaints was the strongest predictor of incident persistent cognitive decline and dementia, which supports the notion that self-report of memory complaints is a valid measure. In line with our findings, a review of studies that reported on the association between memory complaints and cognitive impairment or dementia, concludes that complaints about memory may be very early signs of dementia, and may be considered a valid measure of self-reported memory decline (Jonker et al., 2000).

Low education level was another important, significant predictor of persistent cognitive decline in the study described in Chapter 2, and was defined as an educational level less or equal to primary school. In the sample derived from OCTO-Twin, low education was not a significant predictor of future dementia. However, in OCTO-Twin 71.2% had received primary school or less, compared to 39.8% in the younger LASA sample. The question arises whether education will be an even stronger predictor of dementia in future older cohorts comprising persons with more opportunities for secondary schooling, and thus level of education is more reflective of intellectual capacities or cognitive reserve. Also, it may be questioned whether in future cohorts the cutoff used for low education should be adjusted towards a higher level of education. Previous studies have found evidence for this cognitive reserve hypothesis (Gatz et al., 2001; Ngandu et al., 2007). In the review by Jonker et al. (2000), the authors emphasize that in highly educated older persons with no indication of cognitive impairment on short cognitive screening tests, memory complaints can also be a very early sign of future dementia. Thus, in persons with high education, short dementia screening tests such as the MMSE are relatively insensitive to detect impairment in cognitive function at an early stage of the disease, due to 'ceiling effects' (Cullum et al., 2000; De Jager et al., 2002; Jonker et al., 2000). In line with these findings, the study described in Chapter 2 showed that the MMSE, a short cognitive screening test, was of no significant additive value with respect to predicting risk of developing persistent cognitive decline in persons above the age of 75, with memory complaints and an educational level above elementary school.

Another important predictor of future persistent cognitive decline and dementia was alcohol abstinence, which was assessed by self-report in both cohort studies. Although studies have shown both underreporting and over-reporting of alcohol use (Midanik, 1989; Polich, 1982), self-report of alcohol consumption is still the best available method to acquire information on alcohol consumption. The fact that in the sample derived from LASA as well as the study sample from the OCTO-Twin, drinking no alcohol was an important risk factor of future

dementia, confirms the validity of this measure. In LASA, moderate to excessive alcohol consumption also increased the risk of future persistent cognitive decline, although not significantly, which may have been due to a bias in self-report.

In the extended classification model which was developed using both the basic and extended set of predictors, low total cholesterol was the strongest predictor - in addition to age - of future dementia risk. Total cholesterol was measured in LASA as well as OCTO-Twin using routine measurement methods. In both studies blood was obtained in the morning. In LASA, persons were allowed to have tea and toast, but no dairy products. A study examining the stability and reliability of lipid measurements from a single blood sample concluded that these single measurements were representative of the average blood levels in the study population and can therefore be useful in epidemiologic studies (Lee et al., 2008). In addition, they showed that lipid levels obtained from non-fasting samples were similar to those obtained from fasting blood samples (Lee et al., 2008).

Risk factor, risk marker or predictor?

Another important point that should be commented on is the conceptual difference between a risk factor, risk marker and predictor. Although often used interchangeably, the terms were originally defined in distinct ways. The term risk factor is used to describe factors that increase the risk of developing a disease and are assumed to play a role in the development of the disease, implying cause and effect (Kannel et al., 1961; Seshadri, 2006). The term risk marker was originally invented to describe incidental changes associated with a disease, which are not directly part of the causal pathway, but are considered epiphenomena, i.e. unexpected or atypical symptoms or occurrences during the course of a disease (Nadella, 1979; Seshadri, 2006). The term predictor suggests that the underlying mechanism (causal pathway) is not the focus of study. In the studies described in the present thesis we have shown several significant associations between biological factors and level of cognitive functioning and rate of decline. In addition, we reported on the predictive value of a broad spectrum of variables, such as demographic variables, lifestyle factors and chronic diseases with respect to development of future persistent cognitive decline and dementia. One of the most important findings described in the present thesis, is that low total and LDL cholesterol levels were significantly associated with worse cognitive functioning and faster cognitive decline. Low total cholesterol was also significantly associated with increased risk of persistent cognitive decline and incident dementia. The question is whether low cholesterol is a genuine risk factor, which would imply that low cholesterol is part of a larger group of determinants (causal pathway) playing a role in decline of global functioning and development of dementia. Recent studies have shown that both high midlife cholesterol levels (Solomon et al., 2007, 2009) and a (more pronounced) decrease in cholesterol levels from midlife to late-life are significantly associated with increased risk of late-life cognitive impairment and dementia (Solomon et al., 2007; Stewart et al., 2007). This decrease in cholesterol levels may be a reflection of ongoing disease processes, not the cause, implying that late-life low cholesterol

should be considered a marker of worse cognitive status. Furthermore, a recent Cochrane review based on evidence from randomized controlled trials concluded that statins have no significant effect in preventing dementia when given in late-life to persons at risk of vascular disease (McGuinness et al., 2009). It may be hypothesized that if low cholesterol is a genuine (causal) risk factor in the development of dementia, randomized controlled trials would have found a significant detrimental effect of lowering cholesterol on cognitive functioning. In sum, given these findings the biological factors studied in the present thesis, such as low cholesterol, should be considered risk markers of worse cognitive status and faster cognitive decline in late-life.

Relevance, implications, and recommendations for future research

Improving early detection of dementia in primary practice has been stressed by health care professionals as well as policy makers. Guidelines on dementia diagnosis and management have been developed (Boomsma et al., 2009; Wind et al., 2003). Still, identification of (persons at risk for) dementia and diagnosis of dementia presents many challenges to the primary physician. Often, there are long delays between the first symptoms and diagnosis of dementia (Bond et al., 2005; Bradford et al., 2009; Valcour et al., 2000). In a recent review potential barriers to diagnosis of dementia in primary care were identified. Major contributing factors to missed and delayed diagnosis were limitations to system resources (e.g. time constraints), attitudes towards dementia (e.g. fear of stigmatization, doubts on usefulness of early diagnosis), communication problems and knowledge deficits among physicians, caregivers and patients (Bradford et al., 2009). It has been shown that in hindsight caregivers of persons diagnosed with dementia express their concern regarding the delay in diagnosis and treatment (Bamford et al., 2007; Bond et al., 2005). The classification models for early detection of persons at risk for future dementia described in the first part of this thesis were developed for use in primary practice, to assist the general practitioner in case-finding of patients who are at increased risk for future dementia in a proactive manner. These models have been recently tested for feasibility and user friendliness in a pilot study. Findings of this pilot study indicate that the daily routine of general practitioners may be in conflict with the decision to administer the MMSE when following the classification model. For example, normally the general practitioner would not have administered the MMSE in persons over 75 years old without memory complaints, who report abstinence from alcohol use. However, changing this daily routine could improve early identification of persons at risk for dementia. Future research focusing on the additive value of implementing these models in primary care is recommended.

In the second part of the present thesis, we focused on the effect of several biological markers on cognitive functioning and decline in a population-based cohort study of persons over the age of 65. The results from these studies contribute to our understanding of the complicated role of various components of cholesterol homeostasis, tHcy and interactions with ApoE e4 status and degree of inflammation with respect to the course of cognitive functioning in late-life. Although differences in level of cognitive functioning and rate of decline were small, our findings

confirm the relevance of studying the independent role of biological predictors of the trajectory of cognitive functioning in a large population-based sample of older persons. The results from the studies described in the present thesis shed more light on possible biological processes involved in cognitive decline and dementia, and may have implications for clinical practice and future research, as will be discussed below.

Statins are a class of drugs that inhibit endogenous cholesterol biosynthesis, and lead to a decrease in LDL cholesterol, triglycerides and total cholesterol and an increase in HDL cholesterol in serum (McGuinness et al., 2009; Pahan, 2006). Although some earlier cross-sectional studies showed a beneficial effect of lipid-lowering drugs with respect to decreasing dementia risk (Jick et al., 2000; Wolozin et al., 2000), in a recent Cochrane review it was concluded that statins can not be recommended in late-life for the prevention of dementia (McGuinness et al., 2009). Miettinen and Gylling (2005) state that although statins lead to an initial decrease in cholesterol absorption, inhibition of cholesterol synthesis is eventually accompanied by gradually enhanced cholesterol absorption. Additional use of cholesterol absorption inhibitors, such as plant stanol esters, has been recommended in persons with high baseline plant sterols (Miettinen et al., 1998, 2000). In this thesis the associations between markers of cholesterol homeostasis and cognitive functioning and decline were significantly modified by ApoE e4. In light of the current findings, the effect of statins and plant stanol esters in midlife and late-life taking into account genetic differences should be the focus of future studies. Possibly, lipid-lowering drugs have a different effect on cognitive functioning depending on when they are prescribed in life, in relation to the underlying course of the disease, and to whom, i.e. persons carrying the ApoE e4 allele versus persons who are non-carriers. Also, treatment in which plant sterol levels are decreased may not be effective, or even have detrimental effects on cognitive functioning in ApoE e4 non-carriers. Furthermore, in the present thesis a modifying effect of inflammation was found on the associations between LDL cholesterol, triglycerides and the trajectory of cognitive functioning. Based on the current findings, research should especially focus on the effect of anti-inflammatory drugs in persons with high inflammatory levels and low (LDL) cholesterol levels in late-life and persons who show a pronounced decline in cholesterol levels after midlife. Also, future studies should further focus on the modifying effect of high inflammatory levels with respect to the link between higher levels of triglycerides, the lowest levels of LDL cholesterol and worse cognitive functioning. It is recommended that future studies examine the inter-individual differences and intra-individual changes in markers of cholesterol homeostasis, lipoprotein carriers of cholesterol and inflammation over time with respect to the trajectory of cognitive functioning between midlife and late-life and future dementia risk. In addition, genetic differences, such as in ApoE e4 genotype, and changes in dietary intake should be studied.

In the studies described in the present thesis it was shown that the presence of cardiovascular diseases did not significantly change the strength of the associations found between markers of cholesterol homeostasis, lipoprotein carriers of cholesterol and cognitive functioning over time. Thus, our findings indicate that cardiovascular disease was not a significant mediator of

the associations between e.g. low LDL cholesterol, and worse cognitive functioning and faster decline in late-life. Current guidelines state that persons with cardiovascular disease and LDL cholesterol above 2.5 mmol/L should be treated with statins (Burgers et al., 2007; Dutch Institute for Healthcare Improvement CBO, 2006). However, our findings indicate that LDL cholesterol levels above 2.5 mmol/L and up to 4.2 mmol/L in late-life were associated with better cognitive functioning in a study sample in which about 50% of participants had one or more cardiovascular disease at baseline and/or follow-up. Future longitudinal population-based and experimental studies are needed to further investigate these findings.

The final study described in this thesis, provides further evidence for an independent negative effect of higher levels of tHcy on cognitive functioning and decline in late-life. Again, inflammation was a significant effect modifier, although not consistently suggesting that the enhanced negative effect of high tHcy in increasing inflammatory levels may be a reflection of poor health and comorbidity (Ravaglia et al., 2004). A recent study showed that a high level of tHcy in midlife was independently associated with increased risk of late-life AD in a population-based sample of women (Zylberstein et al., 2009). Future studies should focus on the possible synergistic negative effect of high inflammation and high tHcy levels in midlife and late-life with respect to dementia risk. The question remains whether unknown mediating mechanisms explain the negative effect of higher tHcy levels on the course of cognitive functioning and development of dementia or high tHcy levels have direct toxic effects during the course of life. High levels of tHcy can be easily lowered by vitamin B (Clarke et al., 2005). However, so far randomized trials focusing on the effect of vitamin B_{12} and folate supplementation provide some, but no consistent evidence of a beneficial effect on cognitive functioning (Malouf and Evans, 2008). This may have been due to dosage (either too low or too high), short duration or timing of these trials. Future large randomized controlled trials with longer follow-up, starting as early as midlife, should further investigate the potential protective effect of lowering tHcy on preventing cognitive decline and dementia. Given the present findings, it is recommended that levels of inflammation and the interaction with tHcy levels are taken into account in future trials.

Conclusion

Fairly congruent models for early detection of persons at risk for dementia were developed in two independent longitudinal population-based studies. The sets of markers with the highest predictive value (memory complaints, low education and MMSE $\leq$ 24 in 75 year olds; and low cholesterol and MMSE $\leq$ 24 in 75 year olds) may be used complementary in primary care, to maximize early detection of persons at risk for future dementia in a feasible and cost-effective way.

Furthermore, low cholesterol may be viewed as a marker for cognitive impairment and decline in persons aged 65 years and older, especially in those carrying the ApoE e4 allele. In ApoE e4 carriers, a higher ratio of cholesterol metabolite 27-OH-cholesterol to cholesterol, which may be indicative of increased cholesterol breakdown, was significantly and

independently associated with prolonged lower cognitive functioning. In addition, a higher ratio of cholesterol precursor lanosterol to cholesterol, indicative of a higher rate of cholesterol synthesis was significantly associated with lower general cognitive functioning, in ApoE e4 non-carriers. Also, only in ApoE e4 non-carriers, a lower rate of cholesterol absorption as indicated by a lower ratio of the plant sterols to cholesterol, and a higher rate of cholesterol synthesis relative to cholesterol absorption were significantly and independently associated with prolonged lower information processing speed. Furthermore, we found a synergistic negative effect of low LDL cholesterol and high inflammation, as well as high triglycerides and high inflammation on level of cognitive functioning. Low HDL cholesterol was significantly associated with worse memory performance. Finally, higher total tHcy was significantly and independently associated with prolonged lower cognitive functioning and faster cognitive decline. A modifying effect of inflammation was found; higher levels of the inflammatory markers studied enhanced the negative effect of tHcy on cognition, but not consistently.

The current findings based on two large longitudinal cohort studies emphasize the need for research focusing on identifying subgroups who could benefit from treatment to prevent cognitive decline and dementia, taking into account genetic profile and the interaction between relevant biological markers.

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