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van den Kommer, T.N.

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Tessa Nicole van den Kommer

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ter verkrijging van de graad Doctor aan
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ten overstaan van de promotiecommissie
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door

Tessa Nicole van den Kommer

geboren te Delft

promotoren:	prof.dr. D.J.H. Deeg
	prof.dr. C. Jonker
copromotoren:	dr. M.G. Dik
	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)

Contents

Chapter 1

General Introduction

Cognitive decline and dementia in an aging society

As overall life expectancy has grown between 1990-2007 (World Health Organisation, 2009) and is expected to continue to grow (Christensen et al., 2009), the number of persons experiencing age-related decline in cognitive function increases and the estimated number of incident and prevalent dementia patients will continue to grow in the following years (Ferri et al., 2005; Fratiglioni et al., 2000; Lobo et al., 2000). In a systematic review by Ferri et al. (2005) it was estimated that the current number of persons with dementia worldwide will double every 20 years to 42.3 million in 2010 and 81.1 million by 2040. Most people with dementia live in developing countries (60% in 2001, rising to 71% by 2040). The rate of increase in numbers of people with dementia is predicted to be three to four times higher in developing than in developed countries (Ferri et al., 2005). Studies have emphasized the economic and public health burden accompanying this increase in persons suffering from dementia (Bradford et al., 2009; Haan and Wallace, 2004).

Dementia is a heterogeneous spectrum of clinical syndromes caused by different brain diseases and characterized by multiple disorders in cognition, behaviour or mood to the point where daily functioning is clearly impaired (Dutch Institute for Healthcare Improvement CBO, 2005). A clinical diagnosis of dementia is often preceded by a long period of cognitive decline. In order to contribute to an early diagnosis of dementia it is important to focus on this period of decline in cognitive functioning, its predictors and the transition to persistent cognitive decline and dementia.

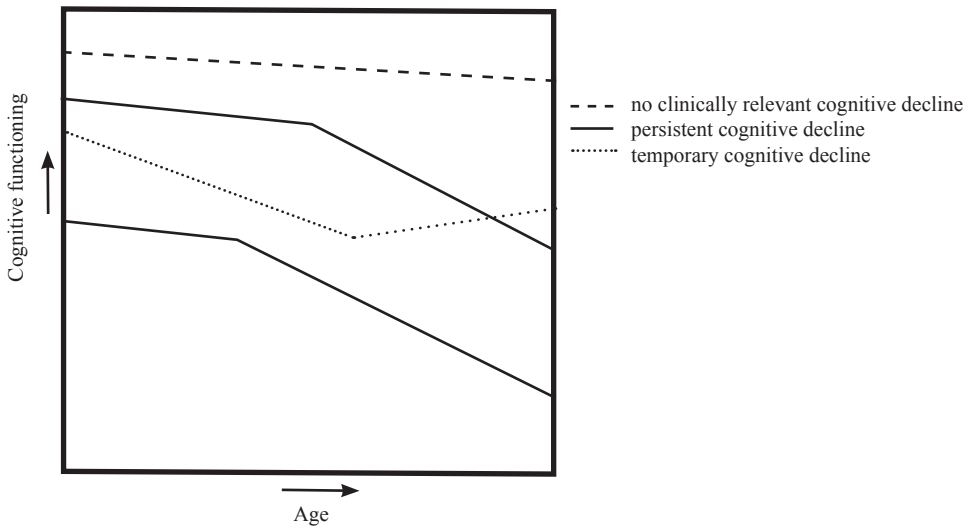

Figure 1 Inter-individual differences in cognitive decline over time

The trajectory of cognitive functioning and rate of cognitive decline shows substantial variation between individuals (Comijs et al., 2004). In Figure 1 these inter-individual differences are shown in a simplified manner, making a distinction between 'normal', in other words no

clinically relevant cognitive decline, temporary cognitive decline and persistent (or progressive) cognitive decline starting at different points in time. Persons who show persistent cognitive decline will at some point meet the formal criteria for dementia.

Early identification of persons at risk for dementia

Although no cure for dementia is available yet, early identification of persons at risk for future dementia is of great importance. Treatment and control of modifiable (vascular) risk factors is possible and may delay onset and prove useful in preventing dementia (Fratiglioni et al., 2000; Haan and Wallace, 2004). Early pharmacological treatment of persons at high risk of dementia could result in preservation of cognitive functions, maintenance of functional independence, and prevention of behavioural problems for as long as possible (Gauthier, 2005; Gauthier et al., 2006, 2008; Standridge, 2004). In addition, to know the diagnosis of dementia in an early phase could help patients and caregivers to anticipate future difficulties. Early psychosocial interventions may reduce the strain on caregivers and reduce the rate of institutionalization (Mittelman et al., 2006; Sørensen et al., 2008; Spijker et al., 2008). In the Netherlands, persons with subjective memory problems or their relatives usually first turn to their general practitioner for help. The role of the primary practitioner as a gatekeeper is increasingly important in terms of early detection of (persons at risk for) dementia. However, this is not an easy task and presents many challenges, and as a result dementia remains under-detected and sub-optimally managed in primary care (Bamford et al., 2007; Bradford et al., 2009; Valcour et al., 2000; Vernooij-Dassen et al., 2005). Therefore, a proactive approach to case-finding of persons at increased risk for future dementia is needed.

In this thesis (*1st main objective*), classification models for early detection of persons at risk for persistent cognitive decline and dementia in primary care are presented. These models were first developed in a large population-based longitudinal study using sets of markers which are relatively easy to determine, based on recent reviews and research on predictors of cognitive decline and dementia (Gauthier et al., 2006; Ownby et al., 2006; Panza et al., 2006; Razay et al., 2006; Román, 2005; Stampfer, 2006; Van der Flier and Scheltens, 2005), and further evaluated in another cohort comprising the oldest old (≥ 80 years) with longitudinal data on cognition and dementia diagnosis based on formal criteria.

Biological predictors of cognitive decline and dementia

It has been well established that cardiovascular disease (CVD) is an important risk factor for cognitive decline and dementia (Breteler et al., 1994; Stampfer, 2006; Van Exel et al., 2002). In addition to increasing the risk of vascular dementia (VaD), CVDs such as stroke and cardiac disease, vascular-related diseases such as diabetes and atherosclerosis, and vascular risk factors such as disturbances in lipid metabolism, inflammation and hyperhomocysteinemia appear to constitute risk for the most common cause of dementia, Alzheimer's disease (AD) (Panza et al., 2006; Román, 2005; Solomon et al., 2007, 2009b; Van Oijen et al., 2007). Although current

evidence supports a strong link, the association between CVD, its risk factors and cognitive decline of neurodegenerative or vascular origin is very complex and causality and underlying mechanisms remain to be clarified. A number of alternative hypotheses have been proposed (Launer, 2002). For example, in addition to a possible direct toxic effect, vascular risk factors may have an indirect effect by creating a condition such as atherosclerosis or stroke, or certain risk factors may have an additive, synergistic effect and create more pathology than either element produces by itself. Also, genetic factors such as Apolipoprotein E (APOE) ε4 may play a role with respect to the degree to which these components contribute to cognitive decline (Van der Flier and Scheltens, 2005). Furthermore, it has been shown that the direction of the association between some vascular risk factors and dementia is different depending on age (midlife versus late-life) (Solomon et al., 2007, 2009a; Van Vliet et al., 2009). Evidence suggests that hypercholesterolemia during midlife is associated with increased risk for future dementia, while the opposite association has been found in late-life (Solomon et al., 2007, 2009a; Van Vliet et al., 2009). Associations and underlying disease mechanisms may be different according to preclinical or clinical phase of dementia and disease severity (Mielke and Lyketsos, 2006; Peila and Launer, 2006; Stewart et al., 2007). Therefore, it is crucial to study these (potential) risk factors and predictors and underlying moderating or mediating mechanisms of cognitive decline in an early phase, by focusing on the trajectory of cognitive functioning in a population-based sample of older persons.

To contribute to a better understanding of some of the biological processes related to cognitive decline, this thesis (*2nd main objective*) focuses on the role of cholesterol homeostasis, lipoproteins, triglycerides and homocysteine on level of cognitive functioning and rate of cognitive decline, i.e. the trajectory of cognitive functioning in persons aged 65 years and older. In addition, possible modifying mechanisms which have been shown to be associated with both vascular disease and increased risk of dementia, namely genetic risk factor ApoE e4 and inflammation, are investigated.

Markers of cerebral and extracerebral cholesterol homeostasis

Homeostasis of cholesterol, which is a necessary component of all cells, is the balance between intestinal sterol absorption, synthesis and excretion (Grundy, 1991). Accordingly, low intestinal absorption of cholesterol upregulates cholesterol synthesis and turnover, while an increase in the intestinal cholesterol flux to the liver suppresses cholesterol synthesis (Sehayek et al., 1998). Lanosterol is the first sterol formed during cholesterol biosynthesis. Lathosterol, another precursor of cholesterol synthesis which is formed at a later step in the pathway, is considered a marker of (hepatic) cholesterol synthesis rate (Miettinen et al., 1990). Serum concentrations of plant sterols, such as campesterol and sitosterol, which are solely of dietary origin, reflect the efficacy of cholesterol absorption (Miettinen et al., 1990). Cholesterol pools in plasma and the brain, the most cholesterol-rich organ in the body containing 25% of total body cholesterol, are separated by the blood-brain barrier (BBB) (Björkhem and Meaney, 2004). In the brain,

cholesterol is the main lipid constituent of neuronal membranes and myelin (Snipes and Suter, 1997). The main mechanism of elimination of excess brain cholesterol and maintenance of brain homeostasis is by conversion to oxysterol 24S-hydroxycholesterol, which is able to pass the BBB and is therefore considered a surrogate marker for brain cholesterol metabolism (Björkhem et al., 1997, 1998; Lütjohann et al., 1996). Furthermore, an opposite flux of oxysterol 27-hydroxycholesterol, a cholesterol metabolite which mainly origins from extracerebral and extrahepatic cells, from circulation into the brain has been shown (Heverin et al., 2005). In addition, a small amount of cholesterol is transported from the human brain into the cerebral spinal fluid (CSF) and circulation by an ApoE dependent mechanism (Pitas et al., 1987). ApoE is the major lipid transport protein in the brain and is known to modulate cholesterol metabolism (Poirier, 1996; Davignon et al., 1988). Furthermore, APOE ε4 is a well-known genetic risk factor for cardiovascular disease and AD (Davignon et al., 1988; Strittmatter and Roses, 1995). The ε4 allele is associated with lower levels of ApoE, which decrease cholesterol transportation from cell bodies to distal axons, and inhibit cell growth by reducing the rate of axonal extension and causing an increase of cholesterol in the cell body (Mielke and Lyketsos, 2006). In this thesis, the potential modifying role of ApoE status on the associations between markers of cholesterol homeostasis and cognitive decline is studied.

Cholesterol circulates as a component of lipoproteins. High-density lipoprotein (HDL) particles extract cholesterol from tissue (including atherosclerotic plaques) and deliver it back to the liver, thus promoting vascular health. Conversely, Low-density lipoprotein (LDL) transports cholesterol through the circulatory system into the cells that require extracellular cholesterol. However, LDL cholesterol does not always reach its most appropriate destination, but rather accumulates in artery walls causing atherosclerosis (Daniels et al., 2009). Triglyceride is the principal fat in diets (exogenous source) and is synthesized in the liver (endogenous source), after which it is mainly secreted into the blood as very low-density lipoprotein (VLDL) and to a lesser extent HDL (Abourjaili et al., 2010; Norum et al., 1983). Figure 2 shows a simplified, schematic illustration of the different components of cholesterol homeostasis and transporters of cholesterol.

Disturbances in lipid metabolism have also been linked to inflammation in relation to atherosclerosis (Lehtimäki et al., 2005), which in turn is linked to dementia (Stampfer, 2006; Van Oijen et al., 2007). Inflammatory processes may play a role in the development of dementia and cognitive decline (Peila and Launer, 2006; McGeer and McGeer, 1995). Previous studies have shown an association between inflammatory markers, including Interleukin-6 (IL-6), C-reactive protein (CRP), and α1-antichymotrypsin (ACT), and increased dementia risk (Engelhart et al., 2004; Schmidt et al., 2002) and cognitive decline (Dik et al., 2005; Weaver et al., 2002). Proinflammatory cytokine IL-6 is expressed in atherosclerotic plaques, and regulates the secretion of CRP, fatty acid, and lipoprotein from the liver and thus affects plasma lipid levels as well as immune and inflammatory responses (Lehtimäki et al., 2005). CRP is a major acute-phase reactant and is deposited in atherosclerotic lesions where it may contribute to the development

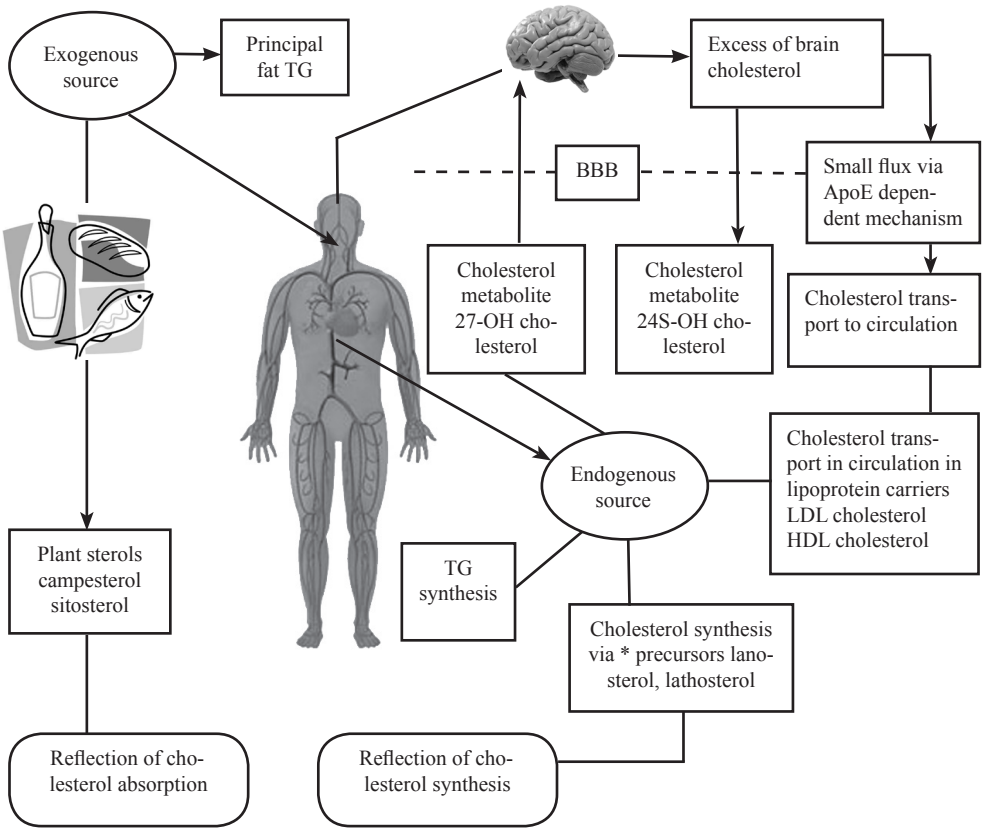

Figure 2 Schematic picture of components of cholesterol homeostasis and carriers of cholesterol
TG triglycerides; *BBB* blood-brain barrier. *ApoE* Apolipoprotein E; *LDL* low-density lipoprotein; *HDL* high-density lipoprotein; * only these precursors of cholesterol were studied in the present thesis.

of atherosclerosis (Taskinen et al., 2005). Protease inhibitor ACT, which is also produced in the liver as a reaction to inflammation, has been identified in amyloid plaques in the brains of AD patients (Abraham et al., 1988). Further evidence for a potentially important role of inflammation with respect to the link between lipid metabolism and dementia comes from studies focusing on the metabolic syndrome. The metabolic syndrome is a clustering of cardiovascular risk factors, namely hypertension, abdominal obesity, low HDL levels, hypertriglyceridemia and/or hyperglycemia (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Previous studies have shown that persons with the metabolic syndrome and elevated levels of inflammation have a higher risk of VaD, cognitive decline and show poorer cognitive functioning than persons with the metabolic syndrome without high levels of inflammation (Dik et al., 2007; Solfrizzi et al., 2010; Yaffe et al., 2004). It has been suggested that the metabolic syndrome contributes to accelerated atherosclerosis, which is associated with an inflammatory response, and in turn atherosclerosis and/or inflammation contribute to

cognitive decline (Grundy, 2003; Ridker et al., 2003; Yaffe, 2007). In this thesis, the modifying effect of inflammatory markers CRP, IL-6 and ACT, and role of lipoproteins HDL and LDL cholesterol, and triglycerides in level of cognitive functioning and rate of cognitive decline are studied.

Homocysteine

Total plasma levels of homocysteine (Hcy), a sulphur-containing amino acid, has numerous determinants, namely genetic factors, life-style factors (e.g. smoking), clinical conditions (e.g. renal failure and vitamin deficiencies), physiologic determinants (e.g. age and sex), and medication (Refsum et al., 1998). High Hcy levels have been linked with increased risk of VaD and AD (Clarke et al., 1998; Seshadri et al., 2002). As stated earlier, elevated levels of tHcy have been shown to be an independent risk factor for cardiovascular disease (Bautista et al., 2002; Clarke et al., 1991; Graham et al., 1997). It has been proposed that elevated Hcy levels promote increased vascular oxidant stress which in turn promotes inflammation of the arterial wall and atherosclerotic plaque formation (Papatheodorou and Weiss, 2007). In addition, increased levels of Hcy may have direct toxic effects on neurons of the central nervous system (Kruman et al., 2000; Lipton et al., 1997). Hcy levels are easily lowered by dietary supplementation with folic acid and vitamin B_{12}. However, a systematic review of randomized trials in which the effect of vitamin B_6, B_{12} and folic acid supplementation was studied showed no effect on cognitive functioning in either persons with normal or impaired cognition (Balk et al., 2007). Thus, so far mechanisms underlying the proposed link with dementia are not fully understood. In this thesis, the potential modifying effect of inflammation, and effect of homocysteine on cognitive functioning and decline is examined.

Main objectives

1) To develop and further evaluate classification models for early identification of persons at risk for persistent cognitive decline and dementia in primary care;
2) To study the role of markers of cholesterol homeostasis, lipoproteins, triglycerides, homocysteine and possible effect modifiers ApoE e4 and inflammation on level of cognitive functioning and rate of cognitive decline.

Cohort studies

Longitudinal Aging Study Amsterdam (LASA)

LASA is an ongoing longitudinal population-based study which focuses on physical, social, emotional and cognitive functioning in late-life in a cohort based on a nationally representative sample, initial ages 55-85 years (born between 1908-1937) with oversampling of men and older old. The sample was initially recruited in 1992 for the NESTOR-study on Living Arrangements

and Social Networks of older adults (N = 3,805). Surviving participants (N = 3,677) were approached after an average of 11 months for the first LASA wave (T_1) from 1992-1993, of whom 3,107 were enrolled. Subjects were examined at three-year intervals. Procedures regarding sampling and data collection have been described in detail (Deeg et al., 2002). More information on the specific number of participants included in the studies described in this thesis and characteristics of the study sample are provided per Chapter (see also Figure 3).

Origins of Variance in the Old-Old: Octogenarian Twins (OCTO-Twin) Study

The OCTO-Twin Study is a longitudinal population-based study in which data on a broad spectrum of bio-behavioural measures of health and functional capacity, personality, well-being, interpersonal functioning, as well as cognition were obtained in twins aged 80 and older (McClearn et al., 1997). The sample was drawn from the oldest cohort of the population-based Swedish Twin Registry (Cederlöf and Lorich, 1978) which comprised twin pairs aged 80 years and older (born 1913 and earlier), who were both alive when contacted for potential participation (737 pairs in 1474 individuals). Of these pairs, some were excluded because one (or both) had deceased before they were scheduled for examination (188 pairs), or because one (or both) declined participation in the study for other reasons (198 pairs). Subjects were examined at five occasions at two-year intervals, starting with the first wave (T_1) of data collection from 1991-1993 (351 pairs, 702 individuals).

Outline of this thesis

Chapters 2 and 3 describe the development and evaluation of classification models for early detection of persons at risk for future persistent cognitive decline and dementia. This was done by using data from the LASA and the OCTO-Twin Study, respectively.

Chapters 4 and 5 focus on the role of markers of cholesterol homeostasis in cognitive functioning and decline. In Chapter 4 the associations between total cholesterol and its metabolites 24S-OH cholesterol and 27-OH cholesterol and cognitive decline are studied. In Chapter 5, the associations between markers of cholesterol synthesis and absorption, and cognitive functioning and decline are studied. Furthermore, in both Chapters potential effect modification by ApoE e4 status was examined.

In Chapter 6, we focus on the role of triglycerides and the major cholesterol transport lipoproteins HDL and LDL cholesterol in the trajectory of cognitive decline, and the potential interaction with inflammation as reflected by CRP, IL-6 and ACT.

In Chapter 7 the associations between homocysteine, inflammation and cognitive decline were studied.

Finally, the General Discussion (Chapter 8) summarizes the main findings and conclusions of the studies described in Chapters 1 to 7, and reflects on methodological issues, relevance and implications. In addition, recommendations for future research are given.

All studies except the study described in Chapter 3, were performed using longitudinal data collected in the LASA study. Figure 3 shows a flow chart of the three-year follow-up cycles of LASA, and shows the sample selection per Chapter.

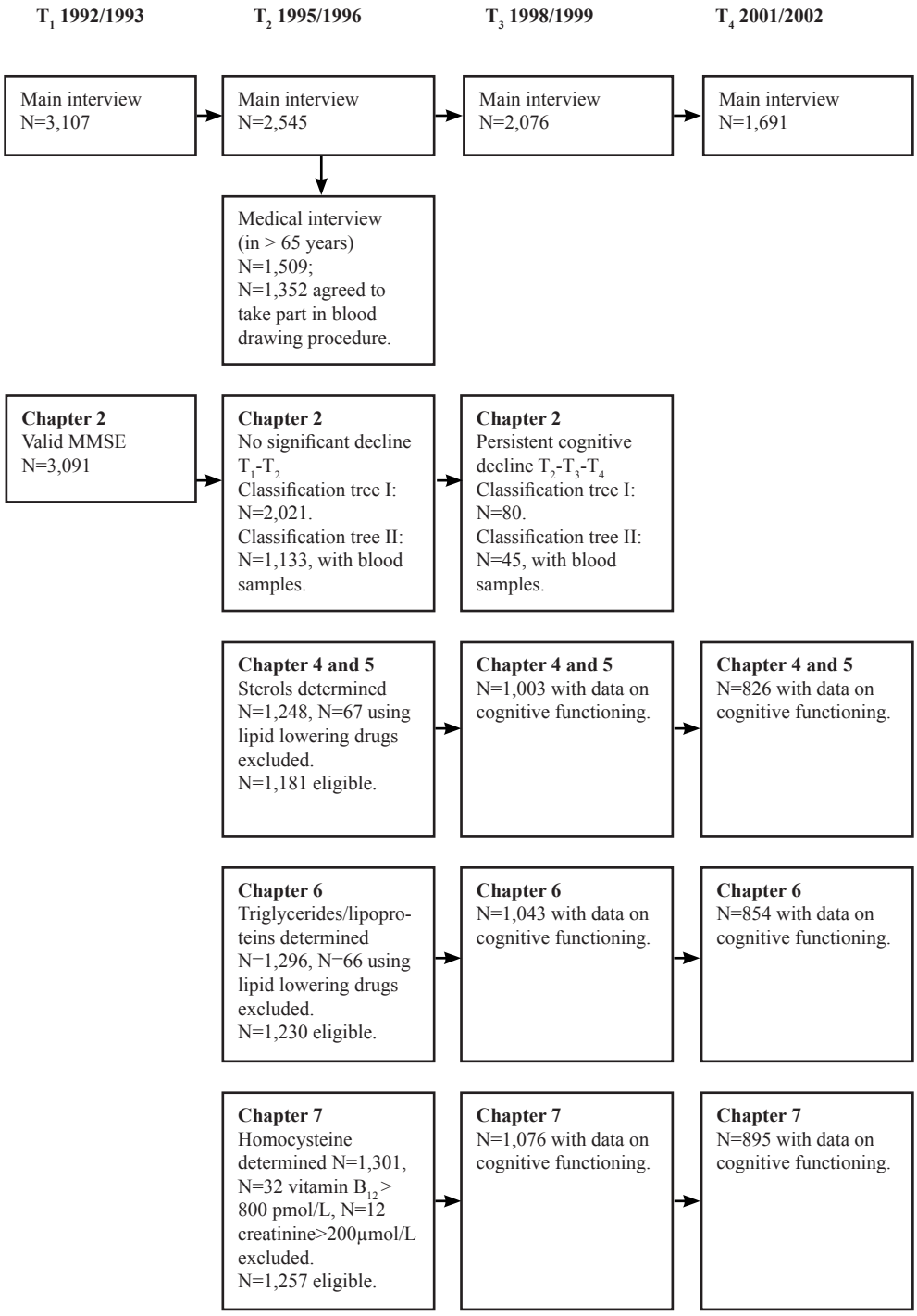

Figure 3 Flow chart of the Longitudinal Aging Study Amsterdam and the sample selection per Chapter

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