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

van den Kommer, T.N.

2011

***document version***
Publisher's PDF, also known as Version of record

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

Summary

Tessa Nicole van den Kommer

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 per-

sons 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 associa-

tions 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.

**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 ≤ 24 in 75 year olds; and low cholesterol and MMSE ≤ 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.