Determinants of cognitive decline in older European men

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Proefschrift

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Voor Mama en Rob

Abstract

In our ageing population, the number of persons with cognitive impairment, dementia and Alzheimer's disease still increase and cause many problems for the elderly themselves, their relatives and caregivers and for health care. Therefore, the need for preventive action is high. In this thesis we identified social, lifestyle and dietary risk factors for the postponement of cognitive impairment and decline in elderly European men.

For the results presented in this thesis, data from the Finland, Italy and the Netherlands Elderly (FINE) Study were used. This prospective population-based cohort study was carried out between 1985 and 2000 among 2,285 Finnish, Italian and Dutch men born between 1900 - 1920. Cognitive functioning was measured with the Mini-Mental State Examination (MMSE).

In the FINE Study, cognitive functioning decreased on average with 1.5 points during the 10-year follow-up period. This decline was due to an age effect, but also to a period and birth cohort effect.

Men who were married or who lived with others during five years had at least a two times smaller subsequent 10-year cognitive decline compared with men who lost a partner, who were unmarried, who started to live alone and who lived alone during these five years.

Cognitive decline did not differ among men with a high or low duration of physical activity at baseline. However, men who participated in activities with at least a medium-low intensity had a 1.8 to 3.5 times smaller cognitive decline compared with men who participated in activities with lowest intensity. Moreover, a decrease in duration or intensity of physical activity resulted respectively in a 2.6 or 3.6 times stronger cognitive decline than maintaining duration or intensity.

Men who consumed coffee had a two times smaller 10-year cognitive decline than non-consumers. In addition, an inverse and J-shaped association between the number of cups of coffee per day consumed and 10-year cognitive decline was present, with the least decline for men consuming three cups of coffee per day.

Fish consumers had significantly less 5-year subsequent cognitive decline than non-consumers. A linear trend was observed for the relation between the intake of the n-3 fatty acids EPA + DHA and cognitive decline. An average difference of about 380 mg/day in EPA + DHA intake was associated with a 1.1 points difference in cognitive decline.

Men whose cognition decreased between 1990 and 1995 had a twofold higher risk of dying in the following five years compared with men whose cognition was stable. Mortality risk of men whose cognition improved between 1995 and 2000 was not different from men with a stable cognition.

The associations between marital status, living situation and physical activity are strong and provide in combination with the existing literature enough evidence for justifying public health recommendations for postponing cognitive decline. However, our findings on coffee and fish consumption and on the intake of the fatty acids EPA + DHA in relation with cognitive functioning need confirmation in other studies.

Contents

Chapter 1

Introduction

Western populations age rapidly. During the second half of the past century, the average lifespan increased with 20 years worldwide.[1] In the European Union (25 countries), the life expectancy increased with 2.4 years for women and 3.2 years for men between 1994 and 2005.[2] In 2005, life expectancy for men in Finland was 75.5 years, for the Netherlands 77.2 years and for Italy 77.6 years[2]. Not only life expectancy has increased, also the number of persons above the year of 65 increased due to the baby boom generation. In 2003, 17% of the total population in the European Union was 65 years or older, 15% in Finland, 14% in the Netherlands and 19% in Italy.[3] In about 30 years this percentage is expected to double.[4] In the older population, the oldest old (80 years or older) is the fastest growing segment of elderly. In 2005, 4% of the European population was 80 years or older, in 2025 this will be 5% and in 2050, 10%.[5]

Because of the growing older population, healthy ageing is an important issue. One aspect of health is cognitive functioning, the ability to think, perceive, reason and remember. Since age is an important risk factor for cognitive impairment,[6,7] the number of persons with cognitive impairment will increase in an ageing population. Cognitive impairment prevalence rates vary in older persons over 65 years from 3 to 23%, depending on the age and definition of cognitive impairment used.[6-10] More detailed information shows even that about 19% of persons aged 65-74 years have some kind of cognitive functioning problems, 28% of persons aged 75-84 years and 38% of persons aged 85 years and older.[7]
Each year, 10 to15% of the individuals with mild cognitive impairment develop dementia.[11] As for cognitive impairment, dementia incidence rates also increase with age,[12-16] even exponentially up to in very old age (at least until 90 years) (figure 1.1).[17] Therefore, when populations age, the number of individuals with cognitive impairment or dementia will further increase.[17]

Cognitive impairment and dementia are major health problems that cause many functional, psychological, emotional, and financial problems and distress, both for individuals as well as for family and caregivers.[18,19] Elderly view dementia as the most dreadful disease. Furthermore, demented persons often need specific medical, day and long-term care, which is associated with high societal healthcare costs. In the Netherlands, dementia is one of the five disorders accounting for the highest percentages of the healthcare costs (5.6% of the total healthcare costs).[20]
Furthermore, elderly with cognitive impairment are at an increased mortality risk compared with those without cognitive impairment.[21] Although even mild cognitive impairment is associated with an increased mortality risk, more severe cognitive impairment and dementia are associated with an even higher mortality risk.[22] Because of the severe consequences of cognitive impairment, the need for preventive action is high.

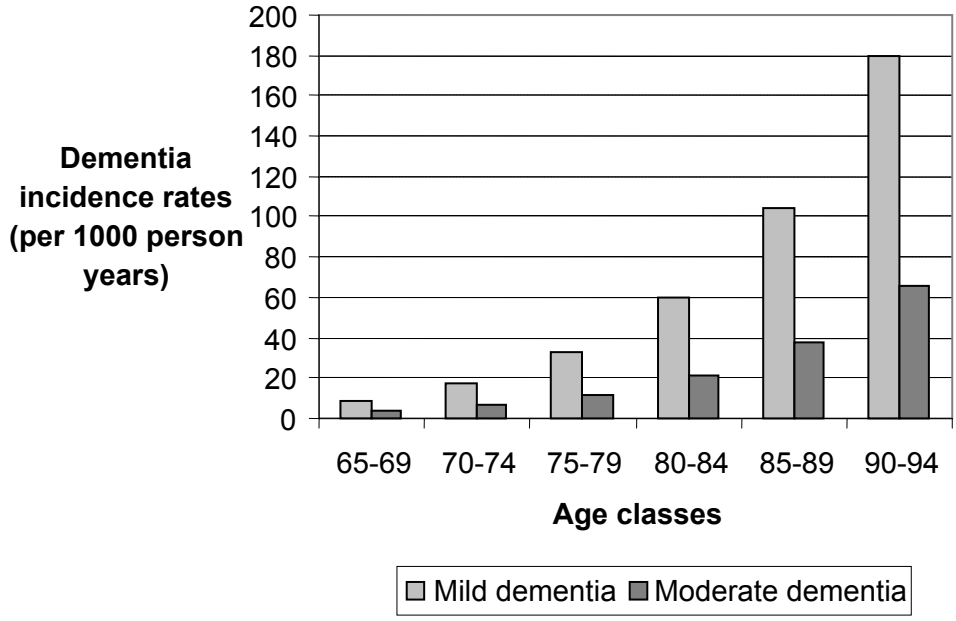

Figure 1.1. *Mild and moderate dementia incidence rates in Europe per age class. (This figure was reproduced with numbers from Jorm et al., 1998).*[17]

No treatment or medication has convincingly shown to cure or even stop the process of cognitive decline and dementia yet.[23] The underlying biological process of cognitive impairment and dementia is very complicated and starts already more than 10 years before dementia becomes clinically apparent. Some potential treatment strategies, like acetyl cholinesterase inhibitors, modulation of different neurotransmitter systems, reducing amyloid formation or abnormal phosphorylation of tau protein (the beginning of neurofibrillary tangle), non-steroidal anti-inflammatory drugs, vitamin B12 or vitamin E supplementation, hormone replacements therapy, and non-drug interventions such as memory training are under clinical evaluation.[19,23] Since an adequate treatment does not exist, the focus should be on preventing and postponing cognitive impairment, cognitive decline and dementia. Already several risk factors for cognitive impairment and decline are identified and modification of these risk factors may reduce the risk. Information on new risk factors may further contribute to the prevention or postponing of cognitive impairment.

Definition of cognitive functioning

Cognitive functioning is the process of receiving, processing, storing and using information (on: http://www.allpsych.com/dictionary/). Main cognitive functions are memory and learning, attention

and concentration, thinking, language, visual and spatial skills. 'Normal' cognitive functioning can decline over the years leading to cognitive impairment, a transitional but progressively degenerative cognitive phase that precedes dementia or Alzheimer's disease.[24,25] More severe cognitive decline can finally lead to dementia or Alzheimer's disease (figure 1.2).[24,25] Dementia is a progressive, neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions such as memory and learning, thereby impairing every day functioning.[26] Different types of dementia exist, such as vascular dementia, mixed dementia, dementia with Lewy bodies, frontotemporal dementia, dementia secondary to disease (e.g. AIDS dementia) and Alzheimer's disease. The latter represents about 70% of the dementia patients.[19,27]

It is difficult to distinguish between elderly with normal cognitive ageing and mild cognitive impairment. Mild cognitive impairment is a transitional stage between cognitive functioning of normal ageing and impaired cognitive functioning caused by the dementing process.[11,28] People with mild cognitive impairment have memory loss greater than what would be expected for the persons age and educational level if cognitive functioning is preserved.[9] However, these persons do not meet the criteria for dementia and Alzheimer's disease and mild cognitive impairment does not interfere with activities of daily life.[9,24] People who 'age healthy' have very little cognitive decline during their life.[24] The level of cognitive functioning, the onset of cognitive decline and the rate of cognitive decline differ between persons (figure 1.2).

Measuring cognitive functioning

Cognitive functioning is assessed in this thesis with the Mini-Mental State Examination (MMSE).[29] This test consists of questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction to measure global cognitive functioning. Originally, the MMSE was used as a screening test in the clinical situation.[29] Nowadays, it is frequently used in epidemiologic studies as well[30] and has proven to be a reliable and valid indicator of cognitive impairment with a good test-retest reliability.[31,32]

The MMSE consists of 20 questions and the maximum score to achieve is 30 points, with a higher score indicating a better cognitive performance. A score of 26-30 indicates 'normal cognitive functioning', a score of 24 or 25 'borderline normal cognitive functioning', a score below 24 'cognitive impairment'[31] and a score below 18 '*severe* cognitive impairment'.[33] In this thesis we used the cut-off values for cognitive impairment and severe cognitive impairment. Our definition of

cognitive impairment is based on one measurement of cognitive functioning and cognitive decline is defined as the difference between two (or more) measurements of cognitive functioning.

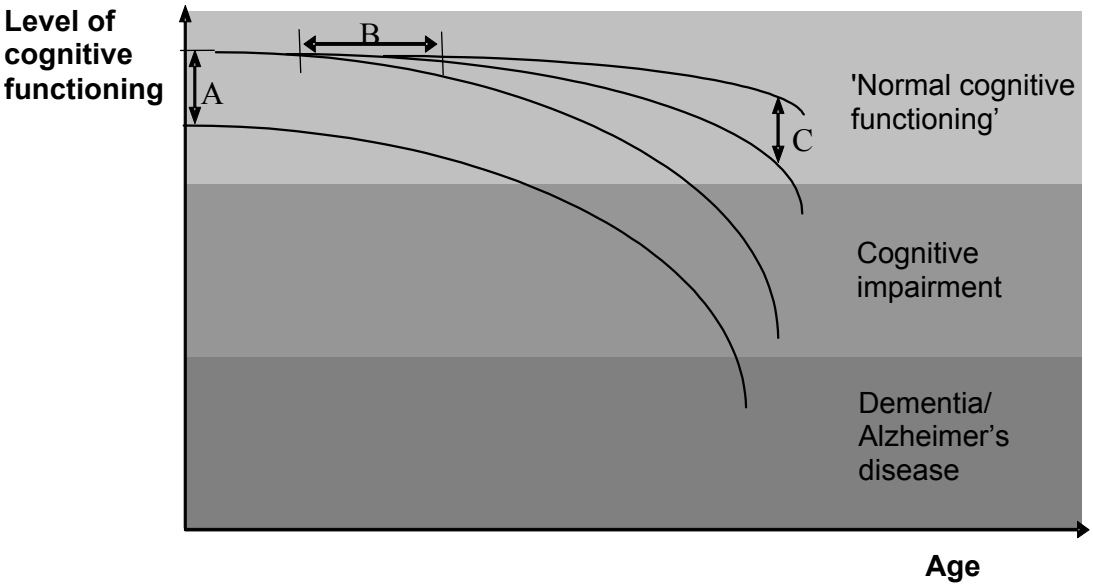

Figure 1.2. *Differences in cognitive functioning over time between persons: A= difference in level of cognitive functioning; B= difference in onset of cognitive decline; C= difference in rate of cognitive decline. Furthermore, different cognitive stages are given from 'normal cognitive functioning' to cognitive impairment and dementia/ Alzheimer's disease.*

Processes underlying cognitive impairment and cognitive decline

Cognitive impairment is a complex degenerative disorder that is caused by several underlying processes. A number of these processes will be briefly discussed below.

Vascular factors. Vascular risk factors, such as high blood pressure, high cholesterol and high homocysteine level, can cause atherosclerosis and may increase the risk of cognitive decline.[34,35] In the atherosclerotic process (thickening and hardening of arteries), plaques may (partially) block blood flow through an artery, which may result, in combination with thrombosis, in complications such as stroke and subsequent degeneration of brain cells, leading to cognitive decline and dementia.[36,37] Furthermore, white matter changes, which are related to vascular risk factors and atherosclerosis,[38] may also result in an increased risk for cognitive impairment and dementia.[38,39]

Inflammation. High levels of inflammation, due to e.g. the synthesis of cytokines and mitogens,[40] may be associated with an increased risk of cognitive decline and dementia.[41,42] Chronic inflammatory conditions have also been found in affected regions of the brain in Alzheimer's disease patients.[43]

Free radicals. Free radicals are produced by for example the catalyzing reactions of metals. These free radicals attack brain neurons and thereby cause oxidative damage to brain cells. Free radicals are also involved in β-amyloid toxicity. Antioxidants provide a protective effect against free radicals.[44] Some studies show that antioxidants may protect against cognitive impairment[45,46] and lower the risk of Alzheimer's disease.[47,48]

Plaques and tangles. Persons with cognitive impairment show increased numbers and abnormally distributed neurofibrillary tangles and β-amyloid plaques in their brain.[23] Significant increase in these neurofibrillary tangles and amyloid plaques can be shown in the brain of patients with dementia and Alzheimer's disease.

Hippocampal atrophy. Shrinkage of the hippocampus, the memory part of the brain, has been observed in patients with cognitive impairment and major atrophy of that part of the brain is also shown in Alzheimer's disease.[23,49]

(Cholinergic) neurotransmitters. Cognitive decline in patients with Alzheimer's disease can also be viewed as a cholinergic disorder,[19,50] because of loss of cholinergic markers (like acetylcholine containing neurons) in the brain. Cholinergic neurotransmitters prevent β-amyloid-induced neurotoxicity in cerebellar neurons.[51]

Cortisol. Furthermore, stress may cause an overactivity of the hypothalamic-pituitary-adrenal axis, which may cause high cortisol levels. High cortisol levels in turn may be toxic to neurons, especially to neurons in the hippocampus, the memory part of the brain.[52,53] This may eventually lead to cognitive decline.[54]

Genetic factors. Genetic factors, e.g. the apolipoprotein E gene, may contribute to cognitive decline and dementia.[55-57] The apolipoprotein E gene plays a role in neuronal growth.

Dementia is a multi-factorial disease and the dementing process is the result of a combination of and interactions between genetic and environmental risk factors.[19] Precise mechanisms are however not yet known.

Risk factors for cognitive decline

Studies on risk factors are important for understanding the aetiology and the pathogenesis of cognitive impairment, cognitive decline and dementia. Some risk factors are modifiable and

therefore suitable for interventions. Therefore, identification of these (modifiable) risk factors is important for developing effective strategies for preventing and postponing cognitive impairment and decline. During the past decade, several risk factors for cognitive decline were identified. Extensively studied risk factors for cognitive impairment, cognitive decline, dementia and Alzheimer's disease are e.g. increasing age,[17,58] female gender,[58,59] low educational level,[58,59] carrying apolipoprotein E4,[55,60] depression[61] and vascular pathology.[62] More recently the focus is also on social, lifestyle and dietary risk factors such as marital status,[63] living situation,[63] physical activity,[64] alcohol consumption,[65] smoking status,[58] coffee consumption,[66] the intake of fatty acids[67] and fish consumption.[67] However, most of these risk factors were identified in cross-sectional studies. Nowadays the emphasis is on research focusing on risk factors for *change* in cognitive functioning using longitudinal data, which will be less prone to bias.

In summary, identifying risk factors for cognitive impairment and decline is an important step towards preventing and postponing cognitive decline. Furthermore, the role of social, lifestyle and dietary determinants in cognitive decline is not well understood and the use of longitudinal data has been limited. Therefore, in this thesis we focus on social, lifestyle and dietary risk factors in relation to cognitive decline.

The present thesis

Besides the study on risk factors, this thesis describes also *changes* in cognitive functioning through time. Finally, results on the relationship between *change* in cognitive functioning and mortality will be presented.

Changes in cognitive functioning

Cognitive functioning decreases with increasing age,[13,17] however, it is not yet clear if this is due to an age effect, a period effect, a birth cohort effect or combinations of the three. An age effect is present when cognitive functioning decreases with increasing age, a period effect when cognitive functioning differs in different survey years, and a birth cohort effect when cognitive functioning is different for persons belonging to different birth cohorts. It is impossible to disentangle the three effects by only cross-sectional or longitudinal analyses. Therefore, we used a mixed longitudinal design.

In this thesis, the age, period and cohort effects were also studied by using both cross-sectional and longitudinal analyses as well as times-series analyses. We hypothesized that cognitive functioning will decrease with increasing age, because of ageing of the human brain.[68] Furthermore, we hypothesized that cognitive functioning would be different in different survey

years, because of changes in the environment such as socio-economic changes.[69] However, we did not a priori know in which survey year cognitive functioning would be better. Finally, also a birth cohort effect may be present, in such a way that people born in a later birth cohort may have better cognitive functioning due to e.g. better living conditions and a higher educational level.

Marital status, living situation and cognitive decline

Being married or living with others is associated with a better health status and a lower mortality risk.[70-73] Recent studies showed that persons who were married or who lived with others also had a lower risk of dementia.[63,74] This may be explained by the 'use-it-or-lose-it' hypothesis, which states that participation in mentally stimulating activities may increase or maintain neuronal brain growth and therefore prevent the brain from neuronal degeneration.[75] Previous studies investigated the association between marital status and living situation measured at one moment in time with cognitive decline. However, especially among elderly, social situations change frequently due to e.g. the loss of a partner. Therefore, we focused on the association between *change* in marital status and living situation and subsequent cognitive decline. We hypothesized that unmarried persons, those losing a partner, those living alone and those who are going to live alone have a stronger cognitive decline than those who are still married or who live with others.

Physical activity and cognitive decline

Physical activity may be associated with better cognitive functioning,[76-78] however, previous studies showed inconsistent results.[79,80] Furthermore, the results of various studies are difficult to compare due to different and frequently global operationalisations of both cognitive functioning and physical activity. In most studies detailed information on the duration and intensity of physical activity is lacking. Therefore, in this thesis, we investigated the associations between (*change* in) duration and intensity of physical activity with subsequent cognitive decline. Since increasing physical activity (duration as well as intensity) may maintain cardiovascular fitness,[81] we hypothesized that both duration and intensity of physical activity are inversely associated with cognitive decline.

Coffee consumption and cognitive decline

Coffee is the most frequently consumed beverage in the world. Many people consume several cups each day. Research on coffee has focused on the effects of coffee consumption on health and chronic diseases such as type 2 diabetes,[82] coronary heart disease,[83] cancer,[84] Parkinson disease,[85] and also cognitive functioning.[66,86,87] With respect to cognitive functioning, evidence exists that coffee consumption is associated with better cognitive functioning, but, results are not univocal. Furthermore, results of longitudinal studies are scarce.[86,87] Therefore, in this thesis, we investigated the association between coffee consumption and subsequent cognitive decline. We

hypothesized that consumption of coffee may protect against cognitive decline because of the antagonistic action of caffeine on the A_{2a} adenosine receptor in the brain, which stimulates the secretion of cholinergic neurons which in turn protects against β-amyloid-induced neurotoxicity.

Fish consumption, intake of n-3 fatty acids and cognitive decline

Consuming fish (the major source of the n-3 polyunsaturated eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the diet) lowers the risk of cardiovascular diseases, such as coronary heart disease[88] and stroke.[89] Since cognitive decline increases after the occurrence of stroke,[90,91] we hypothesized that fish consumption as well as the intake of EPA + DHA, may protect against cognitive decline. Evidence from previous studies on fish consumption and the intake of EPA + DHA on cognitive impairment and decline is sparse and inconsistent.[92] Therefore, we investigated these relationships using data that became recently available on the EPA and DHA content also of foods other than fish.

***Change* in cognitive functioning and mortality**

Ageing of populations is associated with an increased risk of cognitive impairment.[13,17] Persons with cognitive impairment have also a higher mortality risk compared with persons without cognitive impairment.[21] So, ageing of the population will result in more people with cognitive impairment who are at an increased mortality risk. Furthermore, cognitive functioning decreases rapidly in the last years of life.[93,94] In this thesis, we investigated whether *change* in cognitive functioning was associated with a higher mortality risk. Furthermore, we examined whether this was a result of a pre-mortal drop, a decline in cognitive functioning due to a terminal disease, or not. We hypothesized that a terminal disease could result both in cognitive decline and mortality.

Study population

To investigate afore mentioned topics, longitudinal data from the Finland, Italy and the Netherlands Elderly (FINE) Study were used. This study consists of the surviving men of five cohorts of the Seven Countries Study (SCS):[95] East Finland, West Finland, Zutphen (the Netherlands), Montegiorgio and Crevalcore (Italy). The SCS started in the late 1950's in middle-aged men and the surveys carried out in the elderly since 1984 are called the FINE Study. This study was conducted as a broad gerontologic survey that collected information on classical cardiovascular risk factors and on functional status and different aspects of health in elderly men. In 1985, 2285 men aged 65-84 years were examined and repeated examinations took place around 1990, 1995 and 2000. Since 1990, also information about cognitive functioning was collected.

The outline of this thesis

Due to the longitudinal design of the FINE Study, we were able to study *changes* in cognitive functioning as well as (*changes* in) determinants of cognitive decline and the relationship between *change* in cognitive functioning and mortality.

Figure 1.3 shows the topics described in this thesis. In chapter 2 we present *changes* in cognitive functioning through old age. Chapter 3 to 6 describe (*changes* in) social, lifestyle and dietary determinants of cognitive decline. In chapter 7, *change* in cognitive functioning in relation to mortality risk are described. Chapter 8 summarizes the results of this thesis and discusses methodological considerations, strengths of the associations and public health implications.

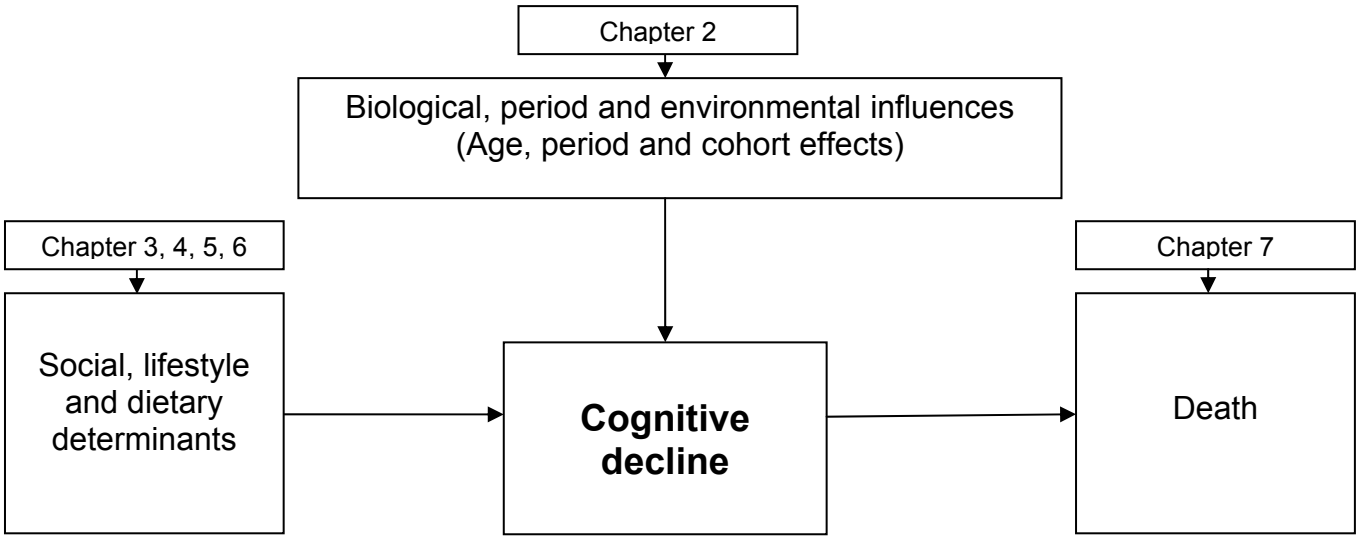

Figure 1.3. *Schematic overview of the outline of this thesis.*

References

1. United Nations. Report of the Second World Assembly on Aging. Madrid, Spain: United Nations, April 8-12, 2002.
2. Eurostat. Life expectancy at birth (years). 19-01-2007.
3. Eurostat. Proportion of population aged 65 and over (% of total population). 10-08-2005.
4. Steel K. Editorial. Research on aging. An agenda for all nations individually and collectively. JAMA 1997;278:1374-1375.
5. United Nations. World population prospects: the 2004 revision, vol. I: comprehensive tables (United Nations publication ST/ESA/SER.A/244); vol. II: Sex and age distribution of populations (United Nations publication ST/ESA/SER.A/245), 2005.
6. Di Carlo A, Baldereschi M, Amaducci L, Maggi S, Grigoletto F, Scarlato G, Inzitari D. Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. J Am Geriatr Soc 2000;48(7):775-782.
7. Unverzagt FW, Gao S, Baiyewu O, Ogunnivi AO, Gureje O, Perkins A, Emsley CL, Dickens J, Evans R, Musick B, et al. Prevalence of cognitive impairment: data from the Indianapolis Study of Health and Aging. Neurology 2001;57:1655-1662.
8. Frisoni GB, Fratiglioni L, Fastbom J, Guo Z, Viitanen M, Winblad B. Mild cognitive impairment in the population and physical health: data on 1435 individuals aged 75 to 95. J Gerontol A Biol Sci Med Sci 2000;55(6):M322-M328.
9. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, et al. International Psychogeriatric Association Expert Conference on mild cognitive impairment. Mild cognitive impairment. Lancet 2006;367(9518):1262-1270.
10. Kivipelto M, Helkala EL, Hanninen T. Midlife vascular risk factors and late-life mild cognitive impairment. Neurology 2001;56:1683-1689.
11. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Current concepts in mild cognitive impairment. Arch Neurol 2001;58(12):1985-1992.
12. Paykel ES, Brayne C, Huppert FA, Gill C, Barkley C, Gehlhaar E, Beardsall L, Girling DM, Pollitt P, O'Connor D. Incidence of dementia in a population older than 75 years in the United Kingdom. Arch Gen Psychiatry 1994;51:325-332.
13. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. Am J Epidemiol 1998;147(6):574-580.
14. Andersen K, Nielsen H, Lolk A, Andersen J, Becker I, Kragh-Sorensen P. Incidence of very mild to severe dementia and Alzheimer's disease in Denmark: the Odense Study. Neurology 1999;52:85-90.
15. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, Lobo A, Martinez-Lage J, Soininen H, Hofman A. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54(11):S10-S15.
16. Berr C, Wancata J, Ritchie K. Prevalence of dementia in the elderly in Europe. Eur Neuropsychopharmacol 2005;15(4):463-471.
17. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. Neurology 1998;51:728-733.
18. Aguglia E, Ono ML, Trevisiol M, Negro C, Saina M, Maso E. Stress in the caregivers of Alzheimer's patients: an experimental investigation in Italy. Am J Alzheimers Dis Other Demen 2004;19(4):248-252.
19. Ritchie K, Lovestone S. The dementias. Lancet 2002;360:1759-1766.
20. Meerding WJ, Bonneux L, Polder JJ, Koopmanschap MA, van der Maas PJ. Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study. BMJ 1998;317: 111-115.

21. Tuokko H, Frerichs R, Graham J, Rockwood K, Kristjansson B, Fisk J, Bergman H, Kozma A, McDowell I. Five-year follow-up of cognitive impairment with no dementia. Arch Neurol 2003;60:577-582.

22. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. Int J Geriatr Psychiatry 2001;16(8):751-761.

23. Burns A, Zaudig M. Mild cognitive impairment in older people. Lancet 2002;360:1963-1965.

24. Petersen RC. Aging, mild cognitive impairment, and Alzheimer's disease. Neurol Clin 2000;18(4):789-806.

25. Shah Y, Tangalos EG, Petersen RC. Mild cognitive impairment: When is it a precursor to Alzheimer's disease? Geriatrics 2000;55:62-68.

26. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition. Washington DC: American Psychiatric Association, 1994.

27. Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, Grobbee DE, Hofman A. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ 1995;310(6985):970-973.

28. Morris JC. Mild cognitive impairment and preclinical Alzheimer's disease. Geriatrics 2005;suppl:9-14.

29. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Research 1975;12:189-198.

30. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992;11:2-13.

31. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115:122-132.

32. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922-935.

33. Murden RA, McRae TD, Kaner S, Bucknam ME. Mini-Mental State exam scores vary with education in blacks and whites. J Am Geriatr Soc 1991;39:149-155.

34. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. BMJ 1994;308(6944):1604-1608.

35. Gussekloo J, de Craen AJ, van Exel E, Bootsma-van der Wiel A, Westendorp RG. [Causes and consequences of cognitive decline in the very elderly; the 'Leiden 85-plus Study']. Ned Tijdschr Geneeskd 2004;148(20):979-983.

36. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, van Duijn CN, van Broeckhoven C, Grobbee DE. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997;349(9046):151-154.

37. Vinkers DJ, Stek ML, van der Mast RC, de Craen AJ, Le Cessie S, Jolles J, Westendorp RG, Gussekloo J. Generalized atherosclerosis, cognitive decline, and depressive symptoms in old age. Neurology 2005;65(1):107-112.

38. De Leeuw FE, De Groot JC, van Gijn J. [Cerebral white matter lesions in the elderly: vascular risk factors and cognitive consequences]. Ned Tijdschr Geneeskd 2001;145(43):2067-2071.

39. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Cerebral white matter lesions and the risk of dementia. Arch Neurol 2004;61(10):1531-1534.

40. Blok WL, Katan MB, van der Meer JW. Modulation of inflammation and cytokine production by dietary (n-3) fatty acids. J Nutr 1996;126(6):1515-1533.

41. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, Launer L, Kuller L, Rubin S, Harris T. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology 2003;61(1):76-80.

42. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, Stijnen T, Hofman A, Witteman JC, Breteler MM. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam Study. Arch Neurol 2004;61(5):668-672.

43. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21(3):383-421.

44. Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nutr 2000;71(2):621S-629S.

45. Jama JW, Launer LJ, Witteman JC, Den Breeijen JH, Breteler MM, Grobbee DE, Hofman A. Dietary antioxidants and cognitive function in a population-based sample of older persons. The Rotterdam Study. Am J Epidemiol 1996;144(3):275-280.

46. La Rue A, Koehler KM, Wayne SJ, Chiulli SJ, Haaland KY, Garry PJ. Nutritional status and cognitive functioning in a normally aging sample: a 6-y reassessment. Am J Clin Nutr 1997;65(1):20-29.

47. Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 2002;287(24):3223-3229.

48. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JC; Cache County Study Group. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004;61(1):82-88.

49. van de Pol LA, Hensel A, Barkhof F, Gertz HJ, Scheltens P, van der Flier WM. Hippocampal atrophy in Alzheimer disease: age matters. Neurology 2006;66(2):236-238.

50. Terry AV Jr, Buccafusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. J Pharmacol Exp Ther 2003;306(3):821-827.

51. Dall'Igna OP, Porciuncula LO, Souza DO, Cunha RA, Lara DR, Dall'Igna OP. Neuroprotection by caffeine and adenosine A2A receptor blockade of beta-amyloid neurotoxicity. Br J Pharmacol 2003;138(7):1207-1209.

52. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocrine Rev 1986;7:284-301.

53. McEwen BS, Sapolsky RM. Stress and cognitive function. Curr Opin Neurobiol 1995;5:205-216.

54. Kalmijn S, Launer LJ, Stolk RP, de Jong FH, Pols HA, Hofman A, Breteler MM, Lamberts SW. A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. J Clin Endocrinol Metab 1998;83:3487-3492.

55. Feskens EJM, Havekes LM, Kalmijn S, De Knijff P, Launer LJ, Kromhout D. Apolipoprotein e4 allelle and cognitive decline in elderly men. BMJ 1994;309:1202-1206.

56. Slooter AJ, Cruts M, Kalmijn S, Hofman A, Breteler MM, van Broeckhoven C, van Duijn CM. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. Arch Neurol 1998;55:964-968.

57. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56(3):303-308.

58. Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research group and Work Groups. European Studies of Dementia. Neurology 1999;52(1):78-84.

59. Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. J Neurol Neurosurg Psychiatry 1999;66(2):177-183.

60. Henderson AS, Easteal S, Jorm AF, Mackinnon AJ, Korten AE, Christensen H, Croft L, Jacomb PA. Apolipoprotein E allele epsilon 4, dementia, and cognitive decline in a population sample. Lancet 1995;346(8987):1387-1390.

61. Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. Gerontology 2000; 46(4):219-227.

62. Breteler MM. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. Neurobiol Aging 2000;21(2):153-160.

63. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000;355:1315-1319.

64. Lautenschlager NT, Almeida OP. Physical activity and cognition in old age. Curr Opin Psychiatry 2006; 19(2):190-193.

65. Ruitenberg A, van Swieten JC, Witteman JC, Mehta KM, van Duijn CM, Hofman A, Breteler MM. Alcohol consumption and risk of dementia: the Rotterdam Study. Lancet 2002;359(9303):281-286.

66. Jarvis MJ. Does caffeine intake enhance absolute levels of cognitive performance? Psychopharmacology (Berl) 1993;110(1-2):45-52.

67. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62(2):275-280.

68. Anderton BH. Ageing of the brain. Mech Agening Dev 2002;123(7):811-817.

69. van 't Hof MA, Burema J. Assessment of bias in the SENECA study. Eur J Clin Nutr 1996;50(2):S4-S8.

70. Iwasaki M, Otani T, Sunaga R, Miyazaki H, Xiao L, Wang N, Yosiaki S, Suzuki S. Social networks and mortality based on the Komo-Ise cohort study in Japan. Int J Epidemiol 2002;31:1208-1218.

71. Johnson NJ, Backlund E, Sorlie PD, Loveless CA. Marital status and mortality: the national longitudinal mortality study. Ann Epidemiol 2000;10(4):224-238.

72. Seeman TE. Social ties and health: the benefits of social integration. Ann Epidemiol 1996;6:442-451.

73. Waldron I, Hughes ME, Brooks TL. Marriage protection and marriage selection-- prospective evidence for reciprocal effects of marital status and health. Soc Sci Med 1996;43:113-123.

74. Helmer C, Damon D, Letenneur L, Fabrigoule C, Barberger-Gateau P, Lafont S, Fuhrer R, Antonucci T, Commenges D, Orgogozo JM, et al. Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology 1999;53:1953-1958.

75. Coyle JT. Use it or lose it—do effortful mental activities protect against dementia? N Engl J Med 2003; 348:2489-2490.

76. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. JAMA 2004;292(12):1447-1453.

77. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003;14(2):125-130.

78. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001;58(3):498-504.

79. Blumenthal JA, Emery CF, Madden DJ, Schniebolk S, Walsh-Riddle M, George LK, McKee DC, Higginbotham MB, Cobb FR, Coleman RE. Long-term effects of exercise on psychological functioning in older men and women. J Gerontol 1991;46(6):P352-P361.

80. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Ambrose AF, Sliwinski M, Buschke H. Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003;348(25):2508-2516.

81. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. JAMA 2002;288:1994-2000.

82. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes. A systematic review. JAMA 2005;294:97-104.

83. Kawachi I, Colditz GA, Stone CB. Does coffee drinking increase the risk of coronary heart disease? Results from a meta-analysis. Br Heart J 1994;72(3):269-275.

84. Tavani A, La Vecchia C. Coffee and cancer: a review of epidemiological studies, 1990-1999. Eur J Cancer Prev 2000;9(4):241-256.

85. Hernán MA, Takkouche B, Caamano-Isorna F, PharmD, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52:276-284.

86. Johnson-Kozlow M, Kritz-Silverstein D, Barrett-Connor E, Morton D. Coffee consumption and cognitive function among older adults. Am j Epidemiol 2002;156(9):842-850.

87. Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002;156(5):445-453.

88. He K, Song Y, Daviglus ML, Liu K, van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation 2004;109(22):2705-2711.

89. He K, Song Y, Daviglus ML, Liu K, van Horn L, Dyer AR, Goldbourt U, Greenland P. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke 2004;35(7):1538-1542.

90. Dik MG, Deeg DJ, Bouter LM, Corder EH, Kok A, Jonker C. Stroke and apolipoprotein E epsilon4 are independent risk factors for cognitive decline: A population-based study. Stroke 2000;31(10):2431-2436.

91. Kase CS, Wolf PA, Kelly-Hayes M, Kannel WB, Beiser A, D'Agostino RB. Intellectual Decline After Stroke. The Framingham Study. Stroke 1998;29:805-812.

92. Solfrizzi V, D'Introno AD, Colacicco AM, Capurso C, Del Parigi A, Capurso S, Gadaleta A, Capurso A, Panza F. Dietary fatty acids intake: possible role in cognitive decline and dementia. Exp Gerontol 2005;40:257-270.

93. Hui JS, Wilson RS, Bennett DA, Bienias JL, Gilley DW, Evans DA. Rate of cognitive decline and mortality in Alzheimer's disease. Neurology 2003;61:1356-1361.

94. Wilson RS, Beckett LA, Bienias JL, Evans DA, Bennett DA. Terminal decline in cognitive function. Neurology 2003;60:1782-1787.

95. Keys A, Aravanis C, Blackburn HW, van Buchem FSP, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl 1966;460:1-392.

Chapter 2

Changes in cognitive functioning among European elderly men during 10 years: age, period and cohort effects. The FINE Study

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Abstract

Objective. Several studies have shown that cognitive functioning decreases with increasing age, but it is not clear whether this decline is the result of age, period or cohort effects. This study describes the influence of aging, period and birth cohort on 10-year cognitive decline in European elderly men.

Methods. Longitudinal data of 1,363 men born between 1900 – 1920 of the Finland, Italy and the Netherlands Elderly (FINE) Study was gathered between 1990 and 2000. Cognitive functioning was measured with the Mini-Mental State Examination (MMSE) (score 0-30), with a higher score indicating better cognitive functioning. Cognition was assessed around 1990 (n=1,363), 1995 (n=546) and 2000 (n=422). Multiple statistical approaches (longitudinal, cross-sectional and times-series) were concurrently used to disentangle age, period and cohort effects. Also, a mixed longitudinal model was used to confirm these results.

Results. Cognitive functioning decreased with 1.5 points during 10 years. This decline was mainly attributable to an age effect; aging of the elderly resulted in cognitive deterioration. A period effect as well as differences in cognitive decline between birth cohorts were also observed, indicating that respondents later in time and of later birth cohorts had a better cognition.

Conclusion. The observed cognitive decline over 10 years is due to an age effect, but also to a period and birth cohort effect.

Introduction

In the European Union, the percentage of persons above age 65 will increase from 15.5 to 24.3% in the period from 2000 to 2030.[1] Worldwide, the average life span is expected to increase with 10 years from 2002 to 2050.[2] In aging populations, the number of people with cognitive impairment will also increase.[3,4] Cognitive impairment is one of the major symptoms of dementia and is an important health problem,[5] for the community as well as for the individual.

Several studies have shown that cognitive functioning decreases with increasing age,[6-9] but it is not clear whether this decline is the result of age, period or cohort effects or a combination of the three or two. If cognitive functioning declines because a person becomes biologically older, an age effect is present. For example, degeneration of the brain and nerve cell loss will lead to cognitive decline.[10] A period effect is present, when cognitive performance of an age group is different in various survey years (because of a difference in calendar time). Period effects are due to (temporary) changes in the environment, such as socio-economic changes.[11] When cognitive functioning is different for persons of the same age but born in another birth cohort, a cohort effect is present. Factors in the first decade of life, such as education or under-nutrition in times of war for example, may influence cognitive functioning. These factors can be different for different birth cohorts.

Both longitudinal and cross-sectional analyses are frequently used for describing cognitive function at different ages.[8,9,12,13] However, it is difficult to disentangle the effects of age, period and birth cohorts by either one of these analyses, because of simultaneous appearance of the effects.[14] It has been shown that both perspectives, together with a times-series analysis, or the use of a mixed longitudinal design (repeated measurements analyses) allows to disentangle the effects of age, period and birth cohort.[11,15-17]

To our knowledge, studies with specific attention to these three influences on change in cognitive functioning over a longer follow-up period are scarce. Such information is important for understanding changes in cognitive functioning over the years and for shedding more light on the aetiology of cognitive decline. Better prediction of decline in cognitive function in a general population is useful for improving diagnosis, treatment interventions and health care planning. We examined by different statistical approaches the influences of age, period and birth cohort effects on 10-year cognitive decline with data of the Finland, Italy and the Netherlands Elderly (FINE) Study.

Methods

Study population

The FINE Study consists of the surviving cohorts of Finland, Italy and the Netherlands of the Seven Countries Study:[18] East Finland, West Finland, Montegiorgio (Italy), Crevalcore (Italy) and Zutphen (The Netherlands). This study started in 1984 among 2285 men born between 1900 - 1920 and repeated examinations of the cohorts were carried out around 1990, 1995 and 2000.[19] From around 1990 onwards information on cognitive functioning was collected for 1363 men, except in 1995 for Finland. Detailed information about the FINE study population has been described elsewhere.[20] In the FINE basic protocol, approval of the Medical Ethical Committee for each participating centre was required and participants have given their informed consent.

Assessment of cognitive function

The Mini-Mental State Examination (MMSE)[21] was used to assess cognitive function and includes questions on orientation to time and place, registration, attention and calculation, recall, language and visual construction. Originally, this screening test was created for clinical use, but now it is extensively used in epidemiological studies and has proven to be a reliable and valid indicator of cognitive impairment and has a good test - retest reliability.[22-24] Although the MMSE is a measure of global cognitive functioning and does not assess different cognitive domains in detail, it is sensitive enough to detect 'clinically significant' global cognitive decline.[25]

The maximum score on the MMSE is 30 points; a higher score indicates better cognitive performance. If a subject did not answer four or more individual items (of a total of 20), the total MMSE score was considered missing.[26] If less than four items were missing, missing items were rated as errors and a total MMSE score was still calculated.[27]

Assessment of demographic variables

Demographic information was obtained with standardised questionnaires. Former occupation was categorised into: employer and employee. Education was assessed as the number of years of education.

Statistical analyses

To investigate the effects of age, period and birth cohort on cognitive decline, we used different statistical approaches to distinguish between the three effects.[28] In longitudinal analyses MMSE scores were compared between the survey years, keeping birth cohort constant. In cross - sectional analyses MMSE scores were compared between different age groups within each survey year (constant period). Third, times - series analyses were used to compare the MMSE scores of

persons with the same age in different survey years (constant age).[16] Consistent findings between two of these analyses and no effect in the third analysis suggest an effect of the variable that was not held constant in the two analyses. E.g. when both longitudinal and cross - sectional analyses are consistent in direction with respect to the age effect (and there is no effect in the times series analyses), this indicates an effect of age on cognitive decline. Consistent effects of period on cognition in the longitudinal and times - series analyses (and no effect in the cross - sectional analyses) suggest an effect of period. An effect of birth cohort is present when the birth cohort effects on cognitive functioning in both the cross - sectional and times - series analyses point into the same direction (and no effect of the longitudinal analyses).[15-17] If all three analyses show an effect, then more than one effect is present.

The data were analyzed using SAS (version 8.2; SAS Institute, Inc., Cary, North Carolina). A two-sided p - value of 0.05 or less was considered to be statistically significant. The MMSE score was entered in the model as a continuous variable. Non - parametric tests (Kruskall - Wallis and Wilcoxon two - sample test) were used for testing statistical differences, because of the skewed distribution of the MMSE scores. The age groups in the times - series analyses were chosen in such a way to exclude overlap of the same respondents between survey years. Times - series analyses for the oldest men who participated in all surveys could not be performed, because of small numbers.

We also applied a mixed longitudinal random coefficient model (SAS Proc Mixed procedure)[29,30] to disentangle the effects of age, period and birth cohort on cognitive decline. The advantage of this procedure is that it takes into account the intra - correlation of measurements performed by the same subject. Moreover, the procedure does not exclude subjects with incomplete data at follow - up (missing MMSE total score). Two models were built: an age - period and an age - birth cohort model. Both models were used to determine the age effect. For this effect, only the most conservative estimates will be shown. Age at examination and age squared, for the best approximation of the relation between age and MMSE score, were entered as continuous variables in the models. Both period (1990, 1995 and 2000) and birth cohort (1900 - 1910, 1911 – 1915 and 1916 - 1920) were entered as class variables in the model. Because of the skewness of the distribution of the MMSE we also performed the analyses after we transformed the MMSE score with the following equation: 'Log ((30 - MMSE) + 2)', which yielded the best approximation of a normal distribution of our data. Analyses with the transformed MMSE showed similar results as analyses with the crude MMSE score. For reasons of simplicity, we only show analyses performed on the crude MMSE scores. In the analyses we additionally adjusted for years of education and country, to examine whether they could explain (part of) the age, period or cohort effects. Because of missing values in these variables, the number of respondents differ between analyses.

Analyses were applied for all the respondents and additionally for the respondents who participated in all three survey years.

Results

Characteristics of the participating respondents during survey 1990, 1995 and 2000 are given in table 2.1. Overall, the MMSE score and the number of years of education was higher in survey 1995 than in survey 1990 and 2000. This is a result of the lower MMSE scores and lower number of years of education for the Finnish respondents, who did not participate in the 1995 survey. Most men were employee.

Table 2.1. *Characteristics of the FINE men born between 1900 - 1920 during the three examinations.*

	Survey 1990 (*n* = 1,363)	**Survey 1995* (*n* = 546)**	**Survey 2000 (*n* = 422)**
Mean age (years)	76.6 (4.5) †	80.5 (4.0)	84.5 (3.5)
Mean MMSE score (0-30)‡	24.5 (4.3)	25.3 (3.7)	24.4 (4.6)
Occupation§ (%)			
Employer	39.5	31.5	36.1
Employee	60.6	68.5	63.9
Education‖ (years)	6.6 (4.4)	8.2 (4.5)	7.1 (4.4)

* Without Finland.
† Standard deviation between parenthesis.
‡ Mean Mini-Mental State Examination (MMSE) score, with 30 indicating the highest cognitive functioning.
§ n = 1,280 FINE men in 1990, 520 in 1995 and 399 in 2000.
‖ n = 1,303 FINE men in 1990, 536 in 1995 and 418 in 2000.

Age effect

According to the longitudinal analyses relating to a period of 10 years for all respondents, the average MMSE scores did not change between survey 1990 (n = 1,363) and 2000 (n = 422) (table 2.2). However, for the FINE respondents who participated in all surveys (n = 422), the average MMSE score significantly decreased from 25.9 to 24.4 points after an increase in age of 10 years. Cross - sectional analyses showed significant differences between the three birth cohorts (1900 - 1910, 1911 - 1915 and 1916 – 1920), with the youngest respondents having a better cognitive performance (table 2.3). This effect was present among all respondents and among the respondents who participated in all three surveys. Thus, the decline in cognitive functioning with

Table 2.2. *Results of longitudinal analyses for men born between 1900 - 1920: changes in cognitive functioning* between survey years, keeping birth cohort constant.*

Measure/ Survey years	**All respondents**		**Respondents who participated in all surveys**	
	n	**mean (SD)**	**n**	**mean (SD)**
Age (years)				
Survey 1990	1,363	76.6 (4.5)	422	74.9 (3.6)
Survey 2000	422	84.5 (3.5)	422	84.5 (3.5)
MMSE (score 0-30)				
Survey 1990	1,363	24.5 (4.3)	422	25.9 (3.0)
Survey 2000	422	24.4 (4.6)	422	24.4 (4.6)
P - value†		.80		< .01

Abbreviation: SD, standard deviation.
* Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning.
† Tested with Wilcoxon test.

Table 2.3. *Results of cross-sectional analyses for men born between 1900 - 1920: changes in cognitive functioning* between birth cohorts in each survey year, keeping period constant.*

	Birth cohort (year of birth)						
	1916 - 1920		**1911 - 1915**		**1900 - 1910**		***P* - value†**
	n	**mean (SD)**	**n**	**mean (SD)**	**n**	**mean (SD)**	
All respondents							
Survey 1990	519	26.0 (3.1)	491	24.6 (4.0)	353	22.3 (5.2)	< .01
Survey 2000	230	25.6 (3.5)	147	23.4 (5.0)	45	21.7 (6.2)	< .01
Respondents in all survey years							
Survey 1990	230	26.5 (2.6)	147	25.4 (2.9)	45	24.2 (4.2)	< .01
Survey 2000	230	25.6 (3.5)	147	23.4 (5.0)	45	21.7 (6.2)	< .01

Abbreviation: SD, standard deviation.
* Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning.
† Tested with Wilcoxon test.

increasing age in the longitudinal analyses was confirmed by cross - sectional analyses, suggesting an age effect.

Repeated measurements analyses with the mixed longitudinal model confirmed the age effect (table 2.4). The age effect influenced the MMSE score with (0.96 * (age at examination) – 0.0068 *

(age at examination)^2). This means that the MMSE score for 90 year old men is 2.6 points lower than for 70 year old men.

After adjusting for country, the results found with the mixed longitudinal model remained similar. After adjusting for years of education, the effects became smaller but remained statistically significant.

Table 2.4. *Results of repeated measurement analyses for all male respondents who participated since survey 1990: changes in cognitive functioning* in terms of age, period and birth cohort effects.*

Effect	FINE men (*n* = 1,303)	
	Coefficient	***P* - value**
Age†		
Age	0.96	< .01
Age*age‡	-0.68	< .01
Period§		
Survey 1990	-1.67	< .01
Survey 1995	-0.67	< .01
Survey 2000	0	-
Birth cohort effect§		
1900-1910	-1.99	< .01
1911-1915	-0.94	< .01
1916-1920	0	-

* Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning.
† Adjusted for birth cohort, years of education and country.
‡ Coefficient $\times 10^{-2}$.
§ Adjusted for age and age^2, years of education and country.

Period effect

Longitudinal analyses showed a lower MMSE score with increasing age in survey 2000 than in survey 1990 for the participants who participated in all surveys (table 2.2). Age matched comparisons in the times - series analyses showed that the respondents of both age - groups (80 - 84 and 85 - 89 years) had a significant higher cognitive performance during survey 2000 than their counterparts in the same age groups during survey 1990 (table 2.5). Thus, the results of the longitudinal and times - series analyses showed period effects in opposite directions. This indicates that a period effect might be present, but the direction of the effect is not clear. However, repeated

measurement analyses showed higher MMSE scores in later surveys than in earlier surveys, suggesting a period effect (table 2.4). Participants in survey 2000 had a 1.67 points higher MMSE score than participants in survey 1990.

Table 2.5. *Results of times-series analyses for all men aged 80 - 89 during survey 1990 or 2000: comparison of cognitive functioning* during survey 1990 and 2000 for men aged 80 - 84 and men aged 85 - 89, keeping age constant.*

Age group (in each survey year)	**Survey years**		
	Survey 1990	**Survey 2000**	***P* - value†**
80 - 84 years			
N	262	236	
Mean (SD)	22.6 (5.0)	25.5 (3.6)	< .01
85 - 89 years			
N	81	144	
Mean (SD)	21.5 (5.4)	23.4 (5.1)	< .01

Abbreviation: SD, standard deviation.
* Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning.
† Tested with Wilcoxon test.

Birth cohort effect

Better cognitive performance of the later born FINE participants in the cross - sectional analyses (table 2.3) is confirmed by better cognitive performance of later born participants in the times - series analyses (table 2.5). Both results suggest a cohort effect with a better cognitive performance for participants born in a later birth cohort.

This effect was confirmed by the repeated measurements analyses, which showed that men born between 1900 - 1910 had a 1.99 lower MMSE score than men born between 1916 - 1920 (table 2.4).

Discussion

This longitudinal European study of elderly men showed that cognitive decline can be explained by an age effect, a period effect and a birth cohort effect.

Age effect

Aging of the population resulted in worse cognitive functioning. We expected cognitive function to deteriorate, because of aging of the human mind. The effect of biological aging on cognition can be explained by the degeneration of the brain, i.e. the formation of neurofibrillary tangles, senile plaques and neuronal cell loss are involved in Alzheimer disease, more than in normal brain aging.[10,31,32] This can eventually result in dementia. While interpreting the effect of aging, selective dropout due to death or non - response has to be taken into account. Over half of the participating men disappeared during 10-years of follow-up. The participating respondents were the healthiest ones. They were younger, had had more years of education and higher cognitive test scores at baseline than the men who dropped out. In the longitudinal analyses with all respondents, survey 2000 comprised a 'healthy' selection of survey 1990. In these analyses no decline in cognitive function could be discerned over the years. To reduce a possible selection effect, we also performed analyses with only participants who completed all surveys. The longitudinal analyses with only survivors showed a decline in cognitive function, which was confirmed by the repeated measurements analyses. Because these subjects were a relatively healthy subset, the observed cognitive decline will probably be an underestimation of the decline in the general population.
Previous longitudinal as well as cross - sectional studies also pointed to an age effect. In the study of Brayne et al., the mean MMSE score declined 1.3 points over 28 months in a population aged 75 years and above.[33] Izaks et al. found an even larger decrease of four points on the MMSE over three years in a population aged 85 years and above.[34] However, Jacqmin-Gadda et al. and Unger et al. both found a very slight cognitive decline among healthy persons of respectively 65 and 50 years of age and older.[9,12] These studies suggest that the decline increased with increasing age, as also observed in our study.

Period effect

Longitudinal and times - series analyses showed period effects in opposite directions. The repeated measurement analyses showed that cognitive function was better in later survey years. Differences in the results can be a consequence of different methods of analyses. In the repeated measurement analyses, we were able to adjust for the age effect (age and age squared), while no age adjustment took place in the longitudinal analysis. So the negative effect in the longitudinal analysis can be explained by the period effect being overruled by a larger aging effect. Also, the repeated measurement procedure includes complete as well as incomplete data. Respondents who died or did not respond at follow - up were also included in the analyses. On the other hand, part of the period effect in the repeated measurements analyses may be explained by a birth cohort effect, for which we could not adjust.

If cognitive functioning would actually be better in later survey years as was suggested in the repeated measurement analyses, this could also be explained by interindividual components of variation, such as situational, environmental or methodological factors. The same standardised cognitive test was translated for each country and used to assess cognitive function among all respondents in all survey years. It is unlikely that small differences in the questionnaire versions, the staff, the administrative procedure and the place of examination (hospital, health centre, at home) have influenced the observed differences in cognitive functioning between the surveys in the same way in all countries. Furthermore, a learning effect may have caused better cognitive performance in later survey years. Finally, it is possible that the elderly in our study were stimulated by the increased complexity of the society and all new technologies, resulting in a better cognitive performance at later points in time.

Other studies showed better cognitive performance later in time as well, which can point towards a period or birth cohort effect or both. Freedman et al. observed that older persons into their 80s, appeared to have better cognitive functioning around 2000 than in the early 1990s.[35] The authors stated that this could be a result of improvement in physical activity accompanied by improvement in cognitive functioning or of a learning effect. Ball et al. showed that cognitive training could still improve cognitive performance in old age.[36]

Birth cohort effect

The observed decline in cognitive functioning can also partly be explained by differences between birth cohorts. Longitudinal, cross - sectional and repeated measurements analyses showed that respondents of earlier birth cohorts had a worse cognitive functioning than respondents of later birth cohorts, irrespective of age. This can be due to differences in the history of each birth cohort. Better living conditions and lifestyles, longer education and better physical health might contribute to the results. Also neonatal influences such as differences in nutrition (breast - feeding vs. bottle - feeding vs. improved bottle - feeding),[37] as well as nutrition later in life[38,39] and improvement in health care may have caused the differences among birth cohorts. Other studies also suggested that later cohorts performed better than earlier cohorts of the same age. In Sweden, the 70 years old persons born in 1906 - 1907 had a significant worse cognitive functioning than the 70 years old persons born in 1922.[40] But this can also be a result of a period effect.

Analyses regarding the age, period and birth cohort effect for each country separate could not be performed because of small numbers per country. To avoid potential influences of the different countries on our analyses, we adjusted for country in all analyses.

Conclusion

Cognitive decline in European elderly men can be explained by an age effect, as well as by a period and birth cohort effect. Cognitive function decreases by increasing age and elderly who were born and lived at a later date had a better cognitive function compared to those who were born and lived earlier. This information increases our understanding of the aetiology of cognitive decline, and is of use for treatment interventions and health care planning. Not only internal influences like aging of the brain can result in cognitive decline, but also external influences like a child's or an elderly's environment. This emphasizes the importance of an optimal and stimulating environment next to biological processes for maintaining a normal cognition.

References

1. Kinsella KVV. An Aging World: 2001. Census Bureau, Washington DC: U.S. Government Printing Office, 2001; Series P95/01-1.
2. United Nations. Report of the Second World Assembly on Aging. Madrid, Spain: United Nations, April 8-12, 2002.
3. Small GW. What we need to know about age related memory loss. BMJ 2002;324(7352):1502-1505.
4. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. Neurology 1998;51(3):728-733.
5. Braekhus A, Laake K, Engedal K. A low, 'normal' score on the Mini-Mental State Examination predicts development of dementia after three years. J Am Geriatr Soc 1995;43(6):656-661.
6. Breteler MM, Claus JJ, van Duijn CM, Launer LJ, Hofman A. Epidemiology of Alzheimer's disease. Epidemiol Rev 1992;14:59-82.
7. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. Am J Epidemiol 1998;147(6):574-580.
8. Korten AE, Henderson AS, Christensen H, Jorm AF, Rodgers B, Jacomb P, Mackinnon AJ. A prospective study of cognitive function in the elderly. Psychol Med 1997;27(4):919-930.
9. Jacqmin-Gadda H, Fabrigoule C, Commenges D, Dartigues JF. A 5-year longitudinal study of the Mini-Mental State Examination in normal aging. Am J Epidemiol 1997;145(6):498-506.
10. Anderton BH. Ageing of the brain. Mech Ageing Dev 2002;123(7):811-817.
11. van 't Hof MA, Burema J. Assessment of bias in the SENECA study. Eur J Clin Nutr 1996;50(2):S4-S8.
12. Unger JM, van Belle G, Heyman A. Cross-sectional versus longitudinal estimates of cognitive change in nondemented older people: a CERAD study. Consortium to Establish a Registry for Alzheimer's Disease. J Am Geriatr Soc 1999;47(5):559-563.
13. Sliwinski M, Buschke H. Cross-sectional and longitudinal relationships among age, cognition, and processing speed. Psychol Aging 1999;14(1):18-33.
14. Kemper HC. [Roaming through methodology. XXVII. Problems with longitudinal studies: confounding of the relationship between age, time of measurement and birth cohort]. Ned Tijdschr Geneeskd 2000; 144(47):2247-2251.
15. Tijhuis MA, De Jong-Gierveld J, Feskens EJ, Kromhout D. Changes in and factors related to loneliness in older men. The Zutphen Elderly Study. Age Ageing 1999;28(5):491-495.
16. Bijnen FC, Feskens EJ, Caspersen CJ, Mosterd WL, Kromhout D. Age, period, and cohort effects on physical activity among elderly men during 10 years of follow-up: the Zutphen Elderly Study. J Gerontol A Biol Sci Med Sci 1998;53(3):M235-M241.
17. Hoeymans N, Feskens EJ, van den Bos GA, Kromhout D. Age, time, and cohort effects on functional status and self-rated health in elderly men. Am J Public Health 1997;87(10):1620-1625.
18. Keys A, Aravanis C, Blackburn HW, van Buchem FS, Buzina R, Djordjevic BD, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl 1966;460:1-392.
19. Huijbregts PP, Feskens EJ, Rasanen L, Alberti-Fidanza A, Mutanen M, Fidanza F, Kromhout D. Dietary intake in five ageing cohorts of men in Finland, Italy and The Netherlands. Eur J Clin Nutr 1995;49(11):852-860.
20. Bijnen FC, Feskens EJ, Caspersen CJ, Giampaoli S, Nissinen AM, Menotti A, Mosterd WL, Kormhout D. Physical activity and cardiovascular risk factors among elderly men in Finland, Italy, and the Netherlands. Am J Epidemiol 1996;143:553-561.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician . J Psychiatr Res 1975;12(3):189-198.
22. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992; 11(1):2-13.

23. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115(2):122-132.

24. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40(9):922-935.

25. Lyketsos CG, Garrett E, Liang KY, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. Am J Epidemiol 1999;149(9):794-800.

26. Fillenbaum GG, George LK, Blazer DG. Scoring nonresponse on the Mini-Mental State Examination. Psychol Med 1988;18(4):1021-1025.

27. Kalmijn S, Feskens EJ, Launer LJ, Stijnen T, Kromhout D. Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. Diabetologia 1995;38(9):1096-1102.

28. Elahi VK, Elahi D, Andres R, Tobin JD, Butler MG, Norris AH. A longitudinal study of nutritional intake in men. J Gerontol 1983;38(2):162-180.

29. Anderssen N, Jacobs DR Jr, Sidney S, Bild DE, Sternfeld B, Slattery ML, Hannan P. Change and secular trends in physical activity patterns in young adults: a seven-year longitudinal follow-up in the Coronary Artery Risk Development in Young Adults Study (CARDIA). Am J Epidemiol 1996; 143(4):351-62.

30. Weijenberg MP, Feskens EJ, Kromhout D. Age-related changes in total and high-density-lipoprotein cholesterol in elderly Dutch men. Am J Public Health 1996;86(6):798-803.

31. Dimakopoulos AC, Mayer RJ. Aspects of neurodegeneration in the canine brain. J Nutr 2002; 132(6):1579S-1582S.

32. Scahill RI, Schott JM, Stevens JM, Rossor MN, Fox NC. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc Natl Acad Sci USA 2002; 99(7):4703-4707.

33. Brayne C, Gill C, Paykel ES, Huppert F, O'Connor DW. Cognitive decline in an elderly population--a two wave study of change. Psychol Med 1995;25(4):673-683.

34. Izaks GJ, Gussekloo J, Dermout KM, Heeren TJ, Ligthart GJ. Three-year follow-up of Mini-Mental State Examination score in community residents aged 85 and over. Psychol Med 1995;25(4):841-848.

35. Freedman VA, Aykan H, Martin LG. Aggregate changes in severe cognitive impairment among older Americans: 1993 and 1998. J Gerontol B Psychol Sci Soc Sci 2001;56(2):S100-S111.

36. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 2002;288:2271-2281.

37. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. Am J Clin Nutr 1999;70(4):525-535.

38. Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42(5):776-782.

39. Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 2002;287(24):3223-3229.

40. Steen G, Berg S, Steen B. Cognitive function in 70-year-old men and women. A 16-year cohort difference population study. Aging (Milano) 1998;10(2):120-126.

Chapter 3

Marital status and living situation during a 5-year period are associated with a subsequent 10-year cognitive decline in older men: the FINE Study

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Abstract

Objective. This study investigates the association between marital status and living situation (over five years) on 10-year subsequent cognitive decline.

Methods. The study population consisted of 1,042 men aged 70-89 years in 1990, who participated in the longitudinal Finland, Italy and the Netherlands Elderly (known as FINE) Study. Cognition was measured by using the Mini-Mental State Examination, and marital status (married versus unmarried) and living situation (living with others versus living alone) were assessed with a standardised questionnaire. Repeated measurement analyses were done and adjustments were made for age, education, country, smoking, alcohol, chronic diseases, marital status or living situation and baseline cognition.

Results. Men who were married or who lived with others in both 1985 and 1990 had the smallest subsequent 10-year cognitive decline. Men who lost a partner and men who were unmarried both years had a two times stronger cognitive decline compared with men who were married both years. Men who started to live alone had a cognitive decline that was two times as strong and men who lived alone in both years even had a cognitive decline that was three and a half times as strong, as that of men who lived with others in both examination years.

Conclusion. Men who are still married or who still live with others after five years have a smaller subsequent cognitive decline than those who do not.

Introduction

Previous studies have shown that marital status, living situation and preservation of a social network are related to health status and mortality.[1-5] One such study showed that participation in social and leisure activities was associated with a lower risk of dementia,[6] which suggests that this lower risk may be due to cognitive stimulation. Furthermore, other studies showed that having few social contacts and a poor social network is associated with a higher risk for cognitive decline and dementia.[7-10]

Research is now focusing on marital status as well as living situation in relation to cognitive functioning. Two longitudinal studies focusing on marital status showed that men and women who were married were at decreased risk for dementia and Alzheimer's disease compared with widowed, divorced, separated or never married men and women. [8,11] Two other studies focusing on living situation showed that men and women who lived alone were at an increased risk for dementia compared with persons who lived with others (with spouse, children, others or in a nursing home).[8,12]

Some possible explanations for the protective effect of being married or living with someone in relation to cognitive decline could be proposed. For example, the cognitive stimulation of a partner or other person may protect the brain from deterioration. Furthermore, the loss of a partner could cause changes in lifestyle (such as changes in smoking, drinking and dietary habits) or even stress and depression. Especially among men, the loss of a partner is associated with more distress and a higher risk for depression,[13] which could cause adverse health effects, including cognitive decline. Therefore, we selected men for the present study.

A drawback of previous studies on social status and cognitive functioning is that marital status or living situation was measured only once in time and not repeatedly during a longer period. Especially in old age, this is important, because social situations change frequently. Furthermore, most previous studies focused on dementia and Alzheimer's disease and not on cognitive decline.

We investigated the associations between types of marital status (married versus unmarried) as well as types of living situation (lived with others versus lived alone) over a period of five years in relation to subsequent 10-year cognitive decline among 1,042 elderly men in Finland, Italy and the Netherlands.

Methods

Study population

The Finland, Italy and the Netherlands Elderly (FINE) Study is a longitudinal study that consists of the surviving men of the Finnish, Italian and Dutch cohorts of the Seven Countries Study.[14] In

1985, at baseline, 2,285 men between 65 and 84 years of age participated (response rate varied between 74% and 94%). In 1990, there were 1,734 men still alive, of whom 1,416 participated in the 1990 survey (response rates in the three countries varied between 77% and 88%). Detailed information on this study population can be found elsewhere.[15] Approval of the Medical Ethics Committee in the different countries was obtained for each participating centre and participants gave their informed consent.

Health surveys were carried out once every five years since 1985. Information on cognitive functioning was available for 1,363 of the 1,416 men examined in 1990. Information about marital status and living situation was collected in both 1985 and 1990 and was available for respectively 1,310 and 1,270 of the 1,363 men. Because low cognitive functioning at baseline may cause a change in marital status or living situation in stead of being a consequence, we excluded men who lived in an institution at baseline (because of their poor health status) and those who were severely cognitively impaired (men with a Mini-Mental State Examination (MMSE) score below 18.[16] Complete information on cognition, possible confounding factors in 1990 and marital status was available for 1,042 men and for living situation for 1,014 men.

Transition in marital status and living situation

Information on marital status and living situation was obtained by using standardised questionnaires. Marital status was categorised into two categories: being married and being unmarried, which also included being separated, divorced and widowed. To analyze transition in marital status, participants were classified according to their marital status in respectively 1985 and 1990: married-married (n=782), married-unmarried (n=98), unmarried-unmarried (n=150) and unmarried-married (n=12). Because of the small number of men in the last category, we excluded these men from the analyses.

Living situation was divided into living alone and living with others, that is, with spouse, with spouse and children, with family or with others. Transition in living situation was defined according to the living situation in 1985 and 1990: living with others-living with others (n=822), living with others-living alone (n=94), living alone-living alone (n=88) and living alone-living with others (n=10). Because of the small number of men, we excluded the last category from the analyses.

Cognitive functioning

Trained researchers assessed overall cognitive functioning during the 1990, 1995 and 2000 surveys with the MMSE.[17] However, information on cognitive functioning was not collected in Finland during the 1995 survey. The MMSE includes questions on orientation to time and place, registration, attention and calculation, recall, language and visual construction. The MMSE is developed as a screening instrument to assess the severity of cognitive impairment and cognitive

changes over time.[18] Originally, this test was created for clinical use,[17] but it is now used extensively in epidemiologic studies.[19] Furthermore, the MMSE has good test-retest reliability; because of its high sensitivity and specificity, it is a valid indicator for normal and impaired cognitive functioning.[20] Although the MMSE is a measure of global cognitive functioning and does not assess different cognitive domains in detail, it is sensitive enough to detect 'clinically significant' global cognitive decline.[21]

The maximum score on the MMSE is 30 points and a higher score indicates better cognitive functioning. If a subject did not answer four or more individual items (of a total of 20), the total MMSE score was considered to be missing (n=9). If fewer than four items were lacking, these missing items were rated as zero and a total MMSE score was still calculated.[22]

Other variables

During all examinations, researchers collected information on demographic, lifestyle and other variables by using standardised questionnaires;[14] physicians and nurses obtained medical information during physical examinations. Education was assessed as the number of years of formal education. Smoking status was categorised into never, former and current smoking and alcohol consumption into consumers and non-consumers. At the end of the physical examination, a physician measured systolic and diastolic blood pressure with a random-zero sphygmomanometer with the participant in a supine position. Information about the use of anti-hypertensive drugs was obtained with a questionnaire. Because of this elderly population, hypertension was defined as having a systolic blood pressure of 160 mmHg or greater, having a diastolic blood pressure of 95 mmHg or greater, or using anti-hypertensive medication.[23] Information on the prevalence of myocardial infarction, stroke, diabetes and cancer was obtained by questionnaire and checked with information from hospital registries or general practitioners (yes or no). Depressive symptoms were assessed by using the Self-rating Depression Scale (SDS) developed by Zung.[24] The score range on the SDS is from 25 to 100 and a higher score indicates having more depressive symptoms. A value of at least 50 was used to indicate the presence of depressive symptoms (yes or no). Functional status was measured with an Activities of Daily Living (ADL) questionnaire and categorised in: not disabled, disabled in Instrumental Activities of Daily Living (IADL) only, disabled in IADL and mobility and disabled in all domains.[25] Physical activity was assessed with a validated self-administered questionnaire, which was originally designed for retired man and was divided into four categories: low active, medium-low active, medium-high active and high active.[26]

Statistical analyses

To test whether characteristics in 1985 of non-participants or of men with missing values in 1990 differed from the participating men in 1990, the Wilcoxon test was used. We also calculated the Spearman correlation coefficient between the variables marital status and living situation in 1990.

Marital status, living situation and cognitive functioning

Differences in characteristics between the three categories of marital status and living situation in 1990 were tested with the Kruskall-Wallis and Chi-square tests. Multiple linear regression analyses were performed to obtain adjusted mean 1990 MMSE scores per marital status or living situation category. In all analyses, adjustments were made for potential confounding factors. These factors will be described at the end of the statistical analyses section.

To investigate the independent effect of marital status as well as living situation on subsequent 10-year cognitive decline, mixed longitudinal random coefficient models (SAS Proc Mixed procedure) were used. These models take into account the intra-correlation of measurements (in 1990, 1995 and 2000) performed by the same person and does not exclude persons with incomplete data at follow-up. To investigate whether 10-year cognitive decline differed between the marital status or living situation categories, the product of these categories with time was included in the model. Cognitive decline (in number of points with 95% confidence interval (CI)) for the reference group married-married (or living with others-living with others) and *additional* cognitive decline (compared with the decline of the reference group) for the other categories were given as output.

To investigate whether marital status or living situation is a stronger predictor for cognitive decline, we performed stratified analyses. Because the number of participants in some stratified groups was very small, we did only two stratified analyses. We used a general linear model to investigate whether 10 - year cognitive decline differed among men who were married and men who were not married, but who both lived with others. In the same way, we investigated whether cognitive functioning differed among men who lived with others or who lived alone, but who both were unmarried.

Potential confounding factors

In all analyses, adjustments were made for the following well-known confounding factors: age (continuous), education (continuous), country (categorical), smoking status (categorical) and alcohol consumption (categorical).[27-29] Because disease status could influence cognitive functioning, we also adjusted for the prevalence of myocardial infarction (categorical), stroke (categorical), diabetes (categorical) and cancer (categorical). To investigate whether the effect of marital status was independent of the living situation of the men, we adjusted for living situation (categorical) in the analyses regarding marital status. We did similar analyses for living situation. In

the longitudinal analyses, we also adjusted for baseline cognitive functioning (continuous), because baseline cognitive functioning may influence cognitive decline. Additionally, we adjusted for hypertension (categorical) as a risk factor for cognitive decline and possible intermediates like physical activity (categorical), depression (categorical) and functional status (categorical). Finally, we additionally excluded participants who, in 1990, had a MMSE score below 24, which indicates impaired cognition (n=234).[20] Two-sided p-values of .05 or less were considered to be statistically significant.

Results

Men who were not included in the present study (because of non-response or missing values) were older (in 1990, mean age of 79 years versus 76 years, p<0.001), had lower education (5 years versus 7 years, p<0.001), and were more likely to have a history of stroke (13% versus 5%, p<0.001) compared with men who participated in the present study. In 1985, almost 77% of the non-participants in 1990 were married and 88% lived with others, whereas among participants these percentages were 84% and 90%. In 1990, 76% of the participants were married and 82% lived with others. The correlation coefficient between the variables marital status and living situation was 0.74.

Marital status, living situation and cognitive functioning

Men who were married in both 1985 and 1990 were the youngest (75.7 years old) and men who lost a partner were the oldest (77.5 years) (p<0.001, table 3.1). Married men had the highest average baseline cognitive test score (25.8 points) and men who were unmarried the lowest (25.2 points) (p=0.01). The percentage of men with depressive symptoms was the highest among men who lost a partner (18%) compared with married and unmarried men (8% and 6%, respectively) (p=0.001). Married men and men who lost a partner both spent 717 minutes per week on physical activities and unmarried men spent 570 minutes per week (p = 0.04). The percentage of men with a history of myocardial infarction was highest for unmarried and married men (respectively 13% and 14%) and lowest for men who lost a partner (5%) (p=0.06). Married and unmarried men were most often of Dutch origin and men who lost a partner were most often of Italian origin (p=0.01).
Cognitive functioning in 1990 did not differ for the three categories of marital status, after multiple adjustments (figure 3.1). Men who were married in both 1985 and 1990 had a subsequent 10-year cognitive decline of 1.1 points (95% confidence interval (CI): [0.9;1.4]), after adjustment for age, education, country, smoking, alcohol consumption, prevalence of myocardial infarction, stroke, diabetes and cancer, living situation and baseline cognitive functioning. Those who were married

Table 3.1. *Characteristics of 1,030 Finnish, Dutch and Italian men in 1990 according to their marital status in 1985 and 1990.*

	Marital status in 1985 and 1990, respectively			P-value
Characteristics in 1990	**Married-married (n=782)**	**Married-unmarried (n=98)**	**Unmarried-unmarried (n=150)**	
Mean age (years)	75.7 (4.1)	77.5 (4.6)	77.1 (4.4)	<.001
Years of education	7.3 (4.5)	6.9 (4.1)	6.6 (4.2)	.23
Cognitive functioning in 1990 (unadjusted)*	25.8 (2.7)	25.4 (2.7)	25.2 (2.5)	.01
Cognitive impairment in 1990 (%)†	22	27	23	.48
Depressive symptoms (%)‡	8	18	6	.001
Disabilities (%)§				.93
Not disabled	54	53	49	
Disabled in IADL only	31	31	34	
Disabled in mobility and IADL only	10	9	12	
Disabled in all domains	5	6	5	
Physical activity (min/wk)‖	717 (721)	717 (855)	570 (591)	.04
Current smoker (%)	17	17	21	.44
Alcohol consumer (%)	77	83	83	.12
Prevalence in 1990 (%):				
Hypertension	57	57	60	.75
Myocardial infarction¶	14	5	13	.06
Diabetes	9	13	9	.34
Stroke	5	6	5	.80
Cancer	9	9	11	.80
Country (%):				.01
Finnish men	25	21	34	
Dutch men	46	38	36	
Italian men	29	41	30	

Values are means (standard deviation) or percentages.
* Cognitive functioning was measured with the Mini-Mental State Examination (MMSE: range 0-30).
† MMSE below 24.
‡ Depressive feelings were measured with the Self-rating Depression Scale (SDS: range 25-100), developed by Zung. A value of at least 50 was used to indicate the presence of depressive symptoms. Numbers for the three groups are 731, 95, 141, respectively.
§ The presence of disabilities. IADL refers to (Instrumental) Activities of Daily Living. Numbers for the three groups are respectively 757, 96, 147.
‖ Numbers for the three groups are 767, 98, 146, respectively.
¶ Hypertension was defined as a systolic blood pressure of 160 mmHg or greater or a diastolic blood pressure of 95 mmHg or greater or using anti-hypertensive medication.

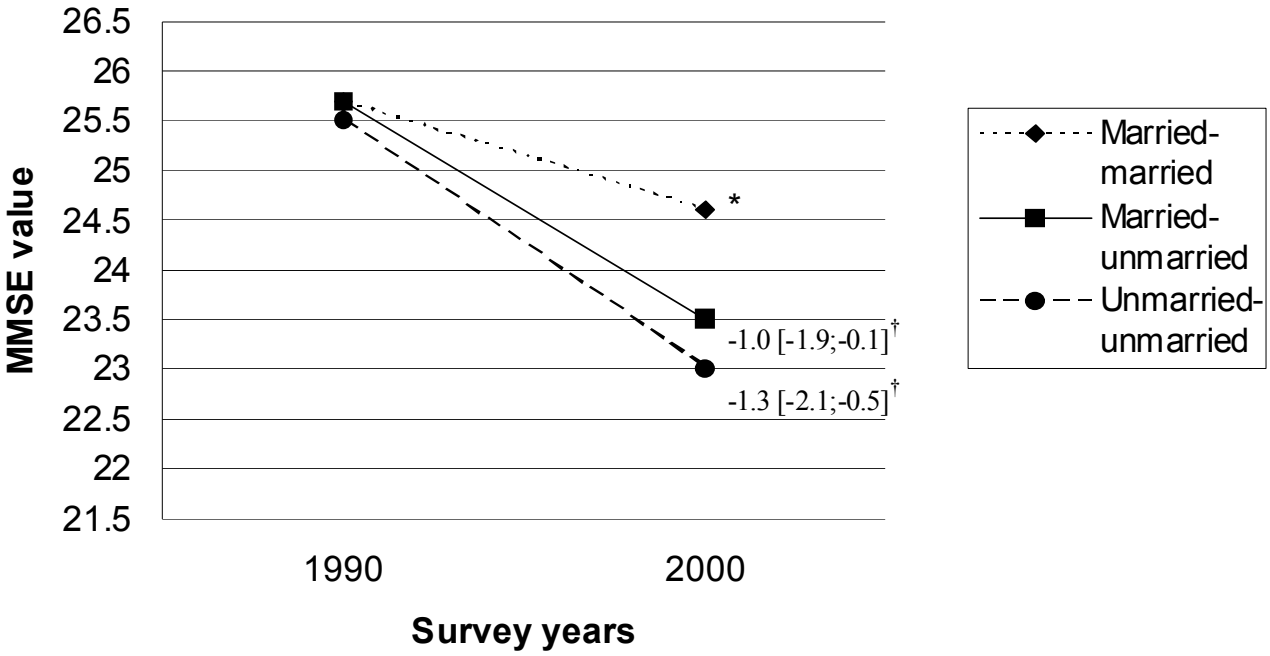

Figure 3.1. *Transition in marital status between 1985 and 1990 with subsequent 10-year cognitive decline for 1,030 Finnish, Dutch and Italian men.*

Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning.
Adjustments were made for age, education, country, smoking, alcohol consumption, prevalence of myocardial infarction, stroke, diabetes and cancer, and living situation in 1990. For analyses regarding *change* in cognitive functioning adjustments for baseline cognitive functioning were made.
* 10-year cognitive decline of the reference group of men who were married-married was 1.1 points (95% CI: [0.9;1.4]).
† *Additional* cognitive decline and 95% CI between brackets compared with reference group.

in 1985 and unmarried in 1990 had a 10-year *additional* decline of 1.0 point (95% CI: [0.1;1.9]), and those who were unmarried both years had an *additional* decline of 1.3 points (95% CI: [0.5;2.1]) compared with those who were married in both years. Additional adjustments for hypertension, physical activity, depression and functional limitations did not alter our results.

Men who lived with others in both 1985 and 1990 were the youngest (75.8 years old) and men who lived with others in 1985 and alone in 1990 were the oldest (77.7 years) ($p<0.001$, table 3.2). Sixteen percent of the men who started to live alone showed depressive symptoms versus 8% and 7% for men who lived with others and men who lived alone, respectively ($p = 0.05$). Men who lived with others were most physically active (716 minutes per week) and men who lived alone were less active (555 minutes per week, $p=0.06$). The highest percentage of alcohol consumers was among

Table 3.2. *Characteristics of 1,004 Finnish, Dutch and Italian men in 1990 according to their living situation in 1985 and 1990.*

	Living situation in 1985 and 1990, respectively			P-value
Characteristics in 1990	**Lived with others-lived with others (n=822)**	**Lived with others-lived alone (n=94)**	**Lived alone-lived alone (n=88)**	
Mean age (years)	75.8 (4.1)	77.7 (4.6)	77.1 (4.6)	<.001
Years of education	7.2 (4.4)	7.5 (4.2)	6.4 (4.1)	.26
Cognitive functioning in 1990 (unadjusted)*	25.7 (2.7)	25.5 (2.7)	25.3 (2.5)	.13
Cognitive impairment in 1990 (%)†	22	23	27	.78
Depressive symptoms (%)‡	8	16	7	.05
Disabilities (%)§				.49
Not disabled	53	53	58	
Disabled in IADL only	32	28	28	
Disabled in mobility and IADL only	10	13	13	
Disabled in all domains	6	5	1	
Physical activity (min/wk)‖	716 (720)	659 (783)	555 (604)	.06
Current smoker (%)	17	16	22	.54
Alcohol consumer (%)	76	86	85	.02
Prevalence in 1990 (%):				
Hypertension¶	57	57	49	.36
Myocardial infarction	14	7	10	.18
Diabetes	9	14	3	.05
Stroke	5	6	6	.66
Cancer	9	12	8	.66
Country (%):				<.001
Finnish men	24	30	44	
Dutch men	46	43	41	
Italian men	30	28	15	

Values are means (standard deviation) or percentages.
* Cognitive functioning was measured with the Mini-Mental State Examination (MMSE: range 0-30).
† MMSE below 24.
‡ Depressive feelings were measured with the Self-rating Depression Scale (SDS: range 25-100) developed by Zung. A value of at least 50 was used to indicate the presence of depressive symptoms. Numbers for the three groups are 769, 90, 83, respectively.
§The presence of disabilities. IADL refers to (Instrumental) Activities of Daily Living. Numbers for the three groups are 796, 92, 86, respectively.
‖Numbers for the three groups are 807, 94, 84, respectively.
¶ Hypertension was defined as a systolic blood pressure of 160 mmHg or greater or a diastolic blood pressure of 95 mmHg or greater or using anti-hypertensive medication.

men who started to live alone and those who lived alone (respectively 86% and 85%), and the lowest percentage among men who lived with others (76%, p=0.02). Fourteen percent of the men who started to live alone had a history of diabetes and 3% of the men who already lived alone had such a history (p=0.05). Most men who lived with others and who started to live alone were of Dutch origin and most men who already lived alone were of Finnish origin (p<0.001).

Cognitive functioning in 1990 did not differ for the three categories of living situation, after multivariate adjustments (figure 3.2). Men who lived with others in both 1985 and 1990 had a 10-year cognitive decline of 1.1 points (95% CI: [0.8;1.4]), after adjustment for age, education, country, smoking, alcohol consumption, prevalence of myocardial infarction, stroke, diabetes and

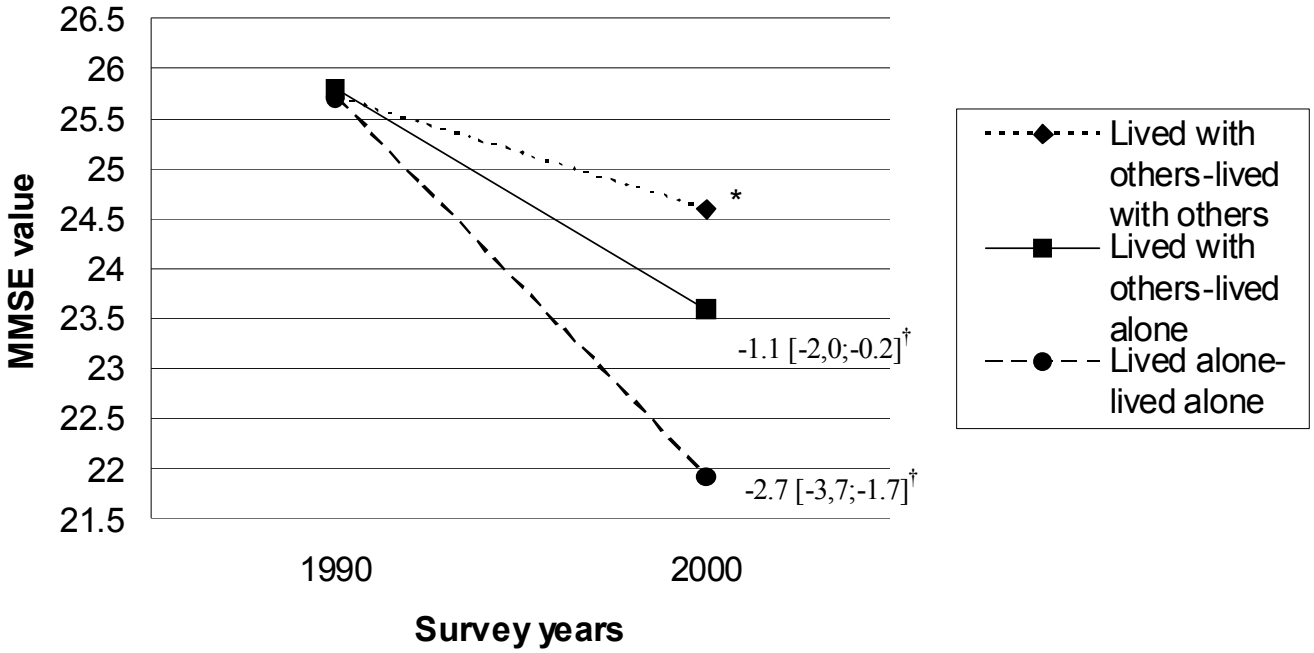

Figure 3.2. *Transition in living situation between 1985 and 1990 with subsequent 10-year cognitive decline for 1,004 Finnish, Dutch and Italian men.*

Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning.
Adjusted were made for age, education, country, smoking, alcohol consumption, myocardial infarction, stroke, diabetes and cancer, and marital status in 1990. For analyses regarding *change* in cognitive functioning adjustments for baseline cognitive functioning were made.
* 10-year cognitive decline of the reference group of men who lived with others-lived with others was 1.1 points (95%CI: [0.8;1.4]).
† *Additional* cognitive decline and 95% CI between brackets compared with reference group.

cancer, marital status and baseline cognition. Those who lived with others in 1985 and alone in 1990 had an *additional* decline of 1.1 points (95% CI: [0.2;2.0]), and those who lived alone in both years had an *additional* decline of 2.7 points (95% CI: [1.7;3.7]) compared with those who lived with others both years. Additional adjustments for hypertension, physical activity, depression and functional limitations did not alter our results. Furthermore, the exclusion of men with impaired cognitive functioning (MMSE below 24) in 1990 did not change the results.

Stratified analysis among men who lived with others showed that those who were unmarried (n=61) had a two times stronger cognitive decline than those who were married (n=753); however, this difference was non-significant (p = 0.14). Among men who were not married, cognitive decline did not differ for those who lived with others (n=61) and those who lived alone (n=170, p=0.91). These results suggest that marital status may be a stronger predictor than living situation for cognitive decline.

Discussion

In this follow-up study of elderly men, those who were married or who lived with others in both 1985 and 1990 had the smallest subsequent 10-year cognitive decline. Men who lost a partner and men who were unmarried in both years had a two times stronger decline than men who were married in both years. Men who started to live alone had a cognitive decline that was two times as strong and men who lived alone in both years even had a cognitive decline that was three and a half times as strong, as that of men who lived with others in both examination years.

A major strength of this study is its prospective design, with a 15-year follow-up and repeated measurements. In addition, adjustments could be made for numerous important confounding factors. The study has also limitations. Selection bias caused by non-response or missing values could have influenced our results. Overall, non-participants were older, had fewer years of education, had a higher prevalence of stroke and were more often unmarried than were men who participated in the present study. Therefore, the strength of the relationships observed in the present study may have been underestimated. Furthermore, response rates in 1985, 1990, 1995 and 2000 were high and varied between 65% and 94%. To deal with the possible selection caused by the drop-out, a mixed longitudinal random coefficient model was used, which does not exclude participants with incomplete data on cognitive functioning at follow-up. We also repeated the analyses among survivors with complete data (until 2000). These analyses confirmed the results found among all men. Therefore, selection bias caused by incomplete data on cognitive functioning at follow-up has not influenced our results.

The MMSE was used to assess global cognitive functioning. Although this is a screening test, the MMSE is a reliable and valid indicator of cognitive impairment, with a good test-retest reliability and often used in epidemiologic studies.[18-20] A limitation of the MMSE is that it measures global cognitive functioning and does not assess specific cognitive domains in detail. Therefore, we recommend that future studies include a more extensive cognitive test battery and focus on specific cognitive domains, such as memory, concentration, attention, learning, language and visual construction.

Because of differences in the percentages of Finnish, Dutch and Italian men in each category of marital status and living situation, it is of interest to know if the observed relationships differ from country to country. However, the number of participants in the different categories for each country was too low for meaningful analyses; therefore, analyses stratified by country could not be performed. However, an adjustment for country in the multivariate analyses did not change the results, suggesting that the findings were the same for each country.

To our knowledge, no other longitudinal study has investigated the effect of marital status and living situation over a 5-year period on subsequent cognitive decline. Most studies have focused on an association between baseline marital status and living situation with cognition. The PAQUID study found that initially non-demented elderly persons who were never married were at a higher risk of dementia or Alzheimer's disease than were married persons.[11] Another study showed that participants who lived alone were diagnosed with dementia at an earlier stage than were participants who did not live alone.[12] The Kungsholmen project showed that unmarried participants who lived alone and who had no friends were at a higher risk of developing dementia.[8] This study also showed that socially or mentally stimulating activities may protect against dementia.[9] Furthermore, our finding that marital status may be a stronger predictor than living situation for cognitive decline confirms the results of the Kungsholmen project, which also suggests that being single (not married) is associated with a higher risk for dementia than is living alone.[8,30]

Several possible underlying mechanisms could explain our findings. Unmarried men or men who lived alone in 1985 and 1990 could have had less social support and cognitive stimulation than married men or men with a housemate. According to the 'use-it-or-lose-it' hypothesis, this may have resulted in a stronger cognitive decline.[31] This hypothesis states that participation in mentally stimulating activities may increase neuronal growth and maintenance and thereby protect the brain from neuronal degeneration and subsequent cognitive decline. Although this hypothesis is speculative, animal research supports it.[32] One study showed that cognitive training resulted in less cognitive decline in older persons without dementia.[33] Other epidemiological studies have also shown that participation in mentally stimulating activities or leisure activities lowers the risk of dementia and Alzheimer's disease.[34,35] However, a Swedish study showed that participation in leisure activities was not protective against dementia and Alzheimer's disease among men.[36]

Because marital status may be a stronger predictor than living situation for cognitive decline, cognitive stimulation or social support from a partner could be more protective against cognitive decline than interaction with or social support from other persons. It may also be the satisfaction of the affiliation with a partner that protects against cognitive decline.

Furthermore, losing a partner, being unmarried, starting to live alone and living alone may cause adverse health effects like stress and depressive symptoms, which lead to an increase in cortisol production. High cortisol levels are implicated in hippocampal damage, the part of the brain where memory is located, and may thereby result in memory deficits.[37-39] Adjustment for depressive symptoms did not affect our results, though. Finally, after the loss of a partner or after a person started to live alone, the person's lifestyle could change, such as a reduction in physical activity or an alteration in alcohol drinking and smoking habits. These lifestyle changes may have an adverse effect on cognitive functioning.[29,40] However, adjustments for these lifestyle factors did not alter our results.

The Kungsholmen Project already suggested that an extensive social network protects against dementia.[8] Probably, an extensive social network is related to marital status and living situation. Therefore, the results of the present study could also be a result of an extensive social network of the participants in stead of their marital status or living situation. Unfortunately, there was no information about social networks available in the present study, so it was unable to investigate this possibility.

In old age, transitions in marital status and living situation as well as cognitive decline are very common. The results of the present study support the hypothesis that having a partner or living together with others is associated with a smaller cognitive decline. This knowledge may have important implications for public health programs aimed at healthy aging. We should stimulate elderly men to be around other people and not to be alone. Furthermore, caretakers should be aware of the fact that elderly men who are unmarried or who live alone carry a higher risk of cognitive decline.

References

1. Johnson NJ, Backlund E, Sorlie PD, Loveless CA. Marital status and mortality: the national longitudinal mortality study. Ann Epidemiol 2000;10:224-238.
2. Waldron I, Hughes ME, Brooks TL. Marriage protection and marriage selection--prospective evidence for reciprocal effects of marital status and health. Soc Sci Med 1996;43:113-123.
3. Iwasaki M, Otani T, Sunaga R, Miyazaki H, Xiao L, Wang N, Yosiaki S, Suzuki S. Social networks and mortality based on the Komo-Ise cohort study in Japan. Int J Epidemiol 2002;31:1208-1218.
4. House JS, Landis KR, Umberson D. Social relationships and health. Science 1988;241:540-545.
5. Seeman TE. Social ties and health: the benefits of social integration. Ann Epidemiol 1996;6: 442-451.
6. Fabrigoule C, Letenneur L, Dartigues JF, Zarrouk M, Commenges D, Barberger-Gateau P. Social and leisure activities and risk of dementia: a prospective longitudinal study. J Am Geriatr Soc 1995;43:583-584.
7. Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. Ann Intern Med 1999;131:165-173.
8. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000;355:1315-1319.
9. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol 2002;155:1081-1087.
10. Zunzunegui MV, Alvarado BE, Del Ser T, Otero O. Social networks, social integration, and social engagement determine cognitive decline in community-dwelling Spanish older adults. J Gerontol B Psychol Sci Soc Sci 2003;58:S93-S100.
11. Helmer C, Damon D, Letenneur L, Fabrigoule C, Barberger-Gateau P, Lafont S, Fuhrer R, Antonucci T, Commenges D, Orgogozo JM, et al. Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology 1999;53:1953-1958.
12. Sibley A, MacKnight C, Rockwood K, Fisk J, Gauthier S, Guzman DA, Hogan DB; Consortium to Investigate Vascular Impairment of Cognition. The effect of the living situation on the severity of dementia at diagnosis. Dement Geriatr Cogn Disord 2002;13:40-45.
13. Lee GR, DeMaris A, Bavin S, Sullivan R. Gender differences in the depressive effect of widowhood in later life. J Gerontol B Psychol Sci Soc Sci 2001;56B:S56-S61.
14. Keys A, Aravanis C, Blackburn HW, van Buchem FS, Buzina R, Djordjevic BD, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl 1966;460:1-392.
15. Bijnen FC, Feskens EJ, Caspersen CJ, Giampaoli S, Nissinen AM, Menotti A, Mosterd WL, Kormhout D. Physical activity and cardiovascular risk factors among elderly men in Finland, Italy, and the Netherlands. Am J Epidemiol 1996;143:553-561.
16. Murden RA, McRae TD, Kaner S, Bucknam ME. Mini-Mental State exam scores vary with education in blacks and whites. J Am Geriatr Soc 1991;39:149-155.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
18. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922-935.
19. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992;11:2-13.
20. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115:122-132.
21. Lyketsos CG, Garrett E, Liang KY, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. Am J Epidemiol 1999;149:794-800.

22. Fillenbaum GG, George LK, Blazer DG. Scoring nonresponse on the Mini-Mental State Examination. Psychol Med 1988;18:1021-1025.

23. Guidelines Sub-committee. Guidelines for the management of mild hypertension. Memorandum from a World Health Organization/International Society of Hypertension meeting. J Hypertens 1993;11:905-918.

24. Zung WW. A Self-rating Depression Scale. Arch Gen Psychiatry 1965;12:63-70.

25. Hoeymans N, Feskens EJ, van den Bos GA, Kromhout D. Measuring functional status: cross-sectional and longitudinal associations between performance and self-report (Zutphen Elderly Study 1990-1993). J Clin Epidemiol 1996;49:1103-1110.

26. Caspersen CJ, Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol 1991;133:1078-1092.

27. Hofman A, Rocca WA, Brayne C, Breteler MM, Clarke M, Cooper B, Copeland JR, Dartigues JF, da Silva Droux A, Hagnell O, et al. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Eurodem Prevalence Research Group. Int J Epidemiol 1991;20:736-748.

28. Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, et al. Rates and risk factors for dementia and Alzheimer's disease. Results from EURODEM pooled analyses. Neurology 1999;52:78-84.

29. Kalmijn S, van Boxtel MP, Verschuren MW, Jolles J, Launer LJ. Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age. Am J Epidemiol 2002;156:936-944.

30. Berkman LF. Which influences cognitive function: living alone or being alone? Lancet 2000;355:1291-1292.

31. Coyle JT. Use it or lose it--do effortful mental activities protect against dementia? N Engl J Med 2003;348:2489-2490.

32. Lucassen PJ, van Someren EJ, Swaab DF. [Are active neurons a better defense against aging in Alzheimer's disease?] Tijdschr Gerontol Geriatr 1998;29:177-184.

33. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 2002;288:2271-2281.

34. Wilson RS, Mendes de Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002;287: 742-748.

35. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Ambrose AF, Sliwinski M, Buschke H. Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003;348:2508-2516.

36. Crowe M, Andel R, Pedersen NL, Johansson B, Gatz M. Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins. J Gerontol B Psychol Sci Soc Sci 2003;58B:249-255.

37. McEwen BS, Sapolsky RM. Stress and cognitive function. Curr Opin Neurobiol 1995;5:205-216.

38. Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. Soc Sci Med 2000;51:843-857.

39. Kalmijn S, Launer LJ, Stolk RP, de Jong FH, Pols HA, Hofman A, Breteler MM, Lamberts SW. A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. J Clin Endocrinol Metab 1998;83:3487-3492.

40. van Gelder BM, Tijhuis MAR, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Physical activity in relation to cognitive decline in elderly men: the FINE Study. Neurology 2004;63:2316-2321.

Chapter 4

Physical activity in relation to cognitive decline in elderly men: the FINE Study

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Abstract

Objective. Physical activity may be associated with better cognition. This study investigates whether *change* in duration and intensity of physical activity is associated with 10-year cognitive decline in elderly men.

Methods. Data of 295 healthy survivors, born between 1900-1920, from the Finland, Italy and the Netherlands Elderly (FINE) Study were used. From 1990 onward, physical activity was measured with a validated questionnaire for retired men and cognitive functioning with the Mini-Mental State Examination (maximum score 30 points).

Results. The rates of cognitive decline did not differ among men with a high or low duration of activity at baseline. However, a decrease in activity duration of more than 60 minutes per day over 10 years resulted in a decline of 1.7 points ($p<0.0001$). This decline was 2.6 times stronger than the decline of men who maintained their activity duration ($p=0.06$). Men in the lowest intensity quartile at baseline had a 1.8 ($p=0.07$) to 3.5 ($p=0.004$) times stronger 10-year cognitive decline than those in the other quartiles. A decrease in intensity of physical activity of at least half a standard deviation was associated with a 3.6 times stronger decline than maintaining the level of intensity ($p=0.003$).

Conclusion. Even in old age, participation in activities with at least a medium-low intensity may postpone cognitive decline. Moreover, a decrease in duration or intensity of physical activity results in a stronger cognitive decline than maintaining duration or intensity.

Introduction

Physical activity has a beneficial effect on risk factors for cardiovascular diseases and thereby improves cerebral blood flow and reduces risk of stroke, which may subsequently diminish the risk of dementia and cognitive decline.[1] In addition, physical activity may directly stimulate neurogenesis in the hippocampus, providing cognitive reserves against decline.[2-4]

Several cross-sectional and intervention studies and a few longitudinal studies have investigated the effect of physical activity on the risk of cognitive decline and dementia, but the results are inconsistent. Some studies reported that increased levels of physical activity are (moderately) associated with better cognitive functions.[5-9] Other studies showed a weak or no relationship between physical activity and cognitive functioning.[10,11] The results of previous studies are difficult to compare owing to different and frequently global operationalisations of both physical activity and cognition. In most studies, detailed information about the duration and the intensity of physical activity was lacking. Therefore, it is not yet clear whether duration and intensity of physical activity are independently related to cognitive decline. Moreover, not only does cognitive functioning decrease with increasing age, physical activity behaviour changes with age. Generally, participation in physical activities decreases and activities will be performed at a lower pace at increasing age. We sought to investigate the independent association of duration and intensity of physical activity at baseline with 10-year cognitive decline in elderly men. We also studied the effect of 10-year *change* in duration and intensity of physical activity on 10-year *change* in cognitive functioning. Data collected in the Finland, Italy and the Netherlands Elderly (FINE) Study were used.

Methods

Study population

The FINE Study consists of the surviving cohorts of the Seven Countries Study:[12] East Finland, West Finland, Zutphen, the Netherlands, Montegiorgio, Italy, and Crevalcore, Italy. This study started in 1984 among 2,285 men born between 1900 and 1920; follow-up examinations of the cohorts were carried out around 1990, 1995 and 2000. In 1990, 1,416 Finnish, Dutch and Italian men were still alive and participated in the survey. Complete baseline information on cognitive functioning, physical activity and possible confounders was available for 1,149 of these men in 1990 and 384 survivors in 2000. Of those survivors, 295 were classified as healthy (without myocardial infarction, stroke, diabetes or cancer and with Mini-Mental State Examination (MMSE) score of 18 or above in 1990 (not severely cognitively impaired)).[13,14] We hypothesized that among healthy participants, the contribution of physical activity would be strongest because their

cardiovascular system is generally fitter than that of participants with a chronic disease. For this reason, analyses were performed on healthy participants only. In 2000, information on cognition was available for all 295 healthy Dutch, Finnish and Italian men. Information on physical activity was available in 2000 for Dutch and Italian men only. The data collected in the FINE Study population have been described in detail elsewhere.[15]

Approval of the medical ethics committee in the different countries was obtained for each participating centre. Participants have given their written informed consent.

Assessment of physical activity

Physical activity was assessed each survey round in the Netherlands and Italy and only in 1990 in Finland. A validated self-administered questionnaire, originally designed for retired men, was used[16]. The questionnaire consisted of questions on the frequency, duration and pace of walking and bicycling during the previous week, the average amount of time spent weekly on hobbies and gardening (in both summer and winter), and the average amount of time spent monthly on odd jobs and sports. The kinds of odd jobs, sports and hobbies were assessed as well. In both the Finnish and the Italian questionnaire, questions about the average amount of time spent weekly on farming or forestry (for Finland only) in both summer and winter were added. Estimated times were converted into minutes per week. All types of activity of an intensity of more than 2 kilocalories/kilogram•hour (e.g., fishing and billiards), reflecting multiples of resting oxygen consumption, were summed to obtain total weekly duration of physical activities.[15] Participants with more than two activities missing were excluded from the analyses (n=53). If one or two activities were missing, the duration and intensity of this activity were assumed to be zero. Total daily duration of physical activity in 1990 and 2000 was calculated and categorised into four groups: ≤ 30, 31 to 60, 61 to 120, and > 120 minutes per day.

A mean intensity score for each participant was calculated as follows: For each person, the intensity code of each activity reported was multiplied by its duration; these values were summed and divided by the total time spent by that individual on all activities to yield a mean intensity score. Mean intensity scores were classified in quartiles based on the mean intensity in 1990. Activities in the lowest quartile are, for example, playing billiards and walking at lower pace than 3 miles per hour (converted to the Ainsworth compendium of physical activities).[17] Activities in the second quartile are playing volleyball and walking at about 3 miles per hour. Activities in the third quartile are, for example, gymnastics and walking at about 3.3 miles per hour. Activities in the highest quartile are swimming and walking at more than 3.5 miles per hour.

Change in duration of physical activities between 1990 and 2000 was categorised as follows: Increased duration was defined as an increase of more than 60 minutes per day (half a standard

deviation), decreased duration equalled a decrease of more than 60 minutes per day, and stable duration was defined as no change or a maximal change of 60 minutes per day.

Change in mean intensity of physical activity between 1990 and 2000 was divided into the following categories: Increased intensity was defined as an increase in intensity of more than 0.8 point (half a standard deviation, which corresponds, e.g., to the difference between playing volleyball and swimming or with a change in walking velocity of 0.5 miles per hour), decreased intensity was classified as a decrease in intensity of more than 0.8 point, and stable intensity was defined as no change or a maximal change of 0.8 point.

Assessment of cognitive function

The MMSE was used to assess cognitive function and includes questions on orientation to time and place, registration, attention and calculation, recall, language and visual construction.[18] Originally, this screening test was created for clinical use, but now it is extensively used in epidemiological studies, has proven to be a reliable and valid indicator of cognitive impairment and has a good test-retest reliability.[13,19,20]

The maximum score on the MMSE is 30 points; a higher score indicates better cognitive performance. If a subject did not answer 4 or more individual items (of a total of 20), the total MMSE score was considered missing (n=4). If less than four items were missing, missing items were rated as errors and a total MMSE score was still calculated.[21]

Assessment of other variables

Demographic, lifestyle and other information was obtained with standardised questionnaires. Education was assessed as the number of years of education. Smoking status was categorised into never, former and current smoking. Alcohol consumption and participation in mental activities (like puzzling) were both categorised into yes/no. Height and weight were measured while men were wearing light clothing and no shoes. Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). Information about the history of myocardial infarction, stroke, diabetes and cancer was collected by standardised questionnaires and validated by hospital registries. Functional status was registered with a self-administered questionnaire, which measures activities of daily living (ADL)[22], and depressive symptoms were assessed with a Self-rating Depression Scale[23]. Information on the use of antihypertensive drugs was collected by a standardised questionnaire, and serum high-density lipoproteins (HDL) cholesterol, serum total cholesterol and blood pressure were determined in standardised laboratories[15].

Statistical analyses

Differences in baseline characteristics between countries were tested using Kruskal-Wallis tests for not normally distributed continuous variables. Categorical data were tested for differences with Chi-square tests. Adjusted differences in baseline cognitive functioning were tested with multivariate linear regression analysis.

The association between physical activity duration and intensity at baseline and 10-year cognitive decline was assessed with multivariate linear regression analysis. The association between 10-year *change* in physical activity duration and intensity with 10-year cognitive decline was assessed with multivariate linear regression analysis in the Netherlands and Italy only. Categories of (*change* in) duration and intensity of physical activity were entered as class variables in the model and the outcome cognitive decline (MMSE 2000 - MMSE 1990) as a continuous outcome variable. We adjusted for the following confounders: age, education, country, alcohol consumption, smoking status, mental activities, and alternately for physical activity intensity or duration. Additional adjustments were made for ADL, depression, BMI, use of antihypertensive drugs, HDL, total cholesterol, blood pressure and baseline cognitive functioning. We also examined whether an interaction was present between duration and intensity of physical activity by adding the product term of these variables to the model.

All statistical analyses were carried out using SAS software (version 8.2; SAS Institute, Inc., Cary, NC). A two-sided p-value of ≤ 0.05 was considered to be significant.

Results

Healthy Italian survivors were older than the Finnish and Dutch survivors (table 4.1). The number of years spent on education as well as cognitive functioning were highest for the Dutch men. Cognitive functioning decreased between 1990 and 2000 for all men. In 1990, Italian men were most physically active. Finnish participants spent most of their time on walking, Dutch men on bicycling and Italian men on gardening. Mean duration of physical activity decreased for both Dutch and Italian men between 1990 and 2000. Mean intensity spent on physical activities did not differ between the countries and decreased between 1990 and 2000. The percentage of men who consumed alcohol or who smoked cigarettes decreased between 1990 and 2000 as well. Average BMI was stable.

Men who did not participate in our study (n=854) were men who did not survive till 2000, who gave incomplete answers or who were unhealthy in 1990. These men were overall older ($p<0.001$), had worse cognitive functioning in 1990 ($p<0.001$), spent less time on physical activities per day

Table 4.1. *Characteristics in 1990 of the 295 healthy participating Finnish, Dutch and Italian male survivors (without myocardial infarction, stroke, diabetes or cancer, and with MMSE score of 18 or above), born between 1900 and 1920.*

	295 Healthy participating survivors			
Characteristic	**Finnish men, n = 46**	**Dutch men, n = 118**	**Italian men, n = 131**	**p Value for difference**
Mean age (years)	73.6 (3.6)	74.2 (3.6)	76.0 (3.2)	<0.001
Mean MMSE score	26.6 (2.9)	27.1 (1.9)	25.2 (2.7)	<0.001
Education (years)	4.6 (2.6)	11.1 (4.2)	5.0 (2.6)	<0.001
Physical activity				
Mean duration (min/wk)	880.8 (796.2)	667.5 (469.3)	991.9 (974.7)	0.19
Type, % of total time				
Walking	34	23	20	0.02
Bicycling	13	30	11	<0.001
Sports	1	5	2	<0.001
Odd jobs	3	12	5	<0.001
Gardening	8	19	35	0.002
Hobbies	16	11	1	<0.001
Farming	24	-	27	<0.001
Mean intensity* (kcal/kg-h)	3.7 (0.8)	3.7 (0.8)	3.7 (1.1)	0.80
Alcohol users (%)	87	84	82	0.77
Current smokers (%)	2	15	16	0.04
BMI (kg/m^2)	26.5 (2.7)	25.8 (2.6)	26.2 (3.7)	0.41

Abbreviations: MMSE, Mini-Mental State Examination; BMI, body mass index.
Values are adjusted means (standard deviation) or percentages.
* Mean intensity weighted for the time spent on the activities.

(p<0.001), performed activities with a lower intensity (p<0.001), drank less alcohol (p<0.01) and more often smoked (p<0.05) than the men who did participate in our study.

Baseline duration of physical activity

Among 295 healthy Finnish, Dutch and Italian survivors, cognitive functioning in 1990 did not differ among the four baseline duration of activity groups, after adjustment for intensity and confounders (figure 4.1). In addition, the rates of the 10-year cognitive decline of the activity groups were also not significantly different (see figure 4.1).

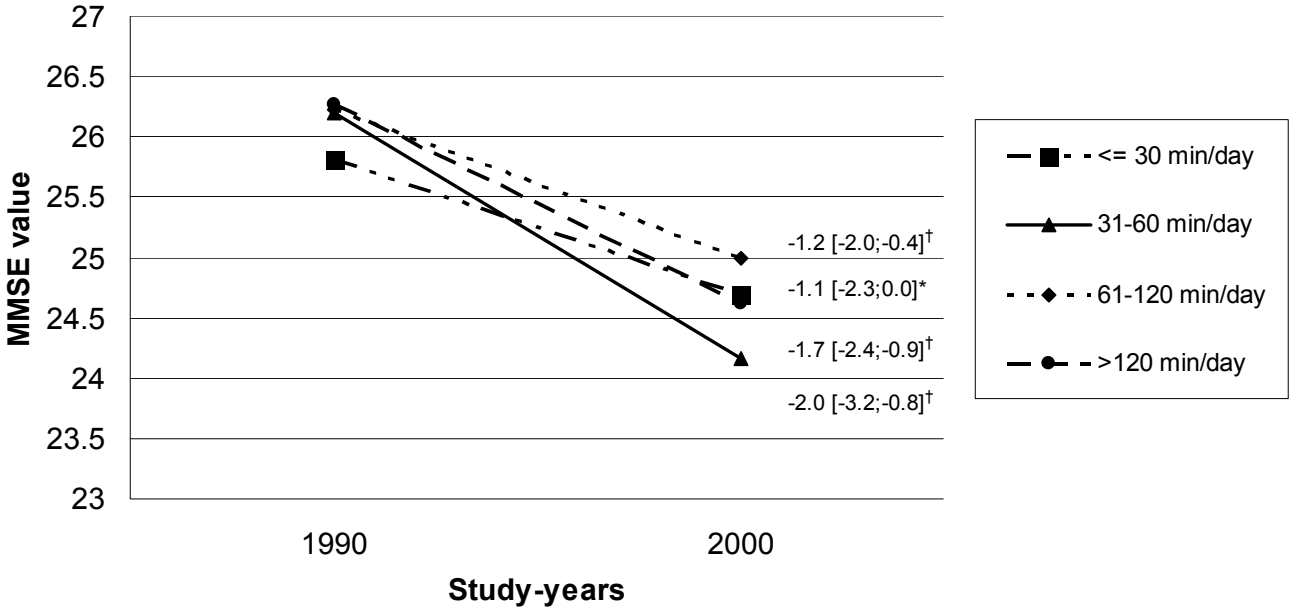

Figure 4.1. *Ten-year cognitive decline per category of baseline duration of physical activity for healthy Finnish, Dutch and Italian survivors.*

Mean *change* in cognitive functioning between 1990 and 2000 [95% CI]. Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning. Adjustments were made for age, education, smoking status, alcohol consumption, country, mental activities and intensity.
* Reference group
† Not significant different from reference group (p≥0.3)

Baseline intensity of physical activity

There were no differences in baseline cognitive functioning among the four quartiles for baseline intensity of activity in 1990, adjusted for duration and confounders (see figure 4.2). Men in the lowest intensity quartile at baseline showed the strongest 10-year cognitive decline of 2.7 points. This decline was 1.8 (p=0.07) to 3.5 (p=0.004) times stronger than the decline among the other quartiles (see figure 4.2).

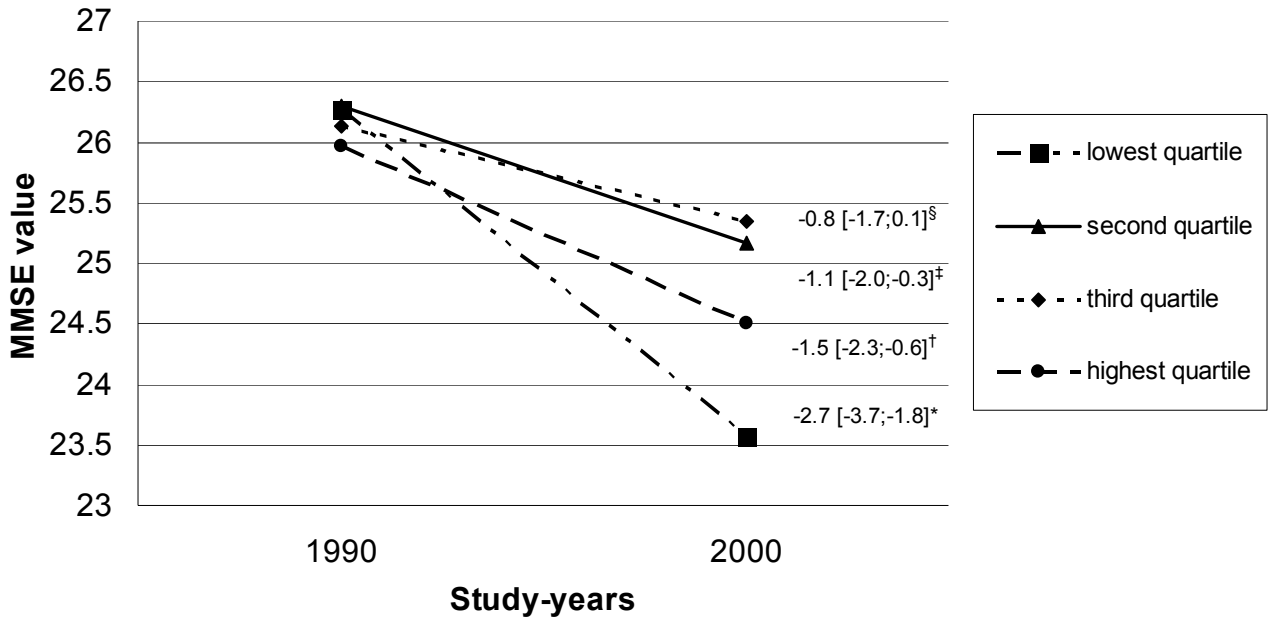

Figure 4.2. *Ten-year cognitive decline per quartile of baseline intensity of physical activity for healthy Finnish, Dutch and Italian survivors.*

Mean *change* in cognitive functioning between 1990 and 2000 [95% CI]. Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning. Adjustments were made for age, education, smoking status, alcohol consumption, country, mental activities and duration.
* Reference group
† Borderline significant different from reference group (p=0.07)
‡ Significant different from reference group (p=0.02)
§ Significant different from reference group (p=0.004)

Ten-year *change* in duration of physical activity

Among the 243 healthy Dutch and Italian survivors for whom information was present on *change* in physical activity, there were no differences in MMSE scores in 1990 among the groups for *change* in activity duration after adjustment for intensity and confounders (figure 4.3). However, cognitive decline was strongest (1.7 points) for those whose duration of activity decreased more than 60 minutes per day (half a standard deviation) during 10 years. This decline was 2.6 times stronger than for those whose duration of activity remained stable (p=0.06) (see figure 4.3). There was no cognitive decline among men who increased their duration of activity. The relationship between *change* in duration of physical activity and cognitive decline showed a linear trend (p=0.02).

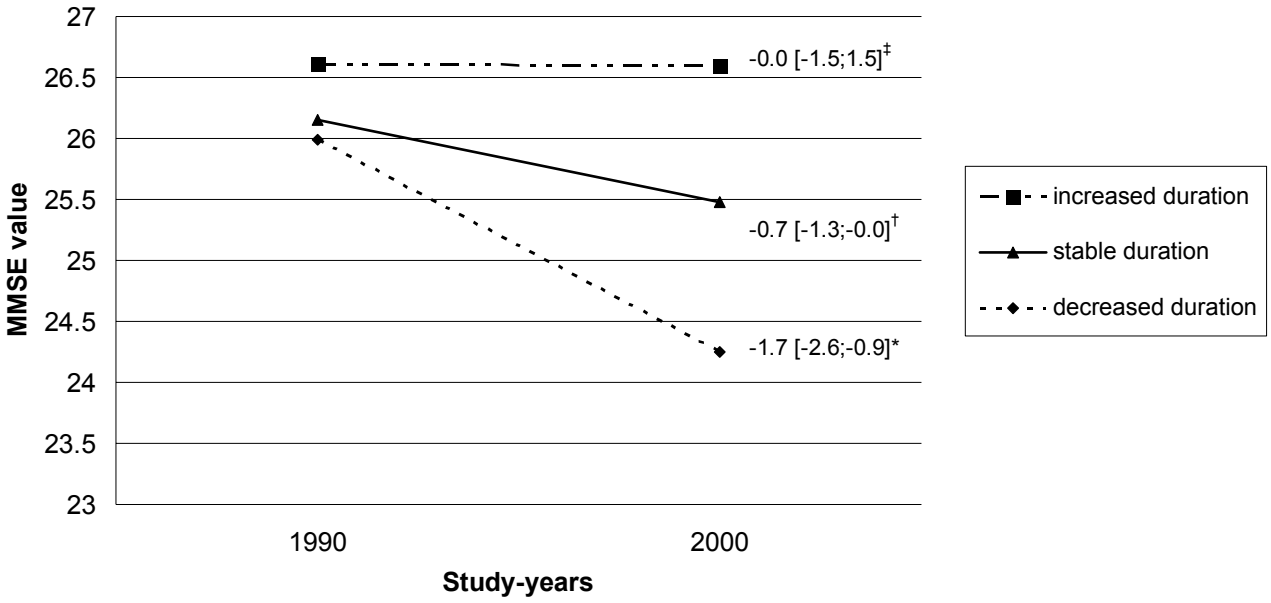

Figure 4.3. *Ten-year cognitive decline per category of 10-year change in duration of physical activity for healthy Dutch and Italian survivors.*

Mean *change* in cognitive functioning between 1990 and 2000 [95% CI]. Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning. Adjustments were made for age, education, smoking status, alcohol consumption, country, mental activities, intensity and baseline duration.
* Reference group
† Borderline significant different from reference group (p=0.06)
‡ Significant different from reference group (p=0.05)

Ten-year *change* in intensity of physical activity

Cognitive functioning in 1990 did not differ among the *change* in activity intensity groups, after adjustment for duration and confounders (see figure 4.4). However, men whose intensity of activity decreased more than half a standard deviation (0.8 point) during 10 years had the strongest cognitive decline of 2.3 points (see figure 4.4). This decline was 3.6 times stronger than the decline of men whose intensity remained stable (p=0.003). There was no cognitive decline in the increased intensity group. A linear trend (p=0.002) was present for the relation between *change* in intensity and cognitive decline.

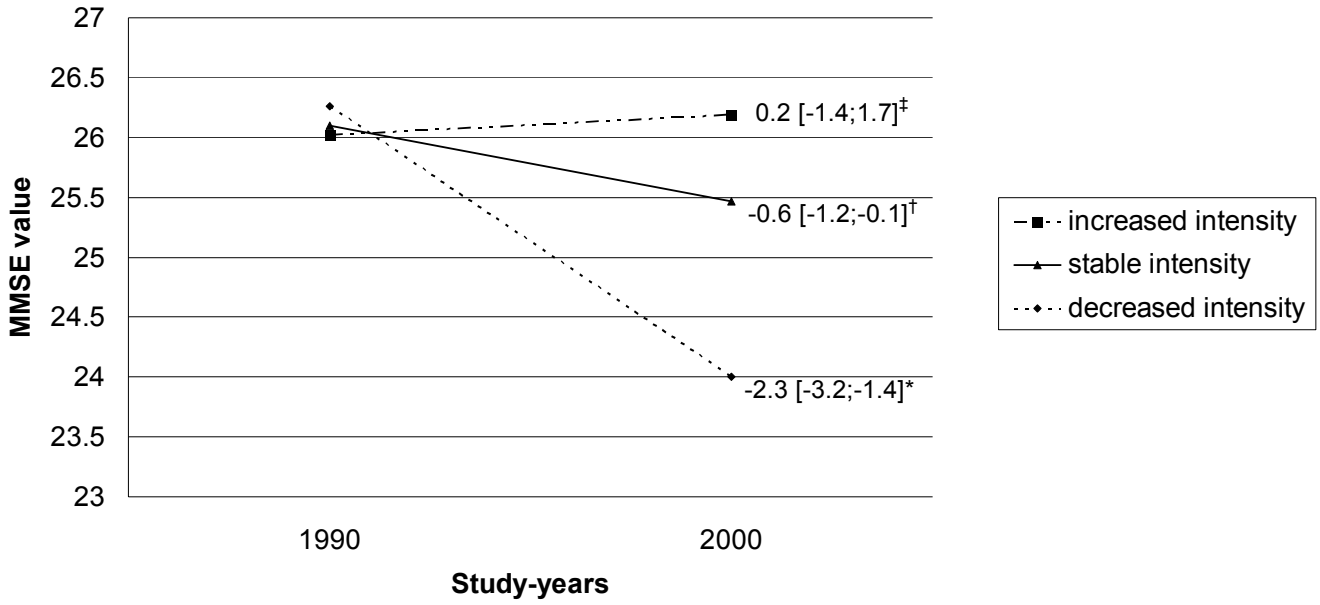

Figure 4.4. *Ten-year cognitive decline per category of 10-year change in intensity of physical activity for healthy Dutch and Italian survivors.*

Mean *change* in cognitive functioning between 1990 and 2000 [95% CI]. Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning. Adjustments were made for age, education, smoking status, alcohol consumption, country, mental activities, duration and baseline intensity.
* Reference group
† Significant different from reference group (p=0.003)
‡ Significant different from reference group (p=0.01)

Additional adjustments for baseline MMSE, possible intermediates like ADL, depression, BMI, use of antihypertensive drugs, HDL, total cholesterol and blood pressure did not influence the results (results not shown). Also, there was no interaction between duration and intensity in relation to cognitive decline (p=0.8) (results not shown).

Discussion

This study showed that in old age, physical activities of at least medium-low intensity at baseline were associated with less cognitive decline than physical activities of lowest intensity. Duration of activity at baseline was not associated with the rate of cognitive decline. However, maintaining or increasing the duration or intensity of physical activity over 10 years resulted in a smaller cognitive decline than decreasing the duration or intensity.

Before interpreting the results, several methodological issues should be addressed. The advantages of this study are its longitudinal design, a long follow-up period, the ability to adjust for a large number of potential confounders, and the possibility of analyzing duration and intensity of physical activity separately and independently in relation to cognitive decline. The longitudinal design of the FINE Study makes it less likely that reduced physical activity was a consequence instead of a cause of cognitive decline. Also, the postulated underlying mechanisms are in favour of a causal relationship. However, in the analyses on *change* in physical activity and cognitive decline, the direction of the association is less obvious and one cannot draw firm conclusions regarding causality.

A disadvantage of this study is the small number of healthy participants. However, despite this small number, we found consistent and significant results. The 854 non-participants in our study were less active and had lower cognitive test scores. Therefore, exclusion of these men probably led to an underestimation of the strength of the relationship between physical activity and cognition. We used the MMSE to assess cognitive decline; although it is a reliable and valid indicator of cognitive impairment and has a good test-retest reliability, it is just a screening test.[13,19] Future studies should therefore include a more extensive cognitive test battery.

We did not observe differences in the rates of cognitive decline among the baseline duration categories. Possibly, all participating elderly already achieved a minimal duration needed for an effect on cognitive decline. In addition, we found that men who performed activities with lowest intensity had the strongest cognitive decline. The rates of cognitive decline among the three other (higher) intensity quartiles did not differ significantly from each other. An activity with at least a medium-low intensity (like playing volleyball and walking at about 3 miles per hour) showed already a borderline significantly smaller cognitive decline. The benefit of the positive effect of an activity with a medium-low intensity is that participation in these kinds of activities will be easier and requires less effort than a more vigorous activity and will therefore be easier to implement in our society.

Precise mechanisms by which physical activity may be beneficial for cognition are unknown. The following mechanisms may be involved.[24,25] First, physical activity may have a beneficial effect on cardiovascular risk factors, such as a reduced risk of hypertension and arteriosclerosis, and may thereby maintain cardiovascular fitness. This stimulates cerebral circulation, resulting in an increased oxygen transport to the brain.[1] In addition, the risk of stroke and white matter lesions will be reduced.[26] These effects will eventually lead to less cognitive decline.

Second, experimental animal research shows that being physically active directly stimulates trophic factors and neuronal networks, which leads to neurogenesis in the hippocampus and regulation of synaptic plasticity and neurotransmitter synthesis, possibly providing cognitive reserves against cognitive decline and dementia.[2-4] Another possible mechanism could be that

physical activity increases the levels of brain serotonin, thereby reducing stress and stress-induced hypercortisolemia and consequently stimulating regeneration of neurons within the hippocampus.[24] Finally, physically active participants may have a healthier lifestyle, such as more adequate nutrition, which may reduce the risk for cardiovascular diseases and consequently of cognitive decline.[27] It may also be possible that the mental aspect needed to perform a certain level of physical activity or a social aspect, like walking with a friend, stimulates cognition. Indeed, frequent participation in cognitively stimulating activities was found to be associated with a reduced risk of cognitive decline.[28,29]

Several studies have found an association between physical activity and cognitive functioning, although they did not investigate duration and intensity of physical activities independently of each other.[6,8,9] For example, a prospective study in the United States showed that women who walked more blocks a week and who spent more energy per week were less likely to develop cognitive decline.[9] In the Canadian Study of Health and Aging, it was shown that regular physical activity (combination of frequency and intensity of an activity) had a significant protective effect on the risk of cognitive decline in the elderly.[8] However, other studies found a weak or no association and did not investigate the independent effect of duration and intensity of physical activity on cognitive decline.[10,11]

For developing specific treatment programs and recommendations for healthy aging, it is necessary to know which aspects of physical activity are associated with cognition. The results of this study suggest that stimulating elderly to be physically active with at least a medium-low intensity or becoming even more physically active (in duration or intensity) could be important for keeping their brains fit.

References

1. Rogers RL, Meyer JS, Mortel KF. After reaching retirement age physical activity sustains cerebral perfusion and cognition. J Am Geriatr Soc 1990;38(2):123-128.
2. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002;25(6):295-301.
3. Gomez-Pinilla F, So V, Kesslak JP. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise. Neuroscience 1998;85(1):53-61.
4. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci USA 1999;96(23):13427-13431.
5. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003;14(2):125-130.
6. Fabre C, Chamari K, Mucci P, Masse-Biron J, Prefaut C. Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. Int J Sports Med 2002;23(6):415-421.
7. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, et al. Ageing, fitness and neurocognitive function. Nature 1999;400(6743):418-419.
8. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001;58(3):498-504.
9. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 2001;161(14):1703-1708.
10. Blumenthal JA, Emery CF, Madden DJ, Schniebolk S, Walsh-Riddle M, George LK, McKee DC, Higginbotham MB, Cobb FR, Coleman RE. Long-term effects of exercise on psychological functioning in older men and women. J Gerontol 1991;46(6):P352-P361.
11. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Ambrose AF, Sliwinski M, Buschke H. Leisure activities and the risk of dementia in the elderly. N Engl J Med 2003;348(25):2508-2516.
12. Keys A, Aravanis C, Blackburn HW, van Buchem FS, Buzina R, Djordjevic BD, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl 1966;460:1-392.
13. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40(9):922-935.
14. Murden RA, McRae TD, Kaner S, Bucknam ME. Mini-Mental State exam scores vary with education in blacks and whites. J Am Geriatr Soc 1991;39(2):149-155.
15. Bijnen FC, Feskens EJ, Caspersen CJ, Giampaoli S, Nissinen AM, Menotti A, Mosterd WL, Kormhout D. Physical activity and cardiovascular risk factors among elderly men in Finland, Italy, and the Netherlands. Am J Epidemiol 1996;143:553-561.
16. Caspersen CJ, Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol 1991;133(11):1078-1092.
17. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32(9):S498-S504.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.
19. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992;11(1):2-13.
20. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115(2):122-132.

21. Fillenbaum GG, George LK, Blazer DG. Scoring nonresponse on the Mini-Mental State Examination. Psychol Med 1988;18(4):1021-1025.

22. Hoeymans N, Feskens EJ, van den Bos GA, Kromhout D. Measuring functional status: cross-sectional and longitudinal associations between performance and self-report (Zutphen Elderly Study 1990-1993). J Clin Epidemiol 1996;49(10):1103-1110.

23. Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63-70.

24. Ball LJ, Birge SJ. Prevention of brain aging and dementia. Clin Geriatr Med 2002;18(3):485-503.

25. Chodzko-Zajko WJ, Moore KA. Physical fitness and cognitive functioning in aging. Exerc Sport Sci Rev 1994;22:195-220.

26. Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. Stroke 2003;34(10): 2475-2481.

27. Stefanick ML, Mackey S, Sheehan M, Ellsworth N, Haskell WL, Wood PD. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. N Engl J Med 1998;339(1):12-20.

28. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 2002;288(18):2271-2281.

29. Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002;287(6):742-748.

Chapter 5

Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study

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Abstract

Objective. To investigate whether coffee consumption is associated with 10-year cognitive decline in elderly men, as results of previous studies obtained hitherto have been controversial and prospective information on this association has been lacking.

Methods. Six hundred and seventy six healthy men born between 1900 and 1920 from Finland, Italy and the Netherlands participated in a 10-year prospective cohort study. Cognitive functioning was assessed using the Mini-Mental State Examination (0-30 points, with a higher score indicating better cognitive performance). Coffee consumption was estimated in cups per day. A mixed longitudinal model was used to investigate the association between baseline coffee consumption and 10-year cognitive decline. Multiple adjustments were made.

Results. Men who consumed coffee had a 10-year cognitive decline of 1.2 points (4%). Non-consumers had an *additional* decline of 1.4 points ($p<0.001$). An inverse and J-shaped association was observed between the number of cups of coffee consumed and cognitive decline, with the least cognitive decline for three cups of coffee per day (0.6 point). This decline was 4.3 times smaller than the decline of non-consumers ($p<0.001$).

Conclusion. Findings suggest that consuming coffee reduces cognitive decline in elderly men. An inverse and J-shaped association may exist between the number of cups of coffee consumed and cognitive decline, with the least cognitive decline for men consuming three cups of coffee per day.

Introduction

Coffee is regularly consumed by millions of people around the world. Most citizens of Western countries start their day with a fresh cup of coffee. Owing to its caffeine content, coffee is the best known psychoactive stimulant world wide[1] and directly improves cognitive performance.[2] Besides this short-term effect, caffeine may also have long-term beneficial effects on brain function.[3]

Although some studies have shown inconsistent results regarding the effect of caffeine on cognition,[4] results from cross-sectional studies provide some evidence that caffeine use[5] or coffee consumption as such[6] is associated with better cognitive functioning. A possible underlying mechanism could be that caffeine enters the bloodstream and acts as an antagonist on the A_{2a} adenosine receptors in the brain, which consequently stimulates cholinergic neurons.[1] Subsequently, these neurons protect against β-amyloid-induced neurotoxicity, a precursor of cognitive decline.[7] If coffee consumption could delay cognitive decline, this could have major public health implications because cognitive decline is very common in the elderly.

Longitudinal studies investigating the association between coffee consumption and cognitive decline in the elderly are not available. A retrospective observational study found that lifetime coffee consumption was positively associated with cognitive performance in elderly women, but not in elderly men.[8] In the present study, we investigated the association between coffee consumption and 10-year cognitive decline in healthy elderly men in the Finland, Italy and the Netherlands Elderly (FINE) Study, a prospective European cohort study.

Methods

Study population

The study population consisted of men born between 1900-1920 of the Finnish, Italian and Dutch cohorts of the Seven Countries Study.[9] Five hundred and twenty three Finnish men were still alive in 1989, of whom 470 men (90%) were re-examined. In 1990, 718 Dutch men were still alive and 560 of them were re-examined (78%). Of the Italian cohorts, 493 men were still alive in 1991 and 391 (79%) were re-examined.

Men with a Mini-Mental State Examination (MMSE) score below 18 (n=118)[10,11] or those whose age, coffee consumption, education, smoking status and alcohol consumption was unknown in 1990 were excluded (n=272). From the remaining 1031 men, subjects with diabetes (n=71) or a history of myocardial infarction (n=70), stroke (n=87), cancer (n=28) or more than one of these diseases (n=68) were excluded from the study population because these men could have changed their coffee consumption habits owing to their disease. Complete information on all possible confounding factors was available for 676 of these 707 men in 1990, of whom 101 were Finnish,

336 were Dutch and 239 were of Italian origin. Repeated examinations of the MMSE took place in 1995 (except for Finland) and 2000. More information about the study population has been described in detail elsewhere.[12] All men were examined according to the international protocol used in the surveys of the Seven Countries Study.[9] Approval of the Medical Ethics Committee in the different countries was obtained for each participating centre and participants have given their informed consent.

Coffee consumption

Information on the frequency of cups of coffee consumption in Finland and Italy was obtained with a standardised self-administered questionnaire (How much coffee do you consume on average each day? (expressed in number of cups per day)). In the Netherlands, this information was collected in a dietary survey in which a cross-check dietary history method was used.[13] Participants were interviewed by a dietician about their usual food consumption including coffee during the past two to four weeks. Both methods provided information about the usual coffee consumption per day during the past month. In Finland and Italy, participants reported the number of cups of coffee consumed per day. In the Netherlands, coffee consumption was coded in millilitre (ml) and converted into cups of coffee by assuming that one cup of coffee contained 125 ml. Coffee consumption was categorised into yes/no and into 0, 1, 2, 3, 4 and >4 cups of coffee per day. The correlation coefficient for coffee consumption in 1985 and 1990 ranged from 0.54 ($p<0.001$) for Finland till 0.72 ($p<0.001$) for the Netherlands.

Assessment of cognitive function

The MMSE was used to assess global cognitive function in each survey year (with the exception of the 5-year follow-up survey in Finland) and includes questions on orientation to time and place, registration, attention and calculation, recall, language and visual construction.[14] The MMSE was originally designed for clinical use, but is now extensively used in epidemiological studies and has proven to be a reliable and valid indicator of cognitive impairment with a good test-retest reliability.[10,15,16] Although the MMSE is a measure of global cognitive functioning and does not assess different cognitive domains in detail, it is sensitive enough to detect 'clinically significant' global cognitive decline.[17]

The MMSE score ranges from 0 to 30; a higher score indicates better cognitive performance. If a subject did not answer four or more individual items (of a total of 20), the total MMSE score was considered missing (n=6). If less than four items were missing, missing items were rated as zero and a total MMSE score was still calculated.[18] In 1990, information on cognitive functioning of 676

Finnish, Italian and Dutch men was obtained. In 1995, 383 Italian and Dutch men participated in the survey and 285 Finnish, Italian and Dutch men in 2000.

Other variables

Demographic and lifestyle information was obtained in all cohorts with standardised questionnaires. Education was assessed as the number of years of education. Height and weight were measured while men were wearing light clothing and no shoes. Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). Smoking status was categorised into non- and current smoker and alcohol consumption into consumers and non-consumers. Physical activity was assessed by a validated questionnaire designed for retired men.[19] The total daily duration of physical activity was calculated and categorised into four groups: ≤ 30, 31-60, 61-120, and >120 minutes per day. Information about the prevalence of diabetes and a history of myocardial infarction, stroke or cancer was obtained by questionnaires and validated with information from hospital registries or general practitioners.

Statistical analyses

Potential differences between consumers and non-consumers of coffee in each country were tested using analyses of variance or Student's t-test for normal distributed continuous variables, and Mann-Whitney U-test in case variables were not normally distributed. Categorical data were tested for difference with Chi-square test. Differences in continuous variables across coffee consumption categories were obtained by analyses of variance.

A general linear model was used to compare baseline cognitive functioning between coffee consumers and non-consumers in 1990. To determine the effect of baseline coffee consumption on 10-year cognitive decline a mixed longitudinal random coefficient model (SAS Proc Mixed procedure) was used, with the intercept and the time period as random effects. This procedure takes into account the intra-correlation of repeated measurements carried out at the same subject and does not exclude subjects with incomplete data at follow-up. Baseline coffee consumption (yes/no) was entered as a class variable in the model and the variable time as a continuous variable. To investigate whether 10-year cognitive decline differed between coffee consumers and non-consumers, the product of coffee consumption (yes/no) with time was included into the model. Cognitive decline (in points) for consumers and *additional* cognitive decline for the non-consumers (compared to the decline of the consumers) were given in the output of the programme.

Additional analyses regarding the association between the number of cups of coffee consumed and cognitive functioning were performed. Again, a general linear model was used to obtain

baseline MMSE scores for each category and a mixed longitudinal random coefficient model for the cognitive decline per category. To test whether the association between the number of cups of coffee consumed per day and the magnitude of cognitive decline fits a parabolic function, we added the quadratic term of the number of cups of coffee consumed, to the model. Then we tested with the likelihood ratio test which model our data best fitted.

Adjustments were made for possible confounding factors age, education, country, alcohol consumption, smoking status and physical activity. Analyses assessing the 10-year cognitive decline between coffee consumption categories were additionally adjusted for baseline cognitive functioning. All statistical analyses were carried out using SAS software (version 8.2; SAS Institute, Inc., Cary, NC, USA). Two-sided p-values of 0.05 or less were considered to be statistically significant.

Results

Consumers and non-consumers

Table 5.1 displays the characteristics of consumers and non-consumers of coffee in Finland, Italy and the Netherlands. Overall, there were no differences in characteristics between consumers and non-consumers of coffee of each country, although Italian coffee consumers tended to be more physically active than Italian non-consumers.

Cognitive functioning in 1990 did not differ between men who consumed (25.7 points) and men who did not consume coffee (25.7 points, p=0.93), after adjustment for potential confounding factors (figure 5.1). However, men who consumed coffee had a 10-year cognitive decline of 1.2 points and men who did not consume coffee had an *additional* decline of 1.4 points (p<0.001). One hundred and nineteen men in the reference category of non-consumers were of Italian descent (82%). Despite this, even among only Italian coffee consumers and non-consumers, similar results were obtained. Baseline cognitive functioning of Italian coffee consumers (24.8 points) and non-consumers did not differ (25.0, p=0.5) and the 10-year cognitive decline of coffee consumers (1.7 points) and non-consumers (2.9 points) did differ (p=0.03). Italian non-consumers had an *additional* cognitive decline of 1.2 points, which was 0.2 point smaller than the *additional* decline of non-consumers of all three countries together.

Number of cups of coffee consumed

The number of cups of coffee consumed was inversely associated with age and positively with years of education and the percentage of smokers (table 5.2). Furthermore, Italian men drank less

Table 5.1. *Selected characteristics of the study population at baseline, stratified by country and coffee consumption (n=676).*

Characteristics	Finland			The Netherlands			Italy		
	Non-consumers (n=10)	Consumers (n=91)	p*	Non-consumers (n=16)	Consumers (n=320)	p*	Non-consumers (n=119)	Consumers (n=120)	p*
Demographics									
Age (mean [SD], years)	75.9 (5.2)	74.9 (4.4)	0.50	75.7 (5.1)	75.7 (4.3)	0.99	77.4 (4.0)	76.7 (3.5)	0.16
Education (mean [SD], years received)	5.0 (2.9)	4.0 (2.5)	0.24	11.0 (2.5)	10.3 (4.3)	0.33	4.8 (2.7)	5.1 (2.5)	0.50
BMI (mean [SD], kg/m^2)	28.3 (4.3)	26.1 (3.9)	0.10	25.4 (2.9)	25.8 (3.0)	0.63	25.9 (3.6)	26.5 (3.6)	0.17
Lifestyle									
Cigarette smokers (numbers [%])	0 (0)	10 (11)	0.59	2 (13)	75 (23)	0.31	18 (15)	26 (22)	0.19
Alcohol consumers (numbers [%])	9 (90)	77 (85)	1.00	10 (63)	242 (76)	0.24	99 (83)	95 (79)	0.43
Leisure time physical activity (mean [SD], min/wk)	910 (1652)	622 (575)	0.60	609 (223)	636 (544)	0.35	698 (732)	883 (791)	0.063
Cognitive functioning									
Unadjusted MMSE score (mean [SD])	25.3 (3.9)	25.4 (3.1)	0.90	26.9 (2.2)	26.4 (2.3)	0.35	24.9 (2.9)	24.9 (2.7)	0.94
Adjusted MMSE score (mean [SE])†	25.1 (0.93)	25.5 (0.30)	0.69	26.7 (0.52)	26.4 (0.12)	0.53	25.0 (0.23)	24.8 (0.23)	0.48

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination; SD, standard deviation; SE, standard error.

* P value for difference between coffee consumers and non-consumers based on Student t-test, Chi-square test, Fisher's exact test or co-variance analysis.

† Adjusted for age (continuous), education (continuous), cigarette smoking (yes/no), alcohol use (yes/no) and physical activity (categorical).

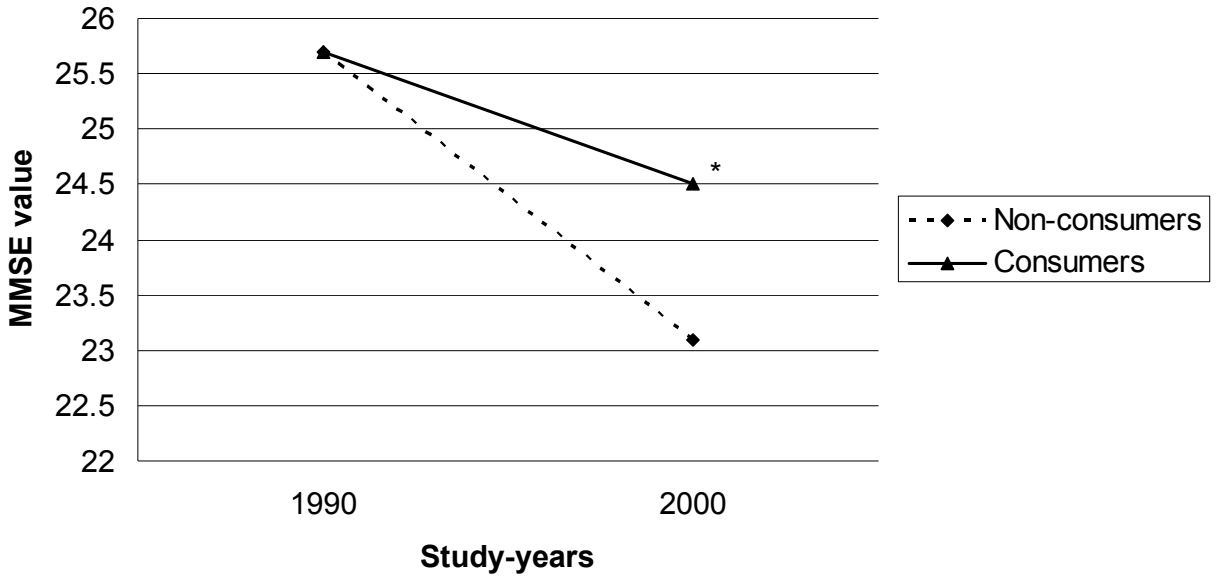

Figure 5.1. *Coffee consumption at baseline and subsequent 10-year cognitive decline in European elderly men.*

Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning. Adjustments were made for age, education, country, alcohol consumption, smoking status and physical activity. In analyses regarding cognitive decline, also adjustments for baseline cognitive functioning were made.
* Cognitive decline of consumers is significantly different from non-consumers ($p<0.001$).

cups of coffee than men from Finland and the Netherlands. A linear trend was present for the number of coffee cups consumed and the unadjusted baseline cognitive test scores, with better cognitive functioning for men consuming more cups of coffee ($p<0.0001$). However, after adjustment for potential confounding factors this linear trend was no longer present ($p=0.20$).
Although baseline cognitive functioning did not differ among men who consumed 0, 1, 2, 3, 4 and >4 cups of coffee per day after adjustments, the 10-year cognitive decline did. An inverse and J-shaped association was present (tested with the likelihood ratio test), with the smallest 10-year cognitive decline for men consuming three cups of coffee per day (0.6 point) (figure 5.2). This decline is two points smaller compared to the decline of non-consumers ($p<0.001$). The decline of 1.6 points in men who consumed more than four cups of coffee was borderline significantly smaller ($p=0.07$) compared to men who did not consume coffee. Cognitive decline of men who consumed 1, 2, 3, 4 and >4 cups of coffee a day did not differ from each other ($p>0.10$).

Table 5.2. *Baseline characteristics of the study population according to categories of coffee consumption.*

Characteristics	Categories of daily coffee consumption						p for trend *
	0 cups n=145	1 cups n=133	2 cups n=107	3 cups n=105	4 cups n=85	>4 cups n=101	
Country							
Finland (No.)	10	1	13	14	34	29	
Italy (No.)	119	85	23	10	0	2	
The Netherlands (No.)	16	47	71	81	51	70	
Demographic variables							
Age (mean [SE], years)	77.2 (0.4)	77.1 (0.4)	75.7 (0.4)	75.6 (0.4)	75.2 (0.5)	74.8 (0.4)	<0.0001
Education (mean [SE], years received)	6.6 (0.3)	6.9 (0.3)	8.4 (0.3)	8.5 (0.4)	7.6 (0.4)	7.7 (0.4)	<0.0001
BMI (mean [SE], kg/m^2)	25.9 (0.3)	26.2 (0.3)	25.7 (0.3)	25.8 (0.3)	26.2 (0.4)	26.1 (0.3)	0.90
Lifestyle							
Cigarette smokers (%)	16	17	19	16	18	33	0.001
Alcohol consumers (%)	80	75	84	76	77	81	0.79
Leisure time physical activity (mean [SE], min/wk)	689 (56)	687 (57)	681 (64)	717 (65)	658 (72)	718 (66)	0.97
Cognitive functioning							
Unadjusted MMSE score (mean [SE])	25.3 (0.2)	25.1 (0.2)	26.0 (0.3)	26.1 (0.3)	26.0 (0.3)	26.2 (0.3)	<0.0001
Adjusted MMSE score (mean [SE]) †	25.7 (0.2)	25.4 (0.2)	25.7 (0.2)	25.8 (0.2)	25.8 (0.3)	26.0 (0.2)	0.20

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination; SE, standard error.

* Linear trend for associations with coffee consumption based on a general linear model, obtained by analyses of variance.

† Adjusted for age (continuous), education (continuous), country, cigarette smoking (yes/no), alcohol use (yes/no) and physical activity (categorical).

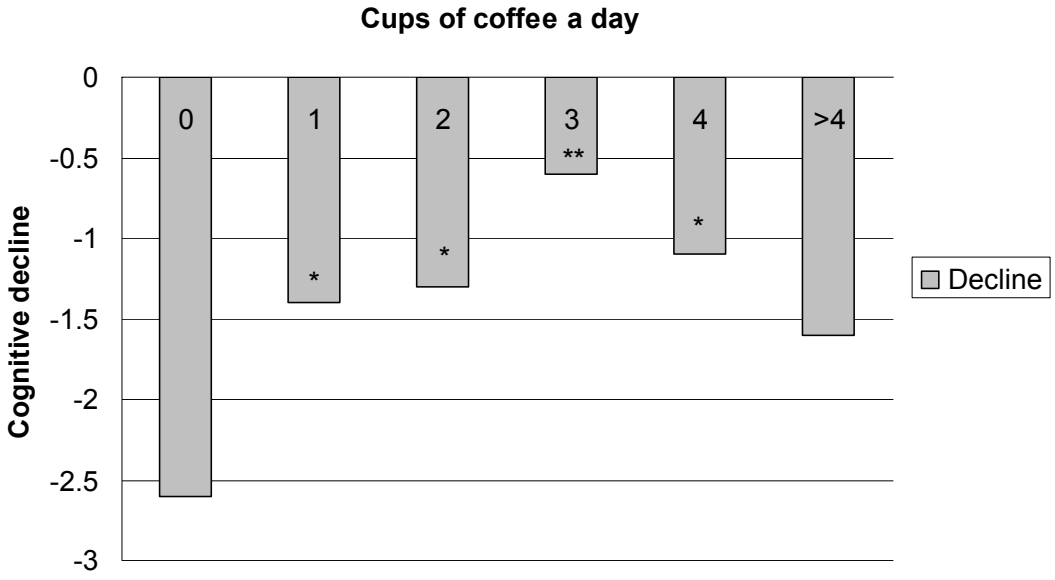

Figure 5.2. *Magnitude of 10-year cognitive decline by number of cups of coffee consumed at baseline.*

Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning.
Adjustments were made for age, education, country, alcohol consumption, smoking status, physical activity and baseline cognitive functioning.
* Significant different from 0 cups of coffee a day ($p<0.05$).
** Significant different from 0 cups of coffee a day ($p<0.001$).

Discussion

The present study showed that coffee consumption was inversely associated with cognitive decline. Men who consumed coffee had a two times smaller 10-year cognitive decline than non-consumers. We also observed an inverse and J-shaped association between the number of cups of coffee per day consumed and 10-year cognitive decline, with the least decline for men consuming three cups of coffee per day.

Some methodological issues deserve to be discussed. Eighty-two percent of the participants in the reference group of non-consumers were of Italian descent, whereas this percentage was only 23% in the consumers, therefore confounding by country may have influenced our results. However, this is less likely because the *additional* cognitive decline of the Finnish, Dutch and Italian non-consumers was even stronger than the *additional* cognitive decline of the Italian non-consumers only. Analyses regarding the dose-response relationship between coffee consumption and cognitive decline could not be performed in each country separately. About 50% of the Italian men did not drink coffee and the number of men in each category of coffee consumption in Finnish and Dutch men was too low for meaningful analyses. It is unlikely that a substantial number of elderly

men in the three countries consumed decaffeinated coffee. However, if that is the case, the observed association between coffee consumption and cognitive decline would have been underestimated if caffeine is the responsible agent for this association.

Our overall results suggest an inverse and J-shaped association. This association was also present when analysing the association between mean coffee consumption of 1985 and 1990 and subsequent cognitive decline, which confirms the inverse and J-shaped association using the 1990 data only. However, the cognitive decline of men who consumed 1, 2, 3, 4 or more than 4 cups of coffee was not statistically different from each other. Therefore, more research is needed to investigate the dose-response relationship between coffee consumption and cognitive decline. High drop-out rates owing to non-response or death may have caused selection bias. To reduce this effect, a mixed longitudinal random coefficient model was used. This procedure takes into account the intra-correlation of at least two measurements performed by the same subject and does not exclude subjects with incomplete data at follow-up. In spite of the high drop-out, analyses with only coffee consumers and non-consumers who participated until 2000 confirmed our results. In addition, analyses regarding the number of cups of coffee consumed among survivors tended also to an inverse and J-shaped (non-significant) association, despite the small number of survivors in each category.

Men with a MMSE score in 1990 below 18 (n=118) were excluded from our study population as these men had already an impaired cognition at baseline and therefore they could have made mistakes when reporting the number of cups of coffee consumed. Additional analyses in which we also included men with a chronic disease at baseline and men with missing values on possible confounding factors at baseline confirmed the results found in the present study among apparently healthy participants. Therefore, the results obtained in the present study can be generalised to the general population. However, men with an impaired cognition at baseline did not participate in the present study, therefore, the results of the present study are particularly generalisable to Western European men with an intact cognition while reporting the number of cups of coffee consumed. Results of other prospective studies on coffee consumption and cognitive decline are not available. Furthermore, coffee consumption behaviour may differ between men and women. Therefore, owing to lack of data, it is not possible to answer the question whether results of our study can be generalised to women.

We used the MMSE to assess global cognitive functioning. Although the MMSE is a screening test, it is a reliable and valid indicator of cognitive impairment and has a good test-retest reliability and is often used in epidemiological studies.[10,15,16] A limitation of the MMSE is that it measures global cognitive functioning and does not assess specific cognitive domains in detail. Therefore, future studies should include a more extensive cognitive test battery and should focus on specific cognitive domains, for example, memory, concentration, attention, learning, language and visual

construction. Furthermore, the MMSE is not sensitive enough to detect mild cognitive impairment and to discriminate among cognitively intact and mildly cognitively impaired persons.[10] However, with the MMSE it is possible to detect 'clinically significant' global cognitive decline.[17] In the present study, differences in baseline cognitive functioning could not be detected between cognitively impaired and cognitively intact persons in the cross-sectional analyses, as these persons were mildly or not cognitively impaired. During the follow-up period, when cognitive impairment increased, differences in cognitive decline among different categories of coffee consumers could be detected. Furthermore, the use of repeated measurements reduces the measurement error in the longitudinal analyses.

Coffee consumption was assessed with a self-administered questionnaire, which could have caused reporting bias. Men could have over-reported or under-reported their actual intake of coffee. An influence of this bias on the results regarding coffee or non-coffee consumption and cognitive decline does not seem likely. Also, men who were severely cognitively impaired at baseline were excluded from our study population and the question regarding coffee consumption was based on current and not on past coffee intake. Information on coffee consumption for the present study population was also collected in the three countries in 1985. The correlation between the amount of cups of coffee consumption in 1985 and 1990 ranged from 0.54 for Finland till 0.72 for The Netherlands. This indicates that the reported amount of cups of coffee consumption was not only an indicator of the number of cups of coffee consumed at the baseline survey but also suggests that the relative position in the distribution of coffee consumers was rather stable over time. Presumably, habitual coffee consumption was responsible for the effect observed in the present study.

The major strengths of this study are its longitudinal design and the opportunity to adjust for several possible confounding factors. No other study had ever investigated this association prospectively among healthy elderly and results of earlier reported epidemiological studies have limitations. The Rancho Bernardo Study showed with a retrospective design that lifetime coffee consumption was associated with better cognitive functioning among women but not among men.[8] The Canadian Study of Health and Aging showed that participants who consumed coffee nearly every day had a lower risk of becoming afflicted with Alzheimer's disease.[20] The Health and Lifestyle survey showed that the more cups of coffee that were consumed the better the cognitive functioning. However this study was cross-sectional.[6] In contrast to the previous results, the present longitudinal study shows that coffee consumption compared to no coffee consumption is associated with a smaller 10-year cognitive decline.

Coffee is a major source of caffeine and one cup of coffee contains about 85 mg of caffeine, almost twice the caffeine content of tea (~45 mg). Caffeine seems to be the major component in coffee that could be responsible for the inverse association between coffee consumption and

cognitive decline. Caffeine intake has been related to a lower risk of Alzheimer's disease[3] and it may improve cognitive functions like memory, learning, vigilance and mood.[2] On the other hand, some studies reported that caffeine intake was not associated with cognitive change[21] or showed inconsistent results.[4,22]

A possible mechanism underlying the association between caffeine intake and cognitive functioning comes from animal experiments. Research with mice showed that while drinking coffee, caffeine enters the bloodstream and acts as an antagonist on the A_{2a} adenosine receptors in the brain.[1] Subsequently, this stimulates the secretion of cholinergic neurotransmitters (like acetylcholine), which in turn prevents β-amyloid-induced neurotoxicity in cerebellar neurons.[7] Precise neuronal cellular mechanisms are not yet known and the generalisability of animal research to humans has its limitations. Furthermore, some animal studies suggest that the A_{2a} adenosine receptor has an effect on the memory part of the brain, the hippocampus.[23]Besides caffeine, coffee contains many other substances, like magnesium and many phenolic acids, of which chlorogenic acid is the most abundant one.[24] Consumption of coffee increases the antioxidant capacity in plasma,[25-26] which may provide a protective effect against free radicals that cause oxidative damage to neurons, which appear to be very vulnerable to the effects of free radicals.[27]

Conclusion

Our study showed that among elderly men coffee consumption was associated with a smaller cognitive decline compared to non-consumers. Consuming three cups of coffee per day was associated with the smallest cognitive decline. Because of the worldwide use of coffee, the increasing ageing of populations and related cognitive decline and because coffee consumption is a modifiable lifestyle habit, the results of the present study could have important public health implications if confirmed in other prospective studies. However, because coffee could also cause adverse health effects, prudence is called for when consuming too much coffee.

References

1. Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev 1999;51(1):83-133.
2. Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL, Tulley R. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. Sea-Air-Land. Psychopharmacology (Berl) 2002;164(3):250-261.
3. Maia L, de Mendonca A. Does caffeine intake protect from Alzheimer's disease? Eur J Neurol 2002;9(4):377-382.
4. Smith A. Effects of caffeine on human behavior. Food Chem Toxicol 2002;40(9):1243-1255.
5. Riedel WJ, Jolles J. Cognition enhancers in age-related cognitive decline. Drugs Aging 1996;8(4):245-274.
6. Jarvis MJ. Does caffeine intake enhance absolute levels of cognitive performance? Psychopharmacology (Berl) 1993;110(1-2):45-52.
7. Dall'Igna OP, Porciuncula LO, Souza DO, Cunha RA, Lara DR, Dall'Igna OP. Neuroprotection by caffeine and adenosine A2A receptor blockade of beta-amyloid neurotoxicity. Br J Pharmacol 2003;138(7):1207-1209.
8. Johnson-Kozlow M, Kritz-Silverstein D, Barrett-Connor E, Morton D. Coffee consumption and cognitive function among older adults. Am J Epidemiol 2002;156(9):842-850.
9. Keys A, Aravanis C, Blackburn HW, van Buchem FS, Buzina R, Djordjevic BD, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl 1966;460:1-392.
10. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40(9):922-935.
11. Murden RA, McRae TD, Kaner S, Bucknam ME. Mini-Mental State exam scores vary with education in blacks and whites. J Am Geriatr Soc 1991;39(2):149-155.
12. Bijnen FC, Feskens EJ, Caspersen CJ, Giampaoli S, Nissinen AM, Menotti A, Mosterd WL, Kromhout D. Physical activity and cardiovascular risk factors among elderly men in Finland, Italy, and the Netherlands. Am J Epidemiol 1996;143(6):553-561.
13. Bloemberg BP, Kromhout D, Obermann-De Boer GL, van Kampen-Donker M. The reproducibility of dietary intake data assessed with the cross-check dietary history method. Am J Epidemiol 1989;130(5): 1047-1056.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.
15. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992; 11(1):2-13.
16. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115(2):122-132.
17. Lyketsos CG, Garrett E, Liang KY, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. Am J Epidemiol 1999;149(9):794-800.
18. Fillenbaum GG, George LK, Blazer DG. Scoring nonresponse on the Mini-Mental State Examination. Psychol Med 1988;18(4):1021-1025.
19. Caspersen CJ, Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol 1991;133(11):1078-1092.
20. Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 2002;156(5):445-453.

21. van Boxtel MP, Schmitt JA, Bosma H, Jolles J. The effects of habitual caffeine use on cognitive change: a longitudinal perspective. Pharmacol Biochem Behav 2003;75(4):921-927.
22. Lorist MM, Tops M. Caffeine, fatigue, and cognition. Brain Cogn 2003;53(1):82-94.
23. Kopf SR, Melani A, Pedata F, Pepeu G. Adenosine and memory storage: effect of A(1) and A(2) receptor antagonists. Psychopharmacology (Berl) 1999;146(2):214-219.
24. Nardini M, Cirillo E, Natella F, Scaccini C. Absorption of phenolic acids in humans after coffee consumption. J Agric Food Chem 2002;50:5735-5741.
25. Svilaas A, Sakhi AK, Andersen LF, Svilaas T, Strom EC, Jacobs DR Jr, Ose L, Blomhoff R. Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. J Nutr 2004;134(3):562-567.
26. Natella F, Nardini M, Giannetti I, Dattilo C, Scaccini C. Coffee drinking influences plasma antioxidant capacity in humans. J Agric Food Chem 2002;50(21):6211-6216.
27. Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nutr 2000;71(2):621S-629S.

Chapter 6

Fish consumption, n-3 fatty acids and subsequent 5-year cognitive decline in elderly men: the Zutphen Elderly Study

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Abstract

Objective. Indications have been seen of a protective effect of fish consumption and the intake of n-3 fatty acids on cognitive decline. However, studies are scarce and results inconsistent. This study examined the associations between fish consumption, the intake of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish and other foods and subsequent 5-year cognitive decline.

Methods. Data on fish consumption of 210 participants in the Zutphen Elderly Study, who were aged 70-89 year in 1990, and data on cognitive functioning collected in 1990 and 1995 were used in the study. The intake of EPA and DHA (EPA + DHA) was calculated for each participant. Multivariate linear regression analysis with multiple adjustments was used to assess associations.

Results. Fish consumers had significantly less 5-year subsequent cognitive decline than did non-consumers (p=0.01). A linear trend was observed for the relation between the intake of EPA + DHA and cognitive decline (p=0.01). An average difference of about 380 mg/day in EPA + DHA intake was associated with a 1.1 points difference in cognitive decline (p=0.01).

Conclusion. A moderate intake of EPA + DHA may postpone cognitive decline in elderly men. Results from other studies are needed before definite conclusions about this association can be drawn.

Introduction

Dementia and Alzheimer's disease are preceded by a progressive degenerative cognitive decline. Evidence is accumulating that fish consumption and the intake of n-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may protect against dementia and Alzheimer's disease.[1-3] Most epidemiologic studies suggested a protective effect of fish or n-3 PUFAs, but one did not.[4]

Less evidence with respect to cognitive functioning is available. A cross-sectional analysis of a Dutch study showed that both fish consumption and EPA + DHA intake were inversely associated with cognitive impairment in middle-aged men and women.[5] In the Zutphen Elderly Study, fish consumption tended to be inversely associated with cognitive impairment and with 3-year cognitive decline, although the results were not significant after multiple adjustments (odds ratio (OR): 0.63, 95% confidence interval (CI): [0.33;1.21] and OR: 0.45, 95% CI: [0.17;1.16]).[6] In addition, the intake of n-3 PUFAs was not related to cognitive impairment or cognitive decline. The Canadian Study of Health and Aging also did not find a protective effect of n-3 PUFAs in plasma on cognitive decline or on dementia after a 5-year follow-up.[7] The Chicago Health and Aging Project showed that fish consumption was associated with less cognitive decline, but no evidence was found for an association between the intake of n-3 fatty acids and cognitive decline.[8]

Several mechanisms have been suggested for the association between n-3 fatty acids and cognitive functioning. N-3 fatty acids have anti-inflammatory and cardiovascular protective effects[9] and may therefore reduce the risk of athero-thrombotic complications such as stroke[10] and subsequent cognitive decline. Furthermore, n-3 fatty acids may improve the composition of cell membranes and therefore stimulate the development and regeneration of nerve cells.[11]

EPA and DHA are frequently called fish fatty acids. However, recent results of fatty acid analysis showed that these n-3 fatty acids are present not only in fish and seafood but also in other animal foods, such as meat and eggs, and in plant foods, such as leek and cereal based products.[12] To study the association between the intake of n-3 fatty acids and cognitive decline, it is necessary also to take into account the intake of n-3 fatty acids in foods other then fish and seafood.

This prospective cohort study used longitudinal data and was focused on *changes* in cognitive functioning. New data recently became available on the content of EPA and DHA in fish and seafood and in other animal foods and plant foods. On the basis of this new data, we calculated the EPA + DHA content of the diet consumed by the participants in the Zutphen Elderly Study in 1990 and 1995, in order to examine both the association between fish consumption and cognitive decline and that between the intake of EPA + DHA from different foods and cognitive decline.

Methods

Study population

The Zutphen Elderly Study is a prospective cohort study of men born between 1900 and 1920 who lived in Zutphen, a town in the eastern part of the Netherlands. In 1985, 939 elderly men were examined (response rate 74%) and follow-up examinations in which information was collected on cognitive functioning were carried out in 1990 and 1995. In 1990, 556 men aged 70-89 year participated in the survey (response rate 77%). In 1995, 307 of those 556 men, then aged 75-94 year, participated. Because poor health status at baseline may influence both cognitive functioning and food consumption, we selected men without myocardial infarction, stroke, diabetes or cancer at baseline (n=228). Complete information on possible confounding factors was available for 210 men.

Written informed consent was obtained from all participants. The Zutphen Elderly Study was approved by the Medical Ethics Committee of the University of Leiden (Leiden, the Netherlands).

Dietary intake assessment

Information about habitual food consumption was collected in 1990 by using the cross-check dietary history method.[13] This method is reproducible[13] and valid.[14] Spearmen correlation coefficient for fish consumption in 1990 and 1995 was 0.62 and that for the intake of EPA + DHA was 0.47.

Dieticians interviewed the participants in their homes with respect to their usual food consumption patterns. A checklist providing information on the frequencies and quantities of foods consumed during the previous two to four weeks was used to verify the participants' food consumption patterns. Total fish consumption per day was calculated by adding the amount of different types of fish. Energy, fatty acid and antioxidant (vitamin C and E and β-carotene) intakes for each participant were calculated with the use of the computerised version of the Dutch Food Composition Table.[15] The fatty acid content of the foods consumed was estimated for each participant. For EPA and DHA, we used recently available data on the content of these fatty acids not only in fish and seafood but also in other animal foods (eggs and meat) and in plant foods (vegetables and cereal-based products).[12]

Assessment of cognitive functioning

The Mini-Mental State Examination (MMSE) was used in 1990 and 1995 as a screening test to assess global cognitive functioning;[16] it includes questions on orientation to time and place, registration, attention and calculation, recall, language and visual construction. The maximum score is 30 points and a higher score indicates a better cognitive functioning. If a subject did not

answer four or more individual items (of a total of 20), the total MMSE score was considered missing. If less than four items were missing, these items were rated as errors and a total MMSE score was calculated.[17] Originally, the MMSE was created for clinical use, but it is now used extensively in epidemiological studies, has a good test-retest reliability and is a valid indicator of cognitive functioning.[18-20]

Other measurements

Demographic, lifestyle and other information was obtained with standardised questionnaires in 1990. Education was assessed as the number of years of education. Smoking status was categorised as current smokers and non-smokers and alcohol consumption into users and non-users. Physical activity was assessed by a validated questionnaire especially designed for retired men and categorised into quartiles.[21] Depressive symptoms were measured with a Self-rating Depression Scale (SDS) developed by Zung.[22] A value of at least 50 was used to indicate the presence of depressive symptoms (yes or no). Information about the prevalence of myocardial infarction, stroke, diabetes and cancer was collected by standardised questionnaires (yes or no) and validated by hospital registries, information obtained from general practitioners, or both.

Statistical analysis

Differences in baseline variables among different categories of fish consumers were evaluated by using the Kruskal-Wallis test for skewed variables and analysis of variance was used for normally distributed continuous variables. Categorical data were tested for differences with Chi-square test. EPA + DHA intake is highly correlated (Spearman correlation coefficient is 0.88), therefore, we used the sum of EPA and DHA in the analyses.

To investigate fish consumption as well as the intake of EPA + DHA in 1990 in relation to cognitive functioning and cognitive decline, different multivariate linear regression models were used. Fish consumption (yes or no and classes of 0, >0-20 and >20 g/day) and the intake of EPA + DHA (in tertiles of 0-56, >56-148 and >148 mg/day) in 1990 were entered as class variables into the model and the outcome variables baseline cognitive functioning and 5-year cognitive decline (MMSE 1995 - MMSE 1990), which were used singly in the different analyses, were treated as continuous variables. Dose-response relations were tested for trend by using a linear regression model.

Adjustments were made for the well-known confounding factors age and education.[23] Because fish consumption may be associated with a healthier lifestyle, we also adjusted for energy intake, alcohol consumption, smoking status and physical activity. In longitudinal analyses, we adjusted for baseline cognitive functioning, because the level of baseline cognitive functioning may influence cognitive decline. Additional adjustments were made for dietary antioxidants on the assumption that fish consumers are more likely than are fish non-consumers to follow a healthy diet rich in fruit

and vegetables.[24] Dietary antioxidants may protect against cognitive decline by scavenging free radicals. Furthermore, a low intake of unsaturated fatty acids may be associated with a high intake of trans fatty acids, which are associated with an increased risk of Alzheimer's disease.[25] Therefore, we also adjusted for these fatty acids. Because depression may be associated with both fish consumption and cognitive functioning, we adjusted for depressive symptoms.[24] Finally, to reduce reporting bias due to impaired cognitive functioning, we excluded participants with a MMSE score below 24 (impaired cognition)[20] in 1990 (n=25).

All statistical analyses were carried out with SAS software (version 9.1; SAS Institute, Inc., Cary, NC). A two-sided p-value of ≤ 0.05 was considered to be statistically significant.

Results

In 1990, 24% of the participants did not consume fish, 41% consumed between > 0 and 20 grams fish per day and 35% consumed more than 20 grams fish per day. Fish consumption in the current study consisted of lean fish (67%, raw lean fish contains < 12 g fat), fatty fish (32%, raw fatty fish contains ≥ 12 g fat) and crustacean and shellfish (1%).

Overall, few differences were found in characteristics and daily nutrient intakes between men in the different categories of fish consumption (table 6.1). Men who did not consume fish were the oldest and had the fewest years of education. Men who did not consume fish had an average EPA + DHA intake of 15 mg/day. This was due to small amounts of these fatty acids in animal foods other than fish and in plant foods.

Some men did not participate in the current study because they died before 1995, they did not respond in 1995, or they had poor health status or missing values in 1990. These men overall were older, had fewer years of education, had lower baseline cognitive test scores, were less physically active and had a lower percentage of alcohol users than did the men who participated. These non-participants also had lower fish consumption and EPA + DHA intake in 1990 than did men who participated in the current study (results not shown).

In the 210 men with complete information, cognitive functioning in 1990 did not differ between those who consumed or did not consume fish in 1990, after adjustment for age, education, alcohol consumption, smoking status, physical activity and energy intake (figure 6.1). However, men who did not consume fish had a subsequent cognitive decline of 1.2 points, which was 4 times the decline in men who consumed fish (p=0.01).

Table 6.1. *Baseline characteristics and daily nutrient intakes of 210 healthy men aged 70-89 year according to fish consumption in 1990.*

Characteristic	Fish consumption			p-value*
	0 g/day (n = 51)	>0 - 20 g/day (n = 86)	> 20 g/day (n = 73)	Differences between groups
Mean age (years)	76.1 (4.5)	75.8 (4.3)	74.1 (3.9)	<0.01
Mean MMSE score†	26.1 (2.4)	26.8 (2.2)	26.7 (2.0)	0.30
Education (years)	9.6 (3.3)	11.1 (4.2)	11.5 (4.7)	0.04
Physical activity (min/wk)	570.8 (358.2)	696.4 (668.1)	541.4 (337.2)	0.65
Alcohol consumers (%)	71	78	85	0.16
Current smokers (%)	9	24	18	0.10
Depressive symptoms (%)‡	6	1	1	0.16
Energy intake (MJ/day)	8.8 (1.8)	8.9 (1.9)	9.1 (2.0)	0.82
Total fat (g)	88.2 (25.8)	91.3 (28.1)	92.4 (29.7)	0.88
Saturated fat (g)	37.9 (13.3)	39.6 (12.9)	37.7 (13.5)	0.39
Mono-unsaturated fatty acid (g)	31.7 (8.6)	32.2 (10.6)	33.1 (10.9)	0.95
Trans fatty acid (g)	7.2 (3.4)	6.1 (3.2)	6.7 (4.1)	0.14
Poly-unsaturated fatty acid (g)	15.7 (8.5)	16.4 (9.5)	18.2 (9.0)	0.11
Linoleic acid (g)	13.4 (8.7)	14.1 (9.3)	15.4 (8.7)	0.19
α-Linolenic acid (g)	1.1 (3.2)	1.1 (3.7)	1.2 (5.8)	0.29
EPA + DHA (mg)§	14.7 (11.1)	126.1 (103.0)	346.8 (291.0)	<0.001
Vitamin C (mg/day)	95.9 (45.9)	102.3 (63.4)	94.9 (44.8)	0.98
Vitamin E (mg/day)	9.5 (8.2)	14.0 (25.1)	10.4 (7.8)	0.38
Beta-carotene (mg/day)	2.2 (1.2)	2.0 (1.3)	2.1 (1.4)	0.64

Values are means (standard deviation) or percentages.
*Based on Kruskal-Wallis test,analysis of variance or chi-square test.
† Cognitive functioning measured with the Mini-Mental State Examination (MMSE) (range 0-30).
‡Depressive feelings measured with the Self-rating Depression Scale (SDS: range 25-100) developed by Zung. A value of at least 50 was used to indicate the presence of depressive symptoms, numbers of the three groups were respectively 49, 86, 71.
§ EPA= eicosapentaenoic acid; DHA= docosahexaenoic acids.

Cognitive functioning in 1990 did not differ among the categories of fish consumers (table 6.2). However, the decline in cognitive functioning was 1.0 point stronger in men who did not than in those who did consume fish.

No differences in cognitive functioning were found in 1990 among the tertiles of EPA + DHA intake (table 6.3). However, a dose-response relation was noted between tertiles of EPA + DHA intake

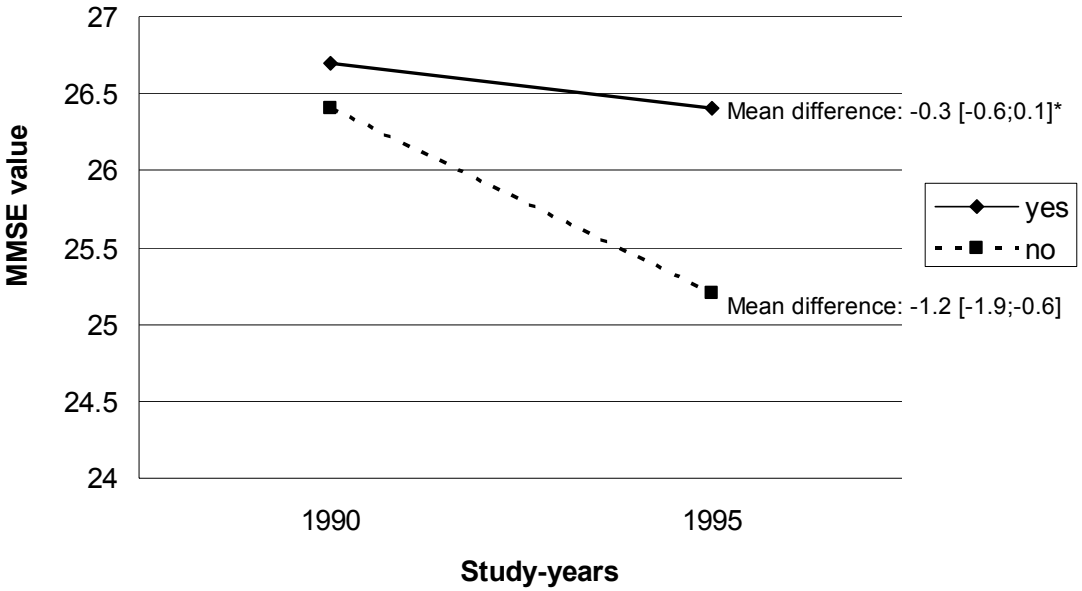

Figure 6.1. *Average five-year cognitive decline of elderly men who consumed fish and who did not consume fish in 1990.*

Multivariate linear regression analysis of 5-year cognitive decline in 210 elderly men in relation to fish consumption in 1990, showing the mean *change* in cognitive functioning between 1990 and 1995 [95% CI]. Cognitive functioning is measured with the Mini-Mental State Examination (MMSE). The score ranges between 0-30, with 30 indicating the highest cognitive functioning. Adjustments were made for age, education, alcohol consumption, smoking status, physical activity, energy intake and baseline cognitive functioning.
* Cognitive decline of 159 fish consumers is significantly different from that of 51 fish non-consumers (p=0.01).

Table 6.2. *Cognitive functioning of 210 elderly men per fish consumption category in 1990*.*

	Fish consumption			
	0 g/day (n = 51)	**>0 - 20 g/day (n = 86)**	**> 20 g/day (n = 73)**	**P for trend†**
Cognitive functioning in 1990‡	26.4 [25.8;26.9]§	26.8 [26.4;27.3]	26.5 [26.0;27.0]	0.81
5-year cognitive decline‖	-1.2 [-1.9;-0.6]	-0.2 [-0.7;0.3]	-0.3 [-0.9;0.2]	0.07

* Mean ± SD consumption was 11 ± 6 and 37 ± 21 g/day in the >0-20 and >20 g/day groups, recpectively.
† Based on a multivariate linear regression.
‡ Adjusted for age, education, alcohol consumption, smoking status, physical activity and energy intake.
§ Values are mean [95% CI].
‖ Adjusted for age, education, alcohol consumption, smoking status, physical activity, energy intake and baseline cognitive functioning.

and 5-year cognitive decline (p=0.01). The difference in cognitive decline between the highest and the lowest tertiles of EPA + DHA intake was 1.1 points.

Additional adjustments for the intakes of trans fatty acids and antioxidants and for depressive symptoms did not attenuate our results. The exclusion of men with impaired cognitive functioning (MMSE score below 24) in 1990 also did not change the results.

Table 6.3. *Cognitive functioning of 210 elderly men per tertile of eicosapentaenoic acid and docosahexaenoic acid (EPA + DHA) intake in 1990*.*

	EPA + DHA intake			
	Lowest tertile (n = 69)	**Middle tertile (n = 70)**	**Highest tertile (n = 71)**	**P for trend†**
Cognitive functioning in 1990‡	26.3 [25.8;26.8]§	26.9 [26.4;27.4]	26.6 [26.1;27.1]	0.36
5-year cognitive decline‖	-0.9 [-1.5;-0.3]	-0.7 [-1.3;-0.2]	0.2 [-0.4;0.7]	0.01

* Mean ± SD intake was 20 ± 15, 104 ± 27 and 398 ± 269 mg/day in the lowest, middle and highest tertile, recpectively.
† Based on a multivariate linear regression.
‡ Adjusted for age, education, alcohol consumption, smoking status, physical activity and energy intake.
§ Values are mean [95% CI].
‖ Adjusted for age, education, alcohol consumption, smoking status, physical activity, energy intake and baseline cognitive functioning.

Discussion

This study showed that fish consumption in older men was associated with less subsequent 5-year cognitive decline than was no fish consumption. Furthermore, a dose-response relation was noted between the combined intake of the n-3 fatty acids EPA and DHA and cognitive decline, which suggests that a higher intake of EPA + DHA was associated with less cognitive decline.

The strengths of the current study are its prospective population-based design, the availability of detailed information on n-3 fatty acids, the ability to adjust for multiple possible confounding factors and the availability of repeated measurements of cognitive functioning. The study has also limitations. Selection bias due to death and non-response could have influenced the results. However, that bias would probably have led only to an underestimation of the strength of the associations, because the men who dropped out of the current study consumed less fish and had a lower intake of EPA + DHA and lower cognitive test scores.

Bias due to cognitive impairment in 1990 could have influenced our results, because men with an impaired cognition could have changed their dietary habits or they may have given imprecise information about their actual food consumption. To reduce this differential misclassification, we also excluded men who were cognitively impaired (MMSE score below 24) in 1990.[20] The results did not change after the exclusion of these men. Therefore, differential misclassification was not a major problem in the current study. Although we adjusted for many possible confounding factors, we can not exclude residual confounding by risk factors that we did not measure.

Because multiple measurements of cognitive functioning were available, we were able to investigate associations for both cognitive impairment and cognitive decline. The results of the current study show that fish consumption and EPA + DHA intake are not significantly related to cognitive impairment but are significantly related to cognitive decline. This finding emphasizes the importance of repeated measures of cognitive functioning. Because the MMSE is a screening test that assesses overall cognitive functioning, we recommend that future studies include a more extensive battery of cognitive tests to obtain information about different cognitive domains.

Only a few studies have investigated the relations between fish consumption and the intake of n-3 fatty acids and cognitive decline. Results of the current study differ from earlier results of the Zutphen Elderly Study, in which no clear inverse association between fish consumption and 3-year cognitive decline could be shown.[6] In the current study, we observed a strong inverse association between the EPA + DHA intake and cognitive decline. Possible explanations for the discrepancy between the earlier results of the Zutphen Elderly Study and the current findings could be the longer follow-up period in the current study and the availability of data on the EPA and DHA content of animal and plant foods in addition to fish and seafood. However, in the Canadian Study of Health and Aging, an inverse relation between n-3 PUFA in plasma (an indicator of the total dietary intake of EPA + DHA) and cognitive decline was not found.[7] The Chicago Health and Aging Project showed that fish consumption but not the intake of n-3 fatty acids (from different food items) was associated with less cognitive decline.[8]

Although fish is the major source of the EPA and DHA consumed (71%), also other foods contain these fatty acids, such as meat (20%), eggs (6%) and plant foods (such as leek and cereal-based products, 3%).[12] In the past few years, several foods have been enriched with n-3 fatty acids because of the suggested positive effect of these n-3 fatty acids on health. Therefore, information on the EPA and DHA content of all foods in the diet is now required when associations between these fatty acids and cognitive functioning are studied.

Several biological mechanisms have been suggested for the associations observed in the current study. The n-3 fatty acids EPA and DHA provide protection against cardiovascular disease[10,26] by lowering blood triglycerides, improving platelet aggregation and endothelial function,[9,27] and increasing anti-arrhythmia.[28] They may also stabilize atherosclerotic plaques and reduce the risk of

athero-thrombotic complications. Furthermore, the n-3 fatty acids have anti-inflammatory effects[9] by inhibiting the synthesis of cytokines and mitogens.[29] High levels of inflammation, possibly due to β-amyloid peptides, could contribute to cognitive decline.[30] Finally, animal studies have shown that n-3 PUFAs have an effect on membrane excitability, play a role in brain development by stimulating synaptic plasticity and increasing neurotransmission,[11,31] and increase memory abilities[32].

Our results suggest that the n-3 fatty acids EPA and DHA may protect against cognitive decline. Elderly men who consumed an average of about 400 mg EPA + DHA per day had less (by 1.1 points) cognitive decline than did those who consumed about 20 mg EPA + DHA per day. In the population in the current study, fish is the main source of EPA and DHA intake and is therefore recommended as a first choice to increase the intake of these fatty acids. However, the results of the current study also show that approximately one-third of EPA + DHA ingested comes from foods other than fish (eg, meat, eggs, leek and cereal products) and thus their consumption can also contribute to higher EPA + DHA intake.

In conclusion, the current study provides evidence that a combined daily intake of about 400 mg n-3 PUFAs EPA and DHA (this is similar to 6 servings of about 140 grams lean fish per week (in total about 850 grams) or 1 serving of 140 grams fatty fish (such as mackerel and herring) per week) is associated with less subsequent cognitive decline in elderly men. Fish is the most important source of these fatty acids in the diet and its consumption is inversely associated not only with cognitive decline but also with cardiovascular disease.[10,26] To prevent cardiovascular disease mortality, the American Heart Association recommends the consumption of fish (preferably fatty fish) at least twice a week.[33] That recommendation is compatible with the results of the current study. However, results of other prospective cohort and intervention studies are needed to make more definitive statements on the association between n-3 fatty acids and cognitive decline.

References

1. Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42(5):776-782.
2. Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues JF, Renaud S. Fish, meat, and risk of dementia: cohort study. BMJ 2002;325(7370):932-933.
3. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60(7):940-946.
4. Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology 2002;59(12):1915-1921.
5. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62(2):275-280.
6. Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol 1997;145(1):33-41.
7. Laurin D, Verreault R, Lindsay J, Dewailly E, Holub BJ. Omega-3 fatty acids and risk of cognitive impairment and dementia. J Alzheimers Dis 2003;5(4):315-322.
8. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Fish Consumption and Cognitive Decline With Age in a Large Community Study. Arch Neurol 2005;62:1-5.
9. Holub DJ, Holub BJ. Omega-3 fatty acids from fish oils and cardiovascular disease. Mol Cell Biochem 2004;263(1-2):217-225.
10. He K, Song Y, Daviglus ML, Liu K, van Horn L, Dyer AR, Goldbourt U, Greenland P. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke 2004;35(7):1538-1542.
11. Newman PE. Alzheimer's disease revisited. Med Hypotheses 2000;54(5):774-776.
12. Meyer BJ. Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. Lipids 2003;38(4):391-398.
13. Bloemberg BP, Kromhout D, Obermann-De Boer GL, van Kampen-Donker M. The reproducibility of dietary intake data assessed with the cross-check dietary history method. Am J Epidemiol 1989;130(5): 1047-1056.
14. Block G. A review of validations of dietary assessment methods. Am J Epidemiol 1982;115(4):492-505.
15. NEVO Foundation. Netherlands Food Composition Table 2001. The Hague, Netherlands: The Netherlands Nutrition Center, 2001.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician . J Psychiatr Res 1975;12(3):189-198.
17. Fillenbaum GG, George LK, Blazer DG. Scoring nonresponse on the Mini-Mental State Examination. Psychol Med 1988;18(4):1021-1025.
18. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992;11 Suppl 1:2-13.
19. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40(9):922-935.
20. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115(2):122-132.
21. Caspersen CJ , Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol 1991;133(11):1078-1092.
22. Zung WW. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63-70.
23. Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, et al. Rates and risk factors for dementia and Alzheimer's disease:

results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology 1999;52(1):78-84.

24. Barberger-Gateau P, Jutand MA, Letenneur L, Larrieu S, Tavernier B, Berr C. Correlates of regular fish consumption in French elderly community dwellers: data from the Three-City study. Eur J Clin Nutr 2005;59(7):817-825.
25. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Schneider J, Wilson RS. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol 2003;60(2):194-200.
26. He K, Song Y, Daviglus ML, Liu K, van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation 2004;109(22):2705-2711.
27. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997;65(5 Suppl):1645S-1654S.
28. Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. Circulation 2003;107(21):2646-2652.
29. Blok WL, Katan MB, van der Meer JW. Modulation of inflammation and cytokine production by dietary (n-3) fatty acids. J Nutr 1996;126(6):1515-1533.
30. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, Launer L, Kuller L, Rubin S, Harris T. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology 2003;61(1):76-80.
31. McGahon BM, Martin DS, Horrobin DF, Lynch MA. Age-related changes in synaptic function: analysis of the effect of dietary supplementation with omega-3 fatty acids. Neuroscience 1999;94(1):305-314.
32. Gamoh S, Hashimoto M, Sugioka K, Shahdat Hossain M, Hata N, Misawa Y, Masumura S. Chronic administration of docosahexaenoic acid improves reference memory-related learning ability in young rats. Neuroscience 1999;93(1):237-241.
33. Kris-Etherton PM, Harris WS, Appel LJ, for the Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002;106:2747-2757.

Chapter 7

Decline in cognitive functioning is associated with a higher mortality risk

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Abstract

Objective. This study investigates the association between 5-year *change* in cognitive functioning and subsequent mortality.

Methods. Four hundred and ninety three Dutch and Italian men from the Finland, Italy and the Netherlands Elderly (FINE) Study, born between 1900 and 1920, participated in the present study between 1990 and 2000.

Cognitive functioning was measured with the Mini-Mental State Examination in 1990 and 1995 and mortality data were obtained until the year 2000. A proportional hazard analysis was used to investigate the association between 5-year *change* in cognitive functioning and subsequent 5-year mortality. Adjustments were made for age, education, country, lifestyle factors, prevalence of chronic diseases and additionally for baseline cognitive functioning.

Results. Men whose cognition decreased (more than one standard deviation) between 1990 and 1995 had a twofold higher risk of dying in the following five years compared with men whose cognition was stable (adjusted hazard ratio=1.9; 95% confidence interval: [1.3;2.7]). Mortality risk of men whose cognition improved between 1995 and 2000 was not different from men whose cognition was stable (adjusted hazard ratio=1.1; 95% confidence interval: [0.7;1.9]).

Conclusion. A decline in cognitive functioning is associated with a higher mortality risk.

Introduction

Currently, one out of every 10 persons is 60 years or older, in 2050 this will be one out of every five persons and by 2150, this will be one out of every three persons.[1] Concomitantly with ageing of the populations, the number of individuals with cognitive impairment[2] and mortality risk will increase tremendously. Various studies have already shown that both mild and severe cognitive impairment, dementia and Alzheimer's disease are associated with an increased mortality risk.[3-9]

Several longitudinal studies have investigated the association between the rate of cognitive decline and mortality and showed that a more rapid cognitive decline was associated with a higher mortality risk.[10-16] However, other studies could not confirm this.[17,18] Most studies investigated this association among persons with Alzheimer's disease, among non-European populations, or with a small number of participants. Less is known about persons in the general population and particularly in Europe.

An advantage of a longitudinal study design is that changes in cognitive functioning can be assessed. This is important, since cognitive functioning of elderly persons may change over time and the rate of cognitive decline is a precursor for dementia and Alzheimer's disease. Furthermore, it is of interest to know the prognosis of (progressive) cognitive decline on mortality. Therefore, the present study investigates the association between 5-year *change* in cognitive functioning with subsequent 5-year mortality in non-demented Northern and Southern European persons, while adjusting for confounding factors. Furthermore, we will investigate whether the association between cognitive *change* and mortality is the result of a pre-mortal drop, i.e. a decline in cognitive functioning due to a terminal disease. The present study was carried out between 1990 and 2000 in elderly men born between 1900 and 1920 in Italy and in the Netherlands.

Methods

Study population

Data of the Italian and Dutch cohorts of the Finland, Italy and the Netherlands Elderly (FINE) Study, a prospective cohort study, was used. The FINE Study consists of surviving men, born between 1900 and 1920 of the Finnish, Italian and Dutch cohorts of the Seven Countries Study (SCS), which was originally designed in 1959 to examine the relationships between cardiovascular risk factors and health.[19] The FINE Study started around 1985 and repeated measurements were carried out around 1990, 1995 and 2000. Cognitive functioning was measured from 1990 onwards. Since cognitive decline between 1990 and 1995 could not be established for the Finnish men - the Mini-Mental State Examination (MMSE) was not examined in 1995 in Finland - our study population consists of Italian and Dutch men only.

In the 1990 survey, 493 Italian men were still alive of whom 391 (79%) were examined. These men lived in Crevalcore, about 30 kilometres north of Bologna and Montegiorgio, 30 kilometres inland from the Adriatic Sea. From the Dutch cohort of Zutphen, a town located in the eastern part of the Netherlands, 718 men were still alive during the 1990 survey, of whom 77% (556 men) participated. In the present study, we only included men whose cognition has been measured in both 1990 (n=925) and 1995 (n=546) and of whom information on demographic, lifestyle and chronic diseases was present. In total, 493 men participated in the present study. Two hundred and eleven men were of Italian and 282 men of Dutch origin. A detailed flow chart of the study population is given in figure 7.1.

More detailed information of this study population is described elsewhere.[20] Data were collected in 1990, 1995 and 2000 according to the international protocol used in previous surveys of the SCS.[19] Approval of the Medical Ethics Committee for each participating cohort was required in the FINE protocol.

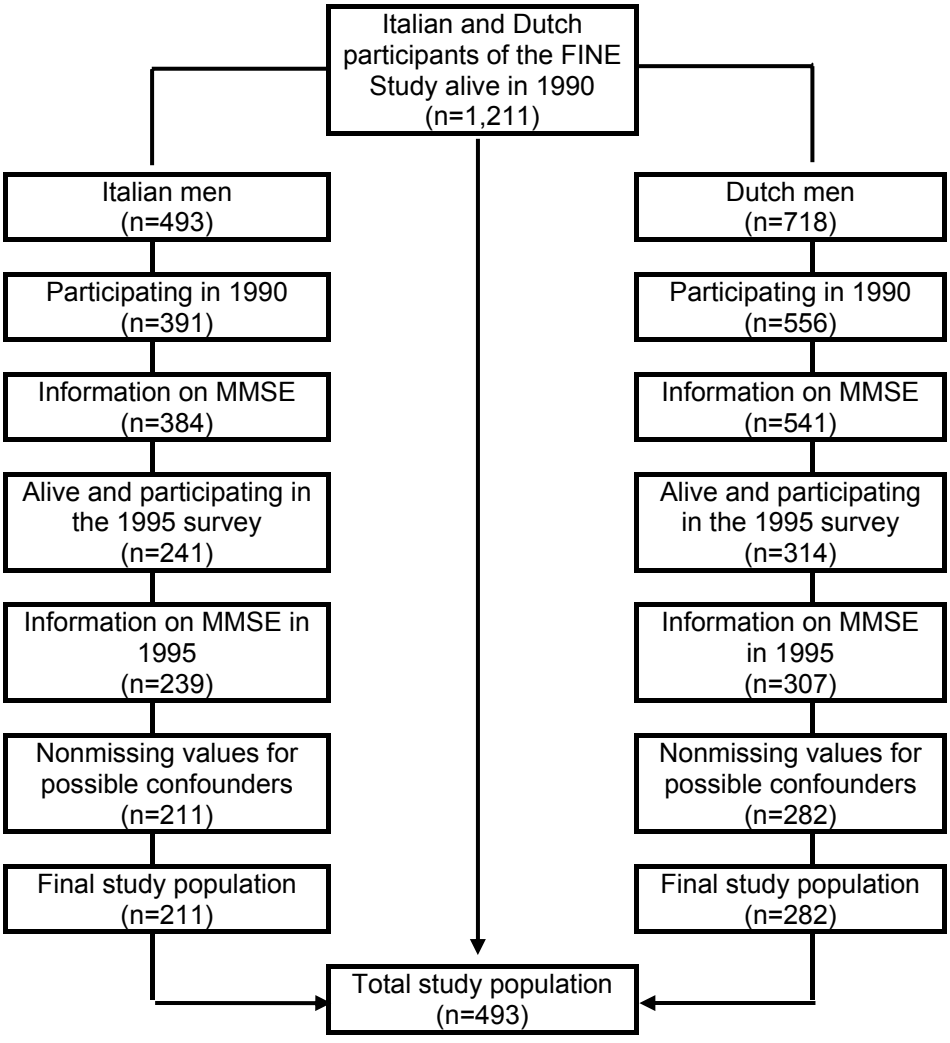

***Figure 7.1**. Flow chart of the study population.*

Cognitive functioning

To measure overall cognitive functioning, the MMSE was used.[21] This screening test includes questions on orientation to time and place, registration, attention and calculation, recall, language and visual construction. The maximum score is 30 points and a higher score indicates a better cognitive functioning. If a subject did not answer four or more individual items (of a total of 20), the total MMSE score was considered missing. If less than four items were missing, missing items were rated as errors and a total MMSE score was still calculated.[22]

Originally, the MMSE was created for clinical use, but now it is extensively used in epidemiological studies and has proven to be a reliable and valid indicator of cognitive impairment, with a good test-retest reliability.[23-25] Although the MMSE is a measure of global cognitive functioning and does not assess different cognitive domains in detail, it is sensitive enough to detect 'clinically significant' global cognitive decline.[26]

Five-year *change* in cognitive functioning was divided into the following categories: better cognition was defined as an increase of more than 2.76 points (one standard deviation (SD) of the mean 5-year *change* in cognition) on the MMSE during five years; worse cognition was defined as a decrease of more than 2.76 points on the MMSE, and stable cognition as no *change* or a *change* of maximal 2.76 points over five years.

Mortality

Mortality data were obtained every five years until the year 2000 from municipal registries of the cohorts concerned. The censor date for the Dutch cohort and the Italian cohort of Montegiorgio was June 2000, and for the Italian cohort of Crevalcore March 2000. Five men were lost to follow-up. These men were censored on the date of the last examination.

Other variables

Demographic, lifestyle and other information was obtained with standardised questionnaires in Italy and the Netherlands. Education was assessed as the number of years of formal education. Smoking status was categorised into never, former and current smoking, and alcohol consumption was categorised into consumers and non-consumers. Information about self-rated health was categorised into healthy and not healthy and marital status was classified into married and unmarried. Physical activity was measured with a validated self-administered questionnaire especially designed for retired men,[27] functional status with a self-administered questionnaire which measures activities of daily living[28] and depressive symptoms with a self-rating depression scale, originally designed by Zung.[29] Height and weight were measured and the body mass index was calculated by dividing the weight by the square of the height (kg/m^2). Information on the

frequency of coffee consumption was obtained with a self-administered questionnaire in Italy and with a cross-check dietary history method in the Netherlands.[30] Information on the use of anti-hypertensive drugs was collected by a standardised questionnaire and information about the prevalence of myocardial infarction, stroke, diabetes and cancer was obtained by questionnaires and validated with information from hospital registries or general practitioners.

Statistical analyses

Differences in characteristics (in 1990 and 1995) according to the vital status of the men in 2000 were tested with the Wilcoxon test for not normally distributed variables and the Chi-square test for categorical variables. The non-parametric Kruskall-Wallis test was used to evaluate differences in continuous baseline characteristics between categories of *change* in cognition (better, worse or stable cognition) and the Chi-square test for differences in categorical data.

To assess the relationship between *change* in cognitive functioning between 1990 and 1995 (decrease, increase, stable) and 5-year mortality, multivariate Cox's proportional hazard models were used. In these models, *change* in cognitive functioning was entered as a dummy variable with stable cognitive functioning as reference category. We inspected the proportional hazard assumption and concluded that this assumption was met.

To investigate whether pre-mortal drop in cognitive functioning and/or disease status in the last years of life have influenced our results, we redid the analyses without the men who had died within the first year after the assessment of cognitive functioning.

Adjustments were made for age, education, country, smoking status, alcohol consumption, physical activity, functional status, depressive symptoms, and prevalence of myocardial infarction, diabetes, stroke and cancer. In the analyses regarding *change* in cognitive functioning, we also adjusted for baseline cognitive functioning. Additional adjustments were made for marital status, self-rated health, coffee consumption, use of anti-hypertensive drugs and body mass index. We also examined whether an interaction was present between *change* in cognitive functioning and mortality by country, by adding the product term of these variables to the model. All statistical analyses were carried out using SAS software (version 9.1; SAS Institute, Inc., Cary, North Carolina, USA). Two-sided p-values of 0.05 or less were considered to be statistically significant.

Results

Men who did not participate in 1995 or who had died before 1995 were overall older ($p<0.0001$), had worse cognitive functioning scores in 1990 ($p<0.0001$), less years of education ($p<0.01$), spent

less time on physical activities per day (p<0.0001), consumed less alcohol (p<0.0001), and had higher prevalence of myocardial infarction, diabetes and stroke (p<0.05).

Of the 493 men who participated in the present study, 311 men survived until the year 2000 and 182 men died between 1995 and 2000. In 1990, the survivors were overall younger, smoked less often, were more physically active, had fewer depressive symptoms and were less often disabled than those who had died (table 7.1). In 1995, the survivors were still younger, had higher cognitive test scores, were still more physically active, less disabled and had a lower prevalence of myocardial infarction and cancer than those who died (table 7.2).

Table 7.1. *Baseline characteristics (1990) of 493 Italian and Dutch participants according to their vital status in 2000.*

	Participants (n=493)		
Characteristics in 1990	**Survivors (n=311)**	**Died (n=182)**	**p-value***
Mean age (years)	75.3 (3.6)	77.2 (4.3)	<0.0001
Years of education	8.2 (4.6)	8.4 (4.6)	0.44
Cognitive functioning in 1990 (unadjusted) †	25.8 (3.0)	25.6 (3.0)	0.27
Current smoker (%)	15	24	0.01
Alcohol consumer (%)	80	81	0.92
Physical activity (min/wk)	796.1 (743.3)	648.9 (665.1)	0.01
Depressive symptoms (%)‡	5	12	0.01
Disabled (%)	7	19	0.0002
Prevalence in 1990:			
Myocardial infarction (%)	8	11	0.27
Diabetes (%)	7	10	0.27
Stroke (%)	4	3	0.63
Cancer (%)	7	8	0.54
Country:			0.14
Dutch men (%)	55	62	
Italian men (%)	45	38	

Values are means (standard deviation) or percentages.
*Calculated with the Wilcoxon test for skewed distributed variables and Chi-square test for categorical variables.
† Cognitive functioning measured with he Mini-Mental State Examination (MMSE: range 0-30).
‡ Depressive feelings measured with the Self-rating Depression Scale (SDS: range 25-100) developed by Zung. A value of at least 50 was used to indicate the presence of depressive symptoms.

Table 7.2. *Characteristics in 1995 of 493 Italian and Dutch participants according to their vital status in 2000.*

	Participants (n=493)		
Characteristics in 1995	**Survivors (n=311)**	**Died (n=182)**	**p-value***
Mean age (years)	79.9 (3.6)	81.8 (4.3)	<0.0001
Years of education	8.2 (4.6)	8.4 (4.6)	0.44
Cognitive functioning in 1995 (unadjusted) †	25.9 (3.1)	24.6 (3.6)	<0.0001
Current smoker (%)‡	13	18	0.11
Alcohol consumer (%)‡	76	70	0.13
Physical activity (min/wk)§	617.4 (678.5)	362.7 (447.4)	<0.0001
Depressive symptoms (%)‖	10	11	0.62
Disabled (%)¶	16	40	<0.0001
Prevalence in 1990:			
Myocardial infarction (%)	12	21	0.001
Diabetes (%)**	11	15	0.17
Stroke (%)	12	13	0.60
Cancer (%)	10	18	0.01
Country:			0.14
Dutch men (%)	55	62	
Italian men (%)	45	38	

Values are means (standard deviation) or percentages.
*Calculated with the Wilcoxon test for skewed distributed variables and Chi-square test for categorical variables.
† Cognitive functioning measured with he Mini-Mental State Examination (MMSE: range 0-30).
‡ Numbers are 311 and 181, respectively.
§ Numbers are 310 and 172, respectively.
‖ Depressive feelings measured with the Self-rating Depression Scale (SDS: range 25-100) developed by Zung. A value of at least 50 was used to indicate the presence of depressive symptoms. Numbers are 308 and 173, respectively.
¶ Numbers are 306 and 179, respectively.
** Numbers are 309 and 182, respectively.

Men whose cognition decreased more than one SD between 1990 and 1995 were overall older at baseline, had higher baseline cognitive test scores and a lower prevalence of cancer than men whose cognition was stable or increased between 1990 and 1995 (table 7.3). Men whose cognition did not change between 1990 and 1995 were the youngest, had had slightly more years of education and were slightly less often disabled. Men whose cognition increased had overall lower cognitive test scores in 1990, had less years of education and a higher prevalence of cancer than the other men.

***Table 7.3**. Baseline characteristics of 493 Italian and Dutch participants according to their change in cognitive function between 1990 and 1995.*

	Participants (n=493)			
Characteristics in 1990	**Decrease in cognition (n=86)**	**Stable cognition (n=350)**	**Increase in cognition (n=57)**	**p-value***
Mean age (years)	77.2 (4.1)	75.6 (3.9)	76.6 (3.8)	0.002
Years of education	8.2 (3.9)	8.5 (4.8)	7.0 (3.8)	0.09
Cognitive functioning in 1990 (unadjusted) †	26.3 (3.1)	26.1 (2.7)	22.4 (3.3)	<0.0001
Current smoker (%)	20	17	21	0.74
Alcohol consumer (%)	77	82	75	0.30
Physical activity (min/wk)	786.7 (744.0)	714.2 (715.2)	842.8 (697.3)	0.33
Depressive symptoms (%)‡	8	8	5	0.76
Disabled (%)	19	10	11	0.08
Prevalence in 1990:				
Myocardial infarction (%)	5	10	9	0.27
Diabetes (%)	3	9	7	0.19
Stroke (%)	3	4	0	0.34
Cancer (%)	1	8	11	0.05
Country:				0.76
Dutch men (%)	58	58	53	
Italian men (%)	42	42	47	

Values are means (standard deviation) or percentages.
*Calculated with the Kruskall-Wallis test for skewed distributed variables and Chi-square test for categorical variables.
† Cognitive functioning measured with he Mini-Mental State Examination (MMSE: range 0-30).
‡ Depressive feelings measured with the Self-rating Depression Scale (SDS: range 25-100) developed by Zung. A value of at least 50 was used to indicate the presence of depressive symptoms.

Men whose cognition decreased more than one SD between 1990 and 1995 had a twofold increased risk of dying in the following five years compared with men whose cognition did not change between 1990 and 1995 (hazard ratio $(HR)_{unadjusted}$=2.0; 95% confidence interval (CI): [1.5;2.9] and $HR_{adjusted}$=1.9; 95% CI: [1.3;2.7]) (table 7.4). Mortality risk of men whose cognition had improved between 1995 and 2000 was not different from men whose cognition was stable ($HR_{unadjusted}$=1.2; 95% CI: [0.7;1.9] and $HR_{adjusted}$=1.1; 95% CI: [0.7;1.9]). After exclusion of the men who had died within the first year after the assessment of cognitive functioning, the results were

only slightly attenuated ($HR_{decrease, adjusted}$=1.7; 95% CI: [1.1;2.7] and $HR_{increase, adjusted}$=1.0; 95% CI: [0.5;1.8]).

Additional adjustments for marital status, self-rated health, coffee consumption, use of anti-hypertensive drugs and body mass index did not influence the results of the present study (results not shown). Also, no interaction was present between *change* in cognitive functioning and mortality by country.

Table 7.4. *Hazard ratios for change in cognitive functioning between 1990 and 1995 on all-cause mortality between 1995 and 2000 among 493 Italian and Dutch men.*

Change* in MMSE-score between 1990 and 1995	**Deceased/ total**	**Deceased %**	**Unadjusted hazard ratio**		**Adjusted hazard ratio†**	
Stable	115/350	33	1.0	-	1.0	-
Increase	20/57	35	1.2	[0.7;1.9]	1.1	[0.7;1.9]
Decrease	47/86	55	2.0	[1.5;2.9]	1.9	[1.3;2.7]

Figures in parentheses are 95% confidence intervals.
* Decrease is defined as a decrease of more than one standard deviation (SD) on the Mini-Mental State Examination (MMSE) during five years; increase is defined as an increase of more than one SD during five years; stable is defined as no *change* or a *change* of maximal one SD over five years.
† Adjustments were made for age, education, country, smoking status, alcohol consumption, physical activity, functional status, depressive symptoms, physical activity, prevalence of myocardial infarction, diabetes, stroke and cancer, and baseline cognitive functioning.

Discussion

This prospective population-based cohort study of Italian and Dutch elderly men showed that men who decreased more than one SD in cognitive performance over five years had an almost two times higher mortality rate in the five years thereafter than men with a stable cognition. This effect was independent of physical and psychological functioning, marital status and life style factors, such as smoking, alcohol consumption and physical activity.

Some methodological issues should be discussed. The advantage of the present study is the prospective assessment of cognitive function, enabling the investigation of the relationship between *change* in cognitive function and subsequent 5-year mortality. Due to the 5-year follow-up, we were also able to exclude men who had died within the first year after the assessment of cognitive decline, to examine whether pre-mortal drop and/or disease status in the last year of life

could have influenced the cognitive test scores and the results of the present study. In addition, numerous important potential confounding factors could be adjusted for in the present study.

A disadvantage of the present study is the relatively small number of participants due to attrition. Only 41% of the men of the initial sample were included in the present study (n=493) and only 59% of the men who participated in the MMSE in 1990 had a MMSE score in 1995. However, despite this small number, consistent and significant results were observed. Men who were excluded from our study population due to death or incomplete data at follow-up were overall older, had less education, lower baseline cognitive test scores, were less physically active, consumed less alcohol and had a higher prevalence of chronic diseases. According to this information, it is likely that the decline in cognitive functioning and the mortality rate are underestimated in the present study. Therefore, the strength of the association between *change* in cognitive functioning and subsequent 5-year mortality is probably an underestimation.

In the present study, we have shown results for Dutch and Italian men together, because there was no interaction present between *change* in cognitive functioning and mortality by country. Cause-specific analyses instead of all-causes mortality could not be performed, because the number of participants for the different causes of death were too small for meaningful analyses.

The MMSE is a screening test that measures global cognitive functioning and does not assess different cognitive domains in detail. In spite of this, the MMSE is sensitive enough to detect 'clinically significant' global cognitive decline and it is still a valid and reliable instrument for measuring cognitive functioning with a good test-retest reliability.[23-26]

Our finding of an association between a decrease in cognition and a higher mortality rate supports the notion that cognitive functioning decreases more rapidly in the last years of life, as observed in other studies.[12,13] The prospective Religious Orders Study showed that in the last three years of life cognitive function sharply decreases[13] and a prospective study in the United States found that the rate of cognitive decline in patients with Alzheimer's disease was associated with mortality.[12] The first study was carried out in older Roman Catholic clergy members from the USA and the second among Americans with Alzheimer's disease. Some previous studies also showed that a more rapid cognitive decline (or memory decline) was associated with an increased mortality risk,[10,11,14-16] but other studies did not find such an association.[17,18] The present study showed that 5-year *change* in overall cognitive functioning is associated with subsequent 5-year mortality in general populations in both Northern and Southern Europe.

Different mechanisms may explain our results. A decrease in cognitive functioning can lead to an unhealthy lifestyle, e.g. not taking good care of oneself or forgetting to take ones medication, which in turn may increase the risk of death. On the other hand, a worse health status can result in cognitive decline and concurrently will increase the risk of dying. This explanation is less likely, because the results of the present study showed that the pre-mortal drop in cognitive functioning

and/or disease status had only a small influence on the association between cognitive decline and all-causes mortality.

Conclusion

The present study showed that a decrease in cognitive functioning is associated with a higher mortality risk.

References

1. United Nations. Report of the Second World Assembly on Aging. Madrid, Spain: United Nations, April 8-12, 2002.
2. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. Neurology 1998;51:728-733.
3. Gussekloo J, Westendorp RG, Remarque EJ, Lagaay AM, Heeren TJ, Knook DL. Impact of mild cognitive impairment on survival in very elderly people: cohort study. BMJ 1997;315:1053-1054.
4. Smits CH, Deeg DJ, Kriegsman DMW, Schmand B. Cognitive functioning and health as determinants of mortality in an older population. Am J Epidemiol 1999;150:978-986.
5. Baldereschi M, Di Carlo A, Maggi S, Grigoletto F, Scarlato G, Amaducci L, Inzitari D. Dementia is a major predictor of death among the Italian elderly. ILSA Working Group. Italian Longitudinal Study on Aging. Neurology 1999;52:709-713.
6. Neale R, Brayne C, Johnson AL. Cognition and survival: an exploration in a large multicentre study of the population aged 65 years and over. Int J Epidemiol 2001;30:1383-1388.
7. Larson EB, Shadlen M, Wang L, McCormick WC, Bowen JD, Teri L, Kukull WA. Survival after diagnosis of Alzheimer Disease. Ann Intern Med. 2004;140:501-509.
8. Brookmeyer R, Corrada MM, Curriero FC, Kawas C. Survival following a diagnosis of Alzheimer disease. Arch Neurol 2002;59:1764-1767.
9. Eaker ED, Vierkant RA, Michel SF. Predictors of nursing home admission and/or death in incident Alzheimer's disease and other dementia cases compared to controls: a population-based study. J Clin Epidemiol 2002;55:462-468.
10. Bassuk SS, Wypij D, Berkman LF. Cognitive impairment and mortality in the community-dwelling elderly. Am J Epidemiol 2000;151:676-688.
11. Deeg DJ, Hofman A, van Zonneveld RJ. The association between change in cognitive function and longevity in Dutch elderly. Am J Epidemiol 1990;132:973-982.
12. Hui JS, Wilson RS, Bennett DA, Bienias JL, Gilley DW, Evans DA. Rate of cognitive decline and mortality in Alzheimer's disease. Neurology 2003;61:1356-1361.
13. Wilson RS, Beckett LA, Bienias JL, Evans DA, Bennett DA. Terminal decline in cognitive function. Neurology 2003;60:1782-1787.
14. Schupf N, Tang MX, Albert SM, Costa R, Andrews H, Lee JH, Mayeux R. Decline in cognitive and functional skills increases mortality risk in nondemented elderly. Neurology 2005;65(8):1218-1226.
15. Brodaty H, McGilchrist C, Harris L, Peters KE. Time until institutionalization and death in patients with dementia. Role of caregiver training and risk factors. Arch Neurol 1993;50(6):643-650.
16. Wilson RS, Li Y, Aggarwal NT, McCann JJ, Gilley DW, Bienias JL, Barnes LL, Evans DA. Cognitive decline and survival in Alzheimer's disease. Int J Geriatr Psychiatry 2006;21:356-362.
17. Bruce ML, Hoff RA, Jacobs SC, Leaf PJ. The effects of cognitive impairment on 9-year mortality in a community sample. J Gerontol B Psychol Sci Soc Sci 1995;50:P289-P296.
18. Hassing LB, Johansson B, Berg S, Nilsson SE, Pedersen NL, Hofer SM, McClearn G. Terminal decline and markers of cerebro- and cardiovascular disease: findings from a longitudinal study of the oldest old. J Gerontol B Psychol Sci Soc Sci 2002;57:P268-P276.
19. Keys A, Aravanis C, Blackburn HW, van Buchem FS, Buzina R, Djordjevic BD, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl 1966;460:1-392.
20. Bijnen FC, Feskens EJ, Caspersen CJ, Giampaoli S, Nissinen AM, Menotti A, Mosterd WL, Kromhout D. Physical activity and cardiovascular risk factors among elderly men in Finland, Italy, and the Netherlands. Am J Epidemiol 1996;143:553-561.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

22. Fillenbaum GG, George LK, Blazer DG. Scoring nonresponse on the Mini-Mental State Examination. Psychol Med 1988;18:1021-1025.

23. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922-935.

24. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115:122-132.

25. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992;11 Suppl 1:2-13.

26. Lyketsos CG, Garrett E, Liang KY, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. Am J Epidemiol 1999;149:794-800.

27. Caspersen CJ , Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol 1991;133:1078-1092.

28. Hoeymans N, Feskens EJ, van den Bos GA, Kromhout D. Measuring functional status: cross-sectional and longitudinal associations between performance and self-report (Zutphen Elderly Study 1990-1993). J Clin Epidemiol 1996;49:1103-1110.

29. Zung WW. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63-70.

30. Kromhout D, Nissinen A, Menotti A, Bloemberg B, Pekkanen J, Giampaoli S. Total and HDL cholesterol and their correlates in elderly men in Finland, Italy, and The Netherlands. Am J Epidemiol 1990;131:855-863.

Chapter 8

General discussion

Baby boomers are now growing into old age. With this ageing of the population, the number of persons with cognitive impairment, dementia and Alzheimer's disease will also increase. 'Normal' cognitive functioning declines over the years and may lead to cognitive impairment, a transitional but progressively degenerative cognitive phase that precedes dementia or Alzheimer's disease.[1,2] Severe cognitive decline can finally lead to dementia or Alzheimer's disease.[1,2] In the Netherlands, the prevalence rate of dementia in persons aged 65 years is about 1% and raises up to approximately 40% in persons aged 90 years and above.[3,4] In 2000, 1 in every 93 persons aged 65 years and above in the Netherlands had dementia. Because of the increasing life expectancy, this will be 1 in every 81 in 2010, 1 in every 57 in 2030 and even 1 in every 44 persons in 2050.[5] About 90% of all demented persons is above the age of 65 years.

It is important to age healthy because it may not only reduce healthcare costs but also diminishes functional, psychological, emotional and financial problems and distress for the elderly themselves as well as for their family and caregivers.[6,7] Since in our ageing population the number of people with cognitive impairment, dementia and Alzheimer's disease increases, the need for preventive action is high. No treatment or medication has convincingly shown to cure or even stop the process of cognitive decline and dementia yet.[8] Therefore, it is important to identify (modifiable) risk factors in order to develop effective strategies for the postponement of cognitive decline and dementia.

The aim of this thesis is to study cognitive decline in older European men and to identify modifiable risk factors for cognitive decline. C*hanges* in cognitive functioning over time, (*changes* in) social, lifestyle and dietary risk factors for cognitive decline and the relationship between *change* in cognitive functioning and mortality are described.

In this chapter, we discuss the main findings of this thesis. Furthermore, methodological considerations, strengths of the associations and public health implications will be discussed.

Main findings

Table 8.1 provides an overview of the main findings presented in this thesis.

Changes in cognitive functioning (Chapter 2)

It is known that cognitive functioning decreases with increasing age.[9,10] However, it was not known if this is due to an age, a period, or birth cohort effect or combinations of these effects. Therefore, we examined, with different statistical methods, the influence of ageing, period and birth cohort on

10-year cognitive decline in 1,363 older men from Finland, Italy and the Netherlands. Our results showed that the 10-year cognitive decline was due to an age effect, but also to a period as well as a birth cohort effect. The age effect is probably due to ageing of the brain, the period effect suggests better cognitive functioning later in time and the cohort effect may be explained by better cognitive functioning in elderly who belong to a later birth cohort. Our results suggest that both the internal (e.g. ageing of the brain) and external environment (e.g. surrounding and time in which someone is born) influence cognitive functioning.

Marital status, living situation and cognitive decline (chapter 3)

Social situations change frequently among older persons, due to for example the loss of a partner. Literature provides evidence that being married or living with others can protect against dementia.[11,12] However, no information was available on change in social situations in the elderly in relation with cognitive decline. We showed that older men from Finland, Italy and the Netherlands who were married or who lived with others during five years had a smaller subsequent 10-year cognitive decline compared with older men who lost a partner, who were unmarried, who started to live alone or who lived alone. In addition, our results suggested that marital status may be a stronger predictor for cognitive decline than living situation. Based on the results of this study we conclude that cognitive decline may be postponed if elderly men are married or surrounded by others in stead of staying alone.

Physical activity and cognitive decline (chapter 4)

Physical activity may help to maintain cognitive functioning,[13-15] however, it was not known which component of physical activity, i.e. duration or intensity, is associated with cognitive functioning. Especially in old age, physical activities will be performed less often and/or at a lower pace. We investigated among older Finnish, Italian and Dutch men whether duration and intensity of physical activity (all activities with an intensity of more than two kilocalories/kilogram•hour) were associated with subsequent 10-year cognitive decline. Furthermore, we also examined whether 10-year *change* in duration or intensity was associated with 10-year cognitive decline. Cognitive decline did not differ among men with a high or low duration of physical activities, but did differ among men in different intensity categories. Performing activities with at least a medium-low intensity (like walking at about three miles per hour) was associated with less subsequent cognitive decline. Furthermore, a decrease in activity duration of more than 60 minutes per day over 10 years or a decrease in intensity of at least half a standard deviation (such as a change in walking velocity of 0.5 miles per hour) over 10 years were both associated with an increase in cognitive decline. Our results suggest that even in old age physical activity may delay cognitive decline.

Table 8.1. *Overview of the results presented in this thesis.*

Ch	Objective	Data	Results	Conclusion
2	To disentangle age, period and birth cohort effects in cognitive functioning.	1,363 men, followed for 10 years (FINE Study).	A decrease in 10-year cognitive decline of 1.5 points (p<0.01) was attributable to an age effect, but also to a period and birth cohort effect. Men aged 90 years had a 2.6 points lower cognitive functioning than men aged 70 years (p<0.01) (age effect). Men born between 1916-1920 had a 1.99 points better cognitive functioning than men of the same age born between 1900-1910 (p<0.01) (birth cohort effect). Men participating in 2000 had a 1.67 points higher cognitive functioning than men of similar age participating in 1990 (p<0.01) (period effect).	The observed cognitive decline over 10 years could be explained by internal influences such as ageing of the brain as well as external influences such as the elderly's environment as well as the time in which a person is born.
3	To investigate 5-year *change* in marital status and living situation on subsequent 10-year cognitive decline.	1,042 men, followed for 15 years (FINE Study).	Men who were married in both 1985 and 1990 had a subsequent 10-year cognitive decline of 1.1 points (95% CI: [0.9;1.4]). Those who were married in 1985 and unmarried in 1990 had a 10-year *additional* decline of 1.0 point (95% CI: [0.1;1.9]) and those who were unmarried both years had an *additional* decline of 1.3 points (95% CI: [0.5;2.1]). Men who lived with others in both 1985 and 1990 had a 10-year cognitive decline of 1.1 points (95% CI: [0.8;1.4]). Those who lived with others in 1985 and alone in 1990 had an *additional* decline of 1.1 points (95% CI: [0.2;2.0]) and those who lived alone in both years had an *additional* decline of 2.7 points (95% CI: [1.7;3.7]).	Elderly men who lost a partner and men who were unmarried during five years had a two times stronger cognitive decline than men who were married in those years. Men who started to live alone and men who lived alone had a respectively two times and three and a half times stronger cognitive decline compared with men who lived with others those years.
4	To investigate the effect of (*change* in) duration and intensity of physical activity on cognitive decline.	295 healthy survivors followed for 10 years (FINE Study).	There were no differences in the rate of cognitive decline among the different categories of duration of physical activity. Men in the lowest intensity quartile had a 1.8 till 3.5 times stronger cognitive decline than men in the other quartiles (p=0.07 till p=0.004). A decrease in duration of more than 60 minutes per day over 10 years was associated with a 2.6 times (p=0.06) stronger cognitive decline than maintaining duration. A decrease in intensity of at least half a SD over 10 years was associated with a 3.6 times stronger decline than maintaining intensity (p=0.003).	Even in old age, participation in activities with at least a medium-low intensity (like walking at about three miles per hour) may postpone cognitive decline. Moreover, a decrease in duration or intensity of physical activity may result in a stronger cognitive decline than maintaining duration or intensity.
5	To examine the association between coffee consumption and cognitive decline.	676 men followed for 10 years (FINE Study).	Coffee consumers had a 10-year cognitive decline of 1.2 points. Non-consumers had an *additional* decline of 1.4 points (p<0.001). An inverse and J-shaped association was observed between the number of cups of coffee consumed and cognitive decline, with the smallest cognitive decline for three cups of coffee per day (0.6 point). This decline was two points smaller than the decline of non-consumers (p<0.001).	Our findings suggest that consuming coffee may postpone cognitive decline in elderly men. An inverse and J-shaped association was observed between the number of cups of coffee consumed and cognitive decline, with the least cognitive decline for those consuming three cups of coffee per day.
6	To examine the relationship of fish consumption and the intake of n-3 fatty acids EPA + DHA (from fish and other foods) on cognitive decline.	210 men followed for 5 years (Zutphen Elderly Study).	Men who did not consume fish showed a four times stronger cognitive decline than fish consumers (p=0.01). No dose-response relationship could be observed between fish consumption and cognitive decline. A dose-response relation was found between intake of EPA + DHA and cognitive decline. Men who had an intake of EPA + DHA of about 400 mg/day had 1.1 points less 5-year cognitive decline compared with men who had an intake of about 20 mg/day (p=0.01).	Fish consumption and a higher intake of EPA + DHA are both associated with less 5-year subsequent cognitive decline among elderly men. Only the intake of EPA + DHA showed a dose-response relationship with cognitive decline. Besides fish, other foods (e.g eggs, meat, leek and cereal based products) contributed to the intake of EPA + DHA.
7	To investigate the association between 5-year *change* in cognitive functioning on subsequent 5-year mortality.	493 men followed for 10 years (FINE Study).	A decrease in cognitive functioning of more than one SD over five years was associated with a twice as high mortality risk compared with no change in cognition (HR=1.9; 95% CI: [1.3;2.7]). An increase in cognitive functioning over five years showed the same mortality risk as no change in cognition (HR=1.1; 95% CI: [0.7;1.9]).	Elderly men with a decline in cognitive functioning had a two times higher mortality risk compared to elderly men with a stable cognition.

Abbreviations: Ch, chapter; FINE, Finland, Italy and the Netherlands Elderly; CI, confidence interval; SD, standard deviation; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; mg, milligram; HR, hazard ratio

Coffee consumption and cognitive decline (chapter 5)

Many people consume several cups of coffee, the main source of caffeine, each day. Coffee consumption may be associated with better cognitive functioning,[16,17] however, literature was scarce. We investigated whether coffee consumption was associated with 10-year cognitive decline among elderly men in Finland, Italy and the Netherlands. Results showed that coffee consumption was inversely associated with cognitive decline. Men who consumed coffee had a two times smaller cognitive decline compared with non-consumers. Furthermore, an inverse and J-shaped association was observed between the number of coffee cups consumed and cognitive decline, with the least cognitive decline for those consuming three cups of coffee per day. This decline was 4.3 times smaller than the decline of non-consumers. The decline of men who consumed more than four cups of coffee a day was borderline significantly smaller (p=0.07) compared to men who did not consume coffee. We conclude that moderate coffee consumption may lower cognitive decline in elderly men.

Fish consumption, intake of n-3 fatty acids and cognitive decline (chapter 6)

Fish is the main source of n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). N-3 fatty acids may reduce the risk of cardiovascular diseases.[18,19] Having a stroke is associated with a higher risk of cognitive decline.[20,21] Therefore, fish consumption may also be beneficial for cognitive functioning. We examined whether fish consumption and intake of the n-3 fatty acids EPA + DHA (from fish and other (animal and plant) foods were associated with 5-year cognitive decline in older Dutch men. Fish consumption was associated with less cognitive decline compared with consuming no fish. A dose-response relationship was observed between the intake of EPA + DHA and cognitive decline, showing that a higher intake of EPA + DHA was associated with less cognitive decline. An intake of EPA + DHA of about 400 mg per day was associated with the lowest cognitive decline. Our results indicate that fish consumption and a higher intake of EPA + DHA may postpone cognitive decline. In addition, about one third of the intake of EPA + DHA was from foods other than fish, such as meat, eggs, leek and cereal products. These products can also contribute to a higher intake of EPA + DHA besides fish.

***Change* in cognitive functioning and mortality** (chapter 7)

Cognitive decline and subsequent dementia are associated with an increased mortality risk.[22-24] Cognitive decline decreases more rapidly in the last years of life.[25,26] We investigated whether *change* in cognitive functioning in cognitively intact Dutch and Italian elderly men was associated with a higher mortality risk. Furthermore, we examined whether this was due to a pre-mortal drop, a decline in cognitive functioning due to a terminal disease. A decrease in cognitive functioning was associated with a twice as high mortality risk compared with stable cognition. A small increase

in cognitive functioning was not associated with a lower mortality risk. These associations could not be explained by a pre-mortal drop in cognitive functioning, because exclusion of men who had died within the first year after the assessment of cognitive functioning and exclusion of men with myocardial infarction, cancer, stroke or diabetes did not change the results. We conclude that older men with a decline in cognitive functioning have a higher mortality risk.

Methodological considerations

This paragraph discusses major methodological strengths and weaknesses of the studies presented in this thesis. We comment on the Mini-Mental State Examination (MMSE)[27] (measurement, reliability, validity, use in cross-cultural studies, interpretation of results and limitations), the internal validity (selection bias, information bias, confounding) and the external validity (generalisability).

Mini-Mental State Examination

Measurement of cognitive functioning

In this thesis, global cognitive functioning is measured with the MMSE.[27] This test assesses the severity of cognitive impairment and documents cognitive change by questions on orientation to time and place, registration of three words, attention and calculation, recall of the three words, language and visual construction. The MMSE is widely used and is available in many languages.[28,29] Originally, the MMSE was designed as a brief screening instrument for a clinical setting to differentiate organic from functional psychiatric patients.[27] Nowadays, this test is also commonly used in epidemiological studies to asses cognitive functioning.[30]

Reliability and validity

The MMSE is a reliable test for measuring cognitive impairment,[31] with a good test-retest reliability (75% of the test-retest comparisons for normally and cognitively impaired persons showed a correlation of at least 0.79).[31] The test is also highly correlated with other cognitive screening tests, psychological and neurological tests that measure specific cognitive domains (correlation varies between 0.66-0.93).[31]

The sensitivity and specificity of the MMSE for correctly classifying cognitively intact and impaired persons are both high (75% of the comparative studies using dementia cases showed a sensitivity of at least 76% and a specificity of at least 73%). Because of this high sensitivity and specificity, the MMSE is a valid indicator for normal and impaired cognitive functioning.[31,32] The MMSE is not

sensitive enough to detect mild cognitive impairment and to discriminate among persons with intact cognition and with mild cognitive impairment.[31] However, with the MMSE it is possible to detect clinically significant global cognitive decline.[33]
The maximum score to be achieved on the MMSE is 30 points, with a higher score indicating better cognitive functioning. We used a score below 24 to indicate cognitive impairment, since this cut-of point is widely used in clinical settings[31] and a score below 18 to indicate *severe* cognitive impairment.[34]

Information on cognitive impairment is based on a cross-sectional measurement of cognitive functioning. In longitudinal studies cognitive functioning can be measured repeatedly. An advantage of repeated measurements is that they reduce the measurement error and in this way information on cognitive decline can be obtained. Most of the risk factors we studied were not associated with cognitive functioning in the cross-sectional analyses carried out in 1990, since the participating persons were not or only mildly cognitively impaired. However, during the follow-up period, when cognitive function decreased, several risk factors were identified when cognitive decline was used as the dependent variable. Cognitive decline is a slow process, therefore the follow-up period must be long enough to detect significant differences in cognitive decline among risk factor levels especially because small effects in cognitive decline may not be detected with the MMSE.[31] Therefore, we used a follow-up period of five to 10 years.

The use of the MMSE in cross-cultural studies
The MMSE is available in many languages[28,29] and therefore often used in studies with different participating countries. Research showed that the MMSE is sensitive for differences between cultures and countries.[35,36] A study carried out among Mexican Americans and European Americans showed that Mexican Americans were more likely to have low MMSE scores, independently of educational level.[35] And another study showed that white elderly American adults performed better on the MMSE than black elderly American adults, also after adjusting for differences in educational level.[36] It is however not known whether differences in the MMSE score between European populations reflect real differences in cognitive function or are due to cultural differences. In the Finland, Italy and the Netherlands Elderly (FINE) Study, each country used its own standardised, adapted (for the cultural context of each country) and translated version of the MMSE. The locally used questionnaires were translated into English and thereafter by other persons back translated to the local language and checked by the research panel. However, since cultural differences between Finnish, Italian and Dutch men exist, we adjusted for country in all our analyses to reduce confounding by questionnaire.

Interpretation of the results of the MMSE

We observed generally small changes in average cognitive functioning. What does a decline of e.g. one point mean? Small changes in MMSE scores should be interpreted with caution because the MMSE is not sensitive enough to pick up small changes in cognitive decline in individuals. However, small declines in cognitive functioning may be an indication for a pathological process leading to cognitive impairment and eventually perhaps even dementia.

Although a small decline in cognitive functioning is not clinically relevant on the individual level, it is of great importance on the population level. A small average change in cognitive function increases the proportion of persons with cognitive impairment in the population to a large extent. This has major public health implications.

Limitations in the use of the MMSE

The MMSE only measures global cognitive functioning and does not assess different cognitive domains in detail. Therefore, it is not possible to estimate which cognitive domains are impaired. There are however several cognitive functioning tests available focusing on specific cognitive domains. For example, the Wechsler Memory Scale[37] and the Auditory Verbal Learning Test[38] can be used to assess memory and learning, the Stroop Colour Word Test[39] for measuring attention and concentration, the Boston Diagnostic Aphasia Examination[40] for measuring language and the Rey Complex Figure Test[41] to assess visuoconstructive abilities. Using all these tests is expensive and time consuming and can therefore not be applied in large epidemiological studies. In conclusion, there is a need for cheap, less time consuming and easy to administer neuropsychological tests focusing on different cognitive domains.

Additionally, imaging techniques such as magnetic resonance imaging and computed tomography scans can be used next to the neuropsychological tests to give more insight in the pathological processes of specific brain areas. However, these techniques are very expensive and should be administered in a hospital. The aim of this study was to examine (modifiable) risk factors for cognitive decline and therefore brain imaging was not performed.

In conclusion, although the MMSE is a screening test that measures global cognitive functioning, it can be used in cross-cultural epidemiological studies in which limited time and money is available. Furthermore, the MMSE is most valuable in longitudinal studies with a long duration of follow-up when multiple measurements of cognitive functioning over time are used to measure cognitive decline.

Internal validity

While studying the associations between risk factors and cognitive functioning, biases may occur. These biases may distort associations between these risk factors and cognitive functioning, undermining the internal validity. In the following paragraphs, we discuss these biases.

Selection bias

Non-response, missing values and death can cause selection bias, a major threat to a longitudinal study design and could lead to an underestimation or overestimation of true associations. In the FINE Study, response rates were high and varied between 65% and 94% in the different survey years. Non-respondents, respondents with missing values and respondents who had died were overall older, less healthy, had overall lower cognitive test scores, were more often unmarried and less physically active, consumed less coffee and less fish and had a lower intake of EPA + DHA than the respondents who participated. This may have lead to an underestimation of the strength of the associations observed in our studies. However, to deal with possible selection due to the drop-out, we used a mixed longitudinal random coefficient model in several analyses, which does not exclude subjects with incomplete data on cognitive functioning at follow-up. Furthermore, we also repeated the analyses among survivors with complete data (till 2000). When those analyses confirmed the results obtained from all men, then selection bias due to incomplete data on cognitive functioning at follow-up probably has not influenced our results.

A major strength of the FINE Study is its longitudinal study design. All participants were followed and re-examined over a 15-year period. This provided the opportunity not only to assess cognitive functioning at one moment in time, but also to estimate cognitive decline over time. The rate of cognitive decline is a marker for dementia and Alzheimer's disease.[42,43] Another strength of a longitudinal design is the time-order in which associations can be studied. It is possible to study the exposure (e.g. risk factor) prior to cognitive decline, a requirement for judging whether relationships are causal.[44,45] When studying relationships between risk factors and cognitive decline, exclusion of participants with impaired cognition at baseline could diminish the chance that impaired cognition could have caused a change in lifestyle/risk factors instead of otherwise in a longitudinal design. Also plausible mechanisms may help in judging the causality of a relationship between a risk factor and cognitive decline. However, relationships should be interpreted with caution and whether or not an association is causal is still a matter of judgment.

Information bias

Self-administered questionnaires were used to measure risk factors and possible confounding factors. Errors in the self-report could introduce information bias/reporting bias and this may lead to

an underestimation or overestimation of the strength of the associations. Since cognitively impaired participants could give imprecise information while answering questions, we excluded cognitively impaired participants at baseline to try to reduce differential misclassification.

Confounding bias

Inadequate adjustment for confounding is a major threat to the validity of observational studies. When studying the relationships between determinants and cognitive decline and between cognitive decline and mortality, adjustments should be made for potential confounding factors. We adjusted for the well-known confounding factors age, education, country, smoking status, alcohol consumption, and additionally for other lifestyle and dietary variables, and chronic diseases. However, inadequate measurement of these factors could lead to residual confounding. Furthermore, we can not exclude residual confounding for risk factors that we did not measure at all. Therefore, residual confounding may exist and may lead to an underestimation or overestimation of the observed associations.

External validity: generalisability

In population-based studies the question is whether the results obtained in a selected population can be generalised to the total population. The FINE Study consists of the surviving men from the Seven Countries Study. This study was originally designed to investigate cardiovascular risk factors in middle-aged men,[46] because cardiovascular disease was at that time viewed as a problem of middle-aged men, but not of middle-aged women. Therefore, women were not enrolled in the present study.

The Finnish, Italian and Dutch men in our study were survivors and healthier than the men who were not included in our study due to e.g. death and non-response. Therefore, our results are particularly generalisable to healthy men who reached old age from Finland, Italy and the Netherlands. More studies are needed before the results of the FINE Study can be generalised to other populations of elderly men. It is not clear if the observed results are also generalisable to younger men, women and other European populations. Therefore, our results should be compared with those of other studies carried out in younger men, women and other populations. Since few studies with respect to the risk factors and cognitive functioning and decline are available, we also used studies regarding dementia and Alzheimer's disease as an approximation.

Strengths of the associations

Before dealing with the public health implications of our findings we like to discuss the strengths of the associations for the risk factors for cognitive decline observed in the studies reported in this thesis.

Marital status and living situation

Marital status and living situation were measured with a self-administered questionnaire. Because the questions on marital status and living situation were easy to answer, major mistakes in answering these questions were unlikely. Therefore, the information on marital status and living situation was probably reliable and valid. We investigated *changes* in marital status and living situation in relation to cognitive functioning, a rather new topic. And found that men who lost a partner, who were unmarried, who started to live alone or who lived alone during five years had at least a two times stronger subsequent 10-year cognitive decline, compared to men who were married or who lived together in those years. Other studies found that being married or living with others was associated with a lower risk of dementia or Alzheimer's disease in both elderly men and women and in different European and non-European countries.[11,12,47] This suggests that our results are also generalisable to other countries and possibly also to older women. Although there are strong indications that being married and living with others is associated with a smaller cognitive decline and subsequent dementia,[11,12,47] confirmation is needed of our results on the association between *change* in marital status and living situation in relation with cognitive functioning in older women and in other countries.

Physical activity

Physical activity was measured with a standardised self-administered questionnaire, especially designed for retired men.[48] This questionnaire has a four months test-retest correlation of 0.93 and has been validated by the doubly labelled water method in the Zutphen elderly population.[49] Our questionnaire can therefore be considered as a reliable and valid method for measuring physical activity in the elderly. Our results confirmed those of other studies that being physically active is beneficial for cognitive functioning.[14,15,50,51] Since detailed information on duration and intensity of physical activity in other studies was lacking, our study investigated the independent association of both duration and intensity of physical activity at baseline in relation to cognitive decline in elderly men. Furthermore, we also investigated the association with 10-year *change* in both duration and intensity of physical activity. Our study showed that not the duration of physical activities, but the intensity performing physical activities may postpone cognitive decline. Performing physical activeties with at least a medium-low intensity (like walking at about three miles per hour) is in accord

with the results of other studies on physical activity in general and cognitive decline, dementia and Alzheimer's disease.[14,15,50,51] Other studies also found an inverse association between physical activity in general and cognitive decline, dementia and Alzheimer's disease among women and in non-European countries. [14,15,50,51] Therefore, it is likely that our results are generalisable to women and other countries. We conclude that physical activity is an important risk factor for cognitive decline in the elderly. However, more studies are needed to replicate the findings on duration and intensity of physical activity separately and especially the findings with respect to *change* in duration and intensity of physical activity in relation to cognitive decline.

Coffee consumption

Coffee consumption was measured with a self-administered questionnaire in Finland and Italy and with the cross-check dietary history method in the Netherlands.[52,53] The latter method was reproducible[53] and valid.[54] The correlation coefficient for coffee consumption in 1985 and 1990 ranged from 0.54 ($p<0.001$) for Finland till 0.72 ($p<0.001$) for the Netherlands. These correlations suggest that elderly men keep their relative position in the distribution of coffee consumption. We did not validate the reported number of cups of coffee consumed by caffeine measurements in blood. Few other studies reported on the association between coffee consumption and cognitive functioning and showed inconsistent results.[16,17] Our study is the first one that prospectively investigated the association between coffee consumption and cognitive decline. Our results that coffee consumption is associated with a smaller cognitive decline and especially the inverse and J-shaped association between the number of cups of coffee consumed and cognitive decline should be replicated in other studies before definitive statements can be made.

Fish consumption and intake of n-3 fatty acids

Information about habitual food consumption was collected with the cross-check dietary history method in the Dutch population of the FINE Study.[53] This method is reproducible[53] and valid.[54] In the Zutphen Elderly Study the Spearmen correlation coefficient for fish consumption in 1990 and 1995 was 0.62 ($p<0.001$) and for the intake of EPA + DHA 0.47 ($p<0.001$). These results show that the estimations of fish consumption and the intake of EPA + DHA are reproducible. Fish consumption was positively associated with red blood cell membrane fatty acids ($r=0.5$, $p\leq 0.001$).[55,56] This result suggests that the estimation of fish consumption is valid. Several studies showed that fish consumption and the intake of EPA + DHA are generally inversely related with dementia and Alzheimer's disease,[57] indicating that there also might be an association with cognitive functioning. However, with respect to cognitive functioning as such, information is scarce and results are inconsistent.[57,58] But there are some indications that fish consumption and/or the intake of EPA + DHA may protect against cognitive impairment among Dutch middle-aged men

and women and against cognitive decline among American men and women aged 65 years and older.[58,59] It is however too early to make general recommendations on fish consumption and the intake of EPA + DHA in relation to cognitive functioning. More research is needed before precise statements can be made on the associations between fish consumption, the intake of EPA + DHA and cognitive functioning.

In conclusion, the associations found with respect to marital status, living situation and physical activity are strong and provide enough evidence for justifying public health recommendations. Our findings on coffee and fish consumption and on the intake of the fatty acids EPA + DHA in relation with cognitive functioning need confirmation in other studies before recommendations can be made.

Public health implications

In this paragraph we discuss public health implications based on the results of the risk factors in relation with cognitive functioning found in this thesis.

Our results on marital status and living situation (chapter 3) suggest that elderly men alone are a vulnerable group that deserves special attention. Since mental and social activities may protect against dementia and Alzheimer's disease,[60,61] we recommend special programs oriented at mental and social activities (such as e.g. making puzzles, reading, talking with others, eating with others) to stimulate cognitive functioning. Furthermore, elderly men should be stimulated not to be alone but to be around with other persons, for example family and friends. When elderly men do not have family or friends, they should be stimulated to be around with other persons by creating social group events or programs in which they have dinner with others, for example. They could also be stimulated to live together with others in sheltered accommodations, service flats or other homes for the elderly.

In the Netherlands, there are special programs for living with others for demented elderly. One such program is called 'Netwerk Kleinschalig Wonen voor Mensen met Dementie', organized by 'Nederlands Instituut voor Zorg en Welzijn (NIZW) (on: http://www.nizw.nl). In this project, demented persons live together in small groups. Their house is placed in the persons own district and town in such a way that the persons feel that they are in their own neighbourhood. Also, special care is given directed to each person's needs. The goal of this project is to increase the quality of life of the demented persons.

Furthermore, it is also possible for (mildly) demented persons to go to a day-care centre or to outpatients' treatment to spend some time with other persons and to undertake activities. During the day, the demented persons are stimulated, supported, and special care is provided to what the person needs. This service supports the person to stay in his/her own home and to take some of the weight of the caregivers' shoulders. Since our study showed that even persons with cognitive decline benefit from being around other persons, going to day-care or outpatients' treatment may also be recommended for persons with cognitive decline in general. These persons may also benefit from the support offered in the day-care.
In addition, caretakers should be aware that unmarried men, those who lost a partner, who live alone or going to live alone carry a higher risk of cognitive decline and subsequent dementia and are more susceptible for other health and emotional problems.

We and others showed that physical activity lowers the risk of cognitive decline (chapter 4). Being physically active also lowers the risk of e.g. coronary heart disease,[62] stroke,[63] death due to cancer[64] and all-cause mortality.[64] Being regularly physically active also improves quality of life and physical health.[65-67] Furthermore, regularly active persons are more and longer able to participate in society.[68] Since physical activity may be beneficial for more than cognitive functioning alone, physical activity is an important lifestyle factor for intervention and for being in good health. Our results showing a beneficial effect on cognitive decline of being physically active with at least medium-low intensity, like playing volleyball and walking at about 3 miles per hour, and of maintaining physical activity or even become more physically active (in duration or intensity) are in line with the Dutch recommendation for physical activity. This guideline recommends to be physically active with at least moderate intensity, like walking and bicycling, for at least 30 minutes for five days or preferably seven days a week.[69] In the Netherlands, 58% of the persons above 65 years do not meet the Dutch guideline of whom 18% is even physically inactive (defined as meeting recommendations on zero days of the week).[70] Therefore, the need for preventive action is high. In the Netherlands, there are already several physical activity programs such as 'Fietsen, Lopen, Actief spelen, Sporten, Huishouden' (FLASH) (on: http://www.flash123.nl), 'Meer Bewegen voor Ouderen' (MBvO), 'Task Force 50+ Sport en Bewegen' and 'Groninger Actief Leven Model' (GALM) (on: http://www.galm.nl) all with the goal to stimulate older persons to be or to become physically active.[71]

In conclusion, it is important to stimulate elderly persons to be physically active and to maintain that activity. To do so, the type and intensity of physical activities should be matched with one's needs and possibilities. And to create a safe, pleasant and attractive environment that makes being physically active (e.g. go for a walk) attractive.[71] We should stimulate elderly persons to be

physically active with at least a medium-low intensity and to stay active both in terms of duration and intensity over time.

There is not enough evidence to make a recommendation for coffee consumption in relation to cognitive decline. However, evidence is accumulating that coffee consumption may also be protective in relation to type 2 diabetes.[72] The recent results of coffee consumption in relation to cognitive decline (chapter 5) and type 2 diabetes indicate that moderate coffee consumption is not bad for your health and may even have protective effects in relation to mental health and chronic diseases such as diabetes type 2. It is however to early for public health recommendations in relation to coffee consumption.

There is also not enough evidence for public health recommendations regarding fish consumption and the intake of n-3 fatty acids EPA + DHA in relation to cognitive decline. However, there is a lot of evidence that fish consumption (with 70% the major source of EPA and DHA) is inversely associated with cardiovascular diseases.[18,19] We showed that fish consumption and a low-dose intake of EPA + DHA (from fish and other foods) may postpone cognitive decline in elderly men (chapter 6). Our result that an intake of about 400 mg of EPA + DHA per day (this is similar to 850 grams lean fish or 140 grams fatty fish such as mackerel and herring per week) is in accordance with the recommendations of the American Heart Association to eat (preferably) fatty fish at least twice a week.[73] In addition, the Health Council of the Netherlands recommends an intake of 450 mg EPA + DHA per day and also suggests to eat fish twice a week of which at least one portion consists of fatty fish.[74] So, fish consumption may not only be beneficial for cardiovascular disease prevention but possibly also for the postponement of cognitive decline.

In conclusion, our study showed that being married, living with others, being physically active at least with medium-low intensity, maintaining duration and intensity of physical activity, drinking coffee moderately, consuming fish regularly and an intake of about 400 mg of the n-3 polyunsaturated fatty acids EPA + DHA per day could all lower the risk of cognitive decline. Although more research on the causality of these associations is needed, our results suggest that a socially and physically active lifestyle and a healthy diet in terms of moderate coffee consumption and regular fish consumption and a low-dose of EPA + DHA may be beneficial for cognitive functioning. There is however much more evidence that lifestyle and diet are beneficial for e.g. cardiovascular diseases and type 2 diabetes. Therefore, we recommend elderly to keep or adopt a socially *and* physically active lifestyle *and* to consume a healthy diet to improve their quality of life, and physical and psychological health. Elderly themselves should make the decision whether or not to live a socially and physically active life and to consume a healthy diet. However, general practitioners,

caregivers and homes for the elderly should inform elderly about how to create a socially and physically active lifestyle and how to consume a healthy diet and they can offer different alternatives for doing so.[71]

References

1. Petersen RC. Aging, mild cognitive impairment, and Alzheimer's disease. Neurol Clin 2000;18(4):789-806.
2. Shah Y, Tangalos EG, Petersen RC. Mild cognitive impairment: When is it a precursor to Alzheimer's disease? Geriatrics 2000;55:62-68.
3. Centraal Bureau voor de Statistiek. Bevolkingsprognose 2000-2050. www.cbs.nl/statline, versie december 2000.
4. Ott A, Breteler MMB, Birkenhäger-Gillesse EB, van Harskamp F, de Koning I, Hofman A. De prevalentie bij ouderen van de ziekte van Alzheimer, vasculaire dementie en dementie bij de ziekte van Parkinson; het ERGO- onderzoek. Ned Tijdschr Geneeskd 1996;140:200-205.
5. Health Council of the Netherlands. Dementia. The Hague: Health Council of the Netherlands, 2002; publication number 2002/04.
6. Meerding WJ, Bonneux L, Polder JJ, Koopmanschap MA, van der Maas PJ. Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study. BMJ 1998;317:111-115.
7. Aguglia E, Ono ML, Trevisiol M, Negro C, Saina M, Maso E. Stress in the caregivers of Alzheimer's patients: an experimental investigation in Italy. Am J Alzheimers Dis Other Demen 2004;19(4):248-252.
8. Burns A, Zaudig M. Mild cognitive impairment in older people. Lancet 2002;360:1963-1965.
9. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. Neurology 1998;51:728-733.
10. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. Am J Epidemiol 1998;147(6):574-580.
11. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000;355:1315-1319.
12. Sibley A, MacKnight C, Rockwood K, Fisk J, Gauthier S, Guzman DA, Hogan DB; Consortium to Investigate Vascular Impairment of Cognition. The effect of the living situation on the severity of dementia at diagnosis. Dement Geriatr Cogn Disord 2002;13:40-45.
13. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. JAMA 2004;292(12):1447-1453.
14. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003;14(2):125-130.
15. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001;58(3):498-504.
16. Jarvis MJ. Does caffeine intake enhance absolute levels of cognitive performance? Psychopharmacology (Berl) 1993;110(1-2):45-52.
17. Johnson-Kozlow M, Kritz-Silverstein D, Barrett-Connor E, Morton D. Coffee consumption and cognitive function among older adults. Am J Epidemiol 2002;156(9):842-850.
18. He K, Song Y, Daviglus ML, Liu K, van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation 2004; 109(22):2705-2711.
19. He K, Song Y, Daviglus ML, Liu K, van Horn L, Dyer AR, Goldbourt U, Greenland P. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke 2004;35(7):1538-1542.
20. Dik MG, Deeg DJ, Bouter LM, Corder EH, Kok A, Jonker C. Stroke and apolipoprotein E epsilon4 are independent risk factors for cognitive decline: A population-based study. Stroke 2000;31(10):2431-2436.
21. Kase CS, Wolf PA, Kelly-Hayes M, Kannel WB, Beiser A, D'Agostino RB. Intellectual decline after stroke. The Framingham Study. Stroke 1998;29:805-812.

22. Baldereschi M, Di Carlo A, Maggi S, Grigoletto F, Scarlato G, Amaducci L, Inzitari D. Dementia is a major predictor of death among the Italian elderly. ILSA Working Group. Italian Longitudinal Study on Aging. Neurology 1999;52:709-713.

23. Gussekloo J, Westendorp RG, Remarque EJ, Lagaay AM, Heeren TJ, Knook DL: Impact of mild cognitive impairment on survival in very elderly people: cohort study. BMJ 1997;315:1053-1054.

24. Neale R, Brayne C, Johnson AL. Cognition and survival: an exploration in a large multicentre study of the population aged 65 years and over. Int J Epidemiol 2001;30:1383-1388.

25. Hui JS, Wilson RS, Bennett DA, Bienias JL, Gilley DW, Evans DA. Rate of cognitive decline and mortality in Alzheimer's disease. Neurology 2003;61:1356-1361.

26. Wilson RS, Beckett LA, Bienias JL, Evans DA, Bennett DA. Terminal decline in cognitive function. Neurology 2003;60:1782-1787.

27. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Research 1975;12:189-198.

28. Heeren TJ, Lagaay AM, von Beek WC, Rooymans HG, Hijmans W. Reference values for the Mini-Mental State Examination (MMSE) in octo- and nonagenarians. J Am Geriatr Soc 1990;38(10):1093-1096.

29. Salmon DP, Riekkinen PJ, Katzman R, Zhang MY, Jin H, Yu E. Cross-cultural studies of dementia. A comparison of mini-mental state examination performance in Finland and China. Arch Neurol 1989;46:769-772.

30. Launer LJ. Overview of incidence studies of dementia conducted in Europe. Neuroepidemiology 1992; 11:2-13.

31. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922-935.

32. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991;115:122-132.

33. Lyketsos CG, Garrett E, Liang KY, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. Am J Epidemiol 1999;149:794-800.

34. Murden RA, McRae TD, Kaner S, Bucknam ME. Mini-Mental State exam scores vary with education in blacks and whites. J Am Geriatr Soc 1991;39:149-155.

35. Espino DV, Lichtenstein MJ, Palmer RF, Hazuda HP. Ethnic differences in mini-mental state examination (MMSE) scores: where you live makes a difference. J Am Geriatr Soc 2001;49(5):538-548.

36. Wood RY, Giuliano KK, Bignell CU, Pritham WW. Assessing cognitive ability in research: use of MMSE with minority populations and elderly adults with low education levels. J Gerontol Nurs 2006;32(4):45-54.

37. Wechsler D. A standardised memory scale for clinical use. Journal of psychology 1945;19:87-95.

38. Rey A. L'examen clinique en psychologie. Paris: Presses Universaires de France, 1964.

39. Stroop JR. Studies of interference in serial verbal reactions. Journal of Experimental Psychology 1935; 18:643-662.

40. Goodglass H, Kaplan E. Boston Diagnostic Aphasia Examination. Philadelphia: Lea & Febiger, 1972.

41. Osterreith PA. La test de copie d'une figure complexe. Archives de Psychologie 1944;30:206-356.

42. Boyle PA, Wilson RS, Aggarwal NT, Tang Y, Bennett DA. Mild cognitive impairment: risk of Alzheimer disease and rate of cognitive decline. Neurology 2006;67(3):441-445.

43. Holtzer R, Wegesin DJ, Albert SM, Marder K, Bell K, Albert M, Brandt J, Stern Y. The rate of cognitive decline and risk of reaching clinical milestones in Alzheimer disease. Arch Neurol 2003;60:1137-1142.

44. Bouter LM, van Dongen MCJM. Epidemiologisch onderzoek, opzet en interpretatie. Houten: Bohn Stafleu van Loghum, 1995.

45. Rothman KJ, Greenland S. Modern Epidemiology. Philadelphia: Lippincott, Williams & Wilkins, 1998.

46. Keys A, Aravanis C, Blackburn HW, van Buchem FSP, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl 1966;460:1-392.

47. Helmer C, Damon D, Letenneur L, Fabrigoule C, Barberger-Gateau P, Lafont S, Fuhrer R, Antonucci T, Commenges D, Orgogozo JM, et al. Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology 1999;53:1953-1958.

48. Caspersen CJ, Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol 1991;133(11):1078-1092.

49. Westerterp KR, Saris WHM, Bloemberg BPM, Kempen K, Caspersen CJ, Kromhout D. Validation of the Zutphen Physical Activity Questionnaire for the Elderly with the doubly labelled water. Med Sci Sports Exerc 1992;24:S68.

50. Weuve J, Kang JH, Manson JE, Breteler MMB, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. JAMA 2004;292(12):1454-1461.

51. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 2001;161(14):1703-1708.

52. Kromhout D, Nissinen A, Menotti A, Bloemberg B, Pekkanen J, Giampaoli S. Total and HDL cholesterol and their correlates in elderly men in Finland, Italy, and The Netherlands. Am J Epidemiol 1990;131(5): 855-863.

53. Bloemberg BP, Kromhout D, Obermann-De Boer GL, van Kampen-Donker M. The reproducibility of dietary intake data assessed with the cross-check dietary history method. Am J Epidemiol 1989;130(5): 1047-1056.

54. Block G. A review of validations of dietary assessment methods. Am J Epidemiol 1982;115(4):492-505.

55. Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, Bovbjerg V, Arbogast P, Smith H, Kushi LH, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA 1995;274(17):1363-1367.

56. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long – chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002;346(15):1113-1118.

57. Solfrizzi V, D'Introno AD, Colacicco AM, Capurso C, Del Parigi A, Capurso S, Gadaleta A, Capurso A, Panza F. Dietary fatty acids intake: possible role in cognitive decline and dementia. Exp gerontology 2005;40:257-270.

58. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Fish consumption and cognitive decline with age in a large community study. Arch Neurol 2005;62:1-5.

59. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62(2):275-280.

60. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol 2002;155:1081-1087.

61. Wilson RS, Mendes de Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002; 287:742-748.

62. Hakim AA, Curb JD, Petrovitch H, Rodriguez BL, Yano K, Ross W, White LR, Abbott RD. Effects of walking on coronary heart disease in elderly men. The Honolulu heart program. Circulation 1999;100:9-13.

63. Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. Stroke 2003;34(10): 2475-2481.

64. Hakim AA, Petrovitch H, Burchfiel CM, Ross W, Rodriguez BL, White LR, Yano K, Curb JD, Abbott RD. Effects of walking on mortality among nonsmoking retired men. N Engl J Med 1998;338(2):94-99.

65. Acree LS, Longfors J, Fjeldstad AS, Fjeldstad C, Schank B, Nickel KJ, Montgomery PS, Gardner AW. Physical activity is related to quality of life in older adults. Health and quality of life outcomes 2006;4:37.

66. Brown DW, Balluz LS, Heath GW, Moriarty DG, Ford ES, Giles WH, Mokdad AH. Associations between recommended levels of physical activity and health-related quality of life. Findings from the 2001 Behavioral Risk Factor Surveillance System (BRFSS) survey. Preventive Medicine 2003;37:520-528.

67. Lim K, Taylor L. Factors associated with physical activity among older people-a population-based study. Prev Med 2005;40:33-40.

68. Wiggers JA. Programmeringsstudie productieve maatschappelijke participatie van ouderen: een literatuurstudie naar verricht en lopend onderzoek naar betaald en onbetaald werk van 55-plussers. Resultaten, hiaten en mogelijkheden voor vervolgonderzoek. Rotterdam: Erasmus Universiteit, Wetenschapswinkel, 1997 (Rapport 175).

69. Kemper HCG, Oijendijk WTM, Stiggelbout M. [Consensus about the Dutch physical activity guideline]. Tijdschr Soc Geneeskd 2000;78:180-183.

70. Wendel-Vos GCW, Ooijendijk WTM, van Baal PHM, Storm I, Vijgen SMC, Jans M, Hopman-Rock M, Schuit AJ, de Wit GA, Bemelmans WJE. Kosteneffectiviteit en gezondheidswinst van behalen beleidsdoelen bewegen en overgewicht. Onderbouwing Nationaal Actieplan Sport en Bewegen (RIVM rapportnr 260701001). Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu, 2005.

71. Ministerie van Volksgezondheid, Welzijn en Sport. Ouderenbeleid in het perspectief van de vergrijzing. 2005 (http://www.minvws.nl).

72. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes. A systematic review. JAMA 2005;294:97-104.

73. Kris-Etherton PM, Harris WS, Appel LJ, for the Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2747-2757.

74. Health Council of the Netherlands. Guidelines for a healthy diet 2006. The Hague: Health Council of the Netherlands, 2006; publication number 2006/21.

Summary

During the last century, life expectancy and the number of persons above the age of 65 has increased rapidly. In the coming decades, there will be a further increase in the number of older persons. This is expected to be accompanied by an increase in the number of persons with cognitive impairment, dementia and Alzheimer's disease. These persons suffer from many functional, psychological, emotional and financial problems and distress and are at an increased mortality risk. Therefore, the need for preventive action is high. To do so, it is important to identify modifiable risk factors for developing effective strategies for postponing cognitive impairment and decline.

This thesis aimed to study cognitive decline in older European men and to identify modifiable risk factors. *Changes* in cognitive functioning over time, (*changes* in) social, lifestyle and dietary risk factors for cognitive decline and the relationship between *change* in cognitive functioning and mortality were described.

We measured cognitive functioning, the process of receiving, processing, storing and using information, with the Mini-Mental State Examination (MMSE). The score on the MMSE ranged from 0 till 30 points, with a higher score indicating better cognitive functioning. Cognitive decline was defined as the difference between two (or more) measurements of cognitive functioning.
For the results presented in this thesis, data from the Finland, Italy and the Netherlands Elderly (FINE) Study were used. This study is an international prospective population-based cohort study among 2,285 Finnish, Italian and Dutch men born between 1900 and 1920. The FINE Study was conducted as a broad gerontologic survey that collected information on risk factors and different aspects of health in older men. Examinations took place around 1985, 1990, 1995 and 2000 and cognition was measured from 1990 onwards.

In chapter 2 of this thesis, we described the influence of ageing, period and birth cohort on 10-year cognitive decline in older European men. Longitudinal data of 1,363 Finnish, Italian and Dutch men of 70 till 90 years old at baseline was gathered around 1990, 1995 and 2000. Multiple statistical approaches (longitudinal, cross-sectional and times-series analyses) were concurrently used to disentangle age, period and cohort effects. In addition, a mixed longitudinal model was used to confirm these results. During the 10-year follow-up period, cognitive functioning decreased on average with 1.5 points. This decline was mainly attributable to an age effect; aging of the elderly resulted in cognitive deterioration. However, a period effect and differences in cognitive decline between birth cohorts were also observed, indicating that respondents later in time and of later birth cohorts had a better cognition. In summary, these data suggest that the observed cognitive decline over 10 years is due to an age effect, but also to a period and birth cohort effect.

The influence of marital status and living situation over five years on 10-year subsequent cognitive decline was examined in 1,042 Finnish, Italian and Dutch men aged 70-90 years in 1990 (chapter 3). Repeated measurement analyses showed that men who were married and who lived with others in both 1985 and 1990 had the smallest subsequent 10-year cognitive decline (1.1 points (95% confidence interval (CI): [0.9;1.4]) and 1.1 points (95% CI: [0.8;1.4]) respectively). Men who lost a partner and men who were unmarried in both years had a two times stronger cognitive decline than men who were married in both years. Men who started to live alone had a two times stronger cognitive decline and men who lived alone in both years even had a 3.5 times stronger cognitive decline than those who lived together in both examination years. These results indicate that having a partner or living together with others is associated with a smaller cognitive decline.

We investigated which aspect of physical activity, i.e. (*change* in) duration or intensity, was associated with 10-year cognitive decline in 295 healthy Finnish, Italian and Dutch survivors (chapter 4). Our results showed that the rates of 10-year cognitive decline were not significantly different among men with a high or low duration of physical activity at baseline. However, a decrease in activity duration of more than 60 minutes per day over 10 years resulted in a 2.6 times stronger cognitive decline than maintaining duration of activity ($p=0.06$). Men in the lowest intensity quartile at baseline showed the strongest 10-year cognitive decline of 2.7 points. This decline was 1.8 ($p=0.07$) to 3.5 ($p=0.004$) times stronger than the decline among the other quartiles. Furthermore, men whose intensity of physical activity decreased more than half a standard deviation (SD) (0.8 point) during 10 years had a 3.6 times stronger cognitive decline than men who maintained the level of intensity ($p=0.003$). In conclusion, even in old age, participation in activities with at least a medium-low intensity such as walking three miles per hour may postpone cognitive decline. Besides, a decrease in duration or intensity of physical activity results in a stronger cognitive decline than maintaining duration or intensity.

Using data of 676 healthy Finnish, Italian and Dutch men, we estimated the association between baseline coffee consumption and 10-year cognitive decline (chapter 5). Coffee consumers had a two times smaller 10-year cognitive decline than non-consumers ($p=0.001$). In addition, an inverse and J-shaped association was present between the number of cups of coffee consumed and cognitive decline, with the smallest 10-year cognitive decline for men consuming three cups of coffee per day (0.6 point). This decline was 4.3 times smaller compared to the decline of non-consumers ($p<0.001$). The decline of 1.6 points in men who consumed more than four cups of coffee was borderline significantly smaller ($p=0.07$) compared to men who did not consume coffee. Our results suggest that moderate coffee consumption may lower cognitive decline in elderly men.

In chapter 6, the associations between fish consumption, the intake of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (from fish and other foods) and subsequent 5-year cognitive decline were examined. This study was performed among 210 survivors aged 70-90 years of the Dutch cohort of the FINE Study (the Zutphen Elderly Study). Men who consumed fish had a smaller 5-year subsequent cognitive decline than non-consumers (p=0.01). A linear trend was observed between the intake of EPA + DHA and cognitive decline (p=0.01). An average difference in the intake of EPA + DHA of about 380 milligram/day was associated with a 1.1 points difference in cognitive decline (p=0.01). Our results suggest that regular fish consumption and a low-dose intake of EPA + DHA may postpone cognitive decline in elderly men. However, our results should be replicated in other studies first before definite statements on this association can be made.

We investigated the association between 5-year *change* in cognitive functioning and subsequent 5-year mortality in 493 Italian and Dutch men (chapter 7). Men whose cognition decreased more than one SD (2.8 points) between 1990 and 1995 had a twofold higher risk of dying in the following five years compared with men whose cognition was stable (Hazard Ratio $(HR)_{adjusted}$=1.9; 95% CI: [1.3;2.7]). Mortality risk of men whose cognition improved between 1995 and 2000 was not different from men whose cognition was stable ($HR_{adjusted}$=1.1; 95% CI: [0.7;1.9]). Adjustments were made for age, education, country, lifestyle factors, prevalence of chronic diseases and for cognitive functioning at baseline. In conclusion, our results show that a decline in cognitive functioning is associated with a higher mortality risk.

In chapter 8, our main results were discussed, some methodological issues (i.e. comments on the Mini-Mental State Examination and the internal and external validity of our results) and strengths of the associations were addressed. Finally, we discussed implications for public health based on the findings in this thesis.

The associations found with respect to marital status, living situation and physical activity are strong and provide in combination with the existing literature on these topics enough evidence for justifying public health recommendations for postponing cognitive decline. Since elderly men alone are a vulnerable group that deserves special attention, we recommend special programs oriented at mental and social activities with the goal to stimulate cognitive functioning. For the demented elderly there are even programs with the goal to increase their quality of life. Furthermore, it is also important to keep elderly men physically active with at least medium-low intensity and to maintain physical activity or even become more physically active (in duration or intensity). There exist already several programs with the aim to stimulate older persons to be physically active. Our

findings on coffee and fish consumption and on the intake of the fatty acids EPA + DHA in relation with cognitive functioning need confirmation in other studies before recommendations can be made. However, there is also evidence that coffee and fish consumption and the intake of n-3 fatty acids EPA and DHA are beneficial for other health aspects besides cognitive functioning.

We conclude that a socially and physically active lifestyle and a healthy diet in terms of moderate coffee consumption and regular fish consumption and a low-dose of EPA + DHA may be beneficial for cognitive functioning. Therefore, we recommend elderly to keep or adopt a socially *and* physically active lifestyle *and* to consume a healthy diet to improve their quality of life and physical and psychological health. Elderly themselves should make the decision whether or not to follow these recommendations. However, general practitioners, caregivers and homes for the elderly should inform and stimulate elderly on how to do so.

In conclusion, although cognitive decline is a major health problem that we can not cure and that is associated with a higher mortality risk, our results are hopeful because they provide evidence that a socially and physically active lifestyle and a healthy diet may postpone cognitive decline.

Samenvatting

De levensverwachting en het aantal ouderen boven de 65 jaar zijn tijdens de vorige eeuw sterk toegenomen en zullen naar verwachting de komende decennia nog verder stijgen. Hierdoor zal ook het aantal mensen met cognitieve achteruitgang, dementie en de ziekte van Alzheimer toenemen. Deze mensen hebben veel last van functionele, psychologische, emotionele en financiële zorgen en problemen en hebben een grotere kans om te sterven. Het is daarom van groot belang preventieve maatregelen te nemen. Voor de ontwikkeling van effectieve strategieën om cognitieve achteruitgang uit te stellen moeten modificeerbare risicofactoren geïdentificeerd worden.

Het doel van dit proefschrift is om cognitieve achteruitgang bij oudere Europese mannen te bestuderen en om modificeerbare risicofactoren voor cognitieve achteruitgang te identificeren. In dit proefschrift hebben we eerst gekeken naar *veranderingen* in het cognitief functioneren in de loop van de tijd. Daarna hebben we de relatie tussen (*veranderingen* in) sociale determinanten, leefstijl- en voedingsfactoren en cognitieve achteruitgang onderzocht. Tot slot hebben we de relatie tussen *veranderingen* in het cognitieve functioneren en sterfte beschreven.

Cognitief functioneren, het proces van ontvangen, verwerken, opslaan en gebruiken van informatie, is in dit proefschrift vastgesteld met de Mini-Mental State Examination (MMSE). De score die op de MMSE gehaald kan worden varieert tussen de 0 en 30 punten, waarbij een hogere score een beter cognitief functioneren impliceert. Cognitieve achteruitgang is gedefinieerd als het verschil tussen twee (of meer) metingen van het cognitief functioneren. Voor dit onderzoek hebben we gebruik gemaakt van de gegevens van de 'Finland, Italy and the Netherlands Elderly (FINE) Study', een internationaal prospectief cohortonderzoek. Deze studie bestaat uit 2.285 Finse, Italiaanse en Nederlandse mannen die geboren zijn tussen 1900 en 1920. De FINE Studie is opgezet als een breed gerontologisch onderzoek waarin gegevens verzameld zijn over risicofactoren en verschillende gezondheidsaspecten bij oudere mannen. De onderzoeken vonden plaats rond 1985, 1990, 1995 en 2000. Vanaf 1990 werd het cognitief functioneren onderzocht.

In hoofdstuk 2 van dit proefschrift hebben we de invloed van leeftijd, periode en (geboorte)cohort op de 10-jaars cognitieve achteruitgang bij oudere Europese mannen beschreven. Longitudinale gegevens van 1.363 Finse, Italiaanse en Nederlandse mannen van 70-90 jaar oud aan het begin waren verzameld rond 1990, 1995 en 2000. Verschillende statistische methodes (longitudinale, cross-sectionele en tijd-serie analyse) zijn afwisselend gebruikt om het leeftijd, periode en cohort effect afzonderlijk te schatten. Aanvullend werd een model met herhaalde metingen gebruikt om de resultaten te bevestigen. De resultaten lieten zien dat gedurende 10 jaar tijd het cognitief functioneren gemiddeld met 1,5 punt afnam. Deze achteruitgang was grotendeels toe te schrijven

aan het leeftijdseffect; het ouder worden resulteerde in cognitieve achteruitgang. Echter, verschillen in cognitieve achteruitgang tussen geboortecohorten en een periode effect werden ook waargenomen. Zo hadden respondenten die later geboren waren en die in een latere tijdsperiode leefden een betere cognitie. Samengevat laten deze gegevens zien dat de geobserveerde 10-jaars cognitieve achteruitgang met name toegeschreven kan worden aan een leeftijdseffect, maar deels ook aan een periode en geboortecohort effect.

De invloed van burgerlijke staat en leefsituatie gedurende een periode van vijf jaar op de daarop volgende cognitieve achteruitgang in een periode van 10 jaar hebben we onderzocht bij 1.042 Finse, Italiaanse en Nederlandse mannen die in 1990, 70-90 jaar oud waren (hoofdstuk 3). Analyses met herhaalde metingen lieten zien dat mannen die getrouwd waren en mannen die met anderen samenleefden in zowel 1985 en 1990 de minste 10-jaars cognitieve achteruitgang hadden (respectievelijk 1,1 punt (95% betrouwbaarheidsinterval (BI): [0,9;1,4]) en 1,1 punt (95% BI: [0,8;1,4])). Mannen die hun partner verloren en mannen die niet getrouwd waren in beide jaren hadden een cognitieve achteruitgang die twee keer zo groot was als bij de mannen die getrouwd waren in beide jaren. Mannen die alleen gingen wonen hadden een twee keer grotere cognitieve achteruitgang en mannen die alleen woonden in beide jaren hadden zelfs een 3,5 keer grotere cognitieve achteruitgang dan mannen die samenleefden in beide onderzoeksjaren. Onze resultaten laten zien dat het hebben van een partner of het samenleven met anderen geassocieerd is met een geringere cognitieve achteruitgang.

In hoofdstuk 4 onderzochten we welk aspect van lichamelijke activiteit, (*verandering* in) duur of intensiteit, gerelateerd is aan de 10-jaars cognitieve achteruitgang bij 295 gezonde Finse, Italiaanse en Nederlandse oudere mannen. Onze resultaten lieten zien dat er geen significant verschil was in de cognitieve achteruitgang bij mannen die kort of lang lichamelijk actief waren aan het begin van het onderzoek. Echter, een afname in de duur van lichamelijke activiteit van meer dan 60 minuten per dag gedurende 10 jaar resulteerde in een 2,6 keer grotere cognitieve achteruitgang dan wanneer de duur van de lichamelijke activiteit gelijk bleef (p=0,6). Mannen die het minst intensief lichamelijk actief waren aan het begin van de studie hadden met 2,7 punten de grootste 10-jaars cognitieve achteruitgang. Deze achteruitgang was 1,8 (p=0,07) tot 3,5 (p=0,004) keer groter dan de achteruitgang van de mannen die meer intensief actief waren. Ook hadden de mannen die meer dan een halve standaard deviatie (SD, 0,8 punt) minder intensief gingen bewegen gedurende 10 jaar een 3,6 keer grotere cognitieve achteruitgang dan de mannen die hun intensiteitniveau op peil hielden (p=0,003). Concluderend laten onze resultaten zien dat deelname aan lichamelijke activiteiten met minstens een matige intensiteit zoals wandelen met vijf kilometer

per uur op oude leeftijd cognitieve achteruitgang kan vertragen. Ook het behouden van de duur en intensiteit van lichamelijke activiteiten kan resulteren in een minder grote cognitieve achteruitgang.

Met de gegevens van 676 gezonde Finse, Italiaanse en Nederlandse oudere mannen hebben we de relatie tussen het drinken van koffie en de daarop volgende 10-jaars cognitieve achteruitgang onderzocht (hoofdstuk 5). Mannen die koffie dronken hadden een twee keer kleinere 10-jaars cognitieve achteruitgang dan mannen die geen koffie dronken (p=0,001). Aanvullend werd er een invers en J-vormig verband gevonden tussen het aantal kopjes koffie en cognitieve achteruitgang, waarbij de geringste 10-jaars cognitieve achteruitgang werd vastgesteld bij mannen die drie koppen koffie per dag dronken (0,6 punt). Deze achteruitgang was 4,3 keer kleiner vergeleken met de achteruitgang van mannen die geen koffie dronken (p<0,001). Mannen die meer dan vier koppen koffie per dag dronken hadden een cognitieve achteruitgang van 1,6 punt welke kleiner was vergeleken met de cognitieve achteruitgang van mannen die geen koffie dronken (p=0,07). Onze resultaten laten zien dat matige koffieconsumptie geassocieerd is met minder cognitieve achteruitgang.

In hoofdstuk 6 hebben we gekeken naar de relatie tussen visconsumptie, de inname van de n-3 vetzuren eicosapentaeenzuur (EPA) en docosahexaeenzuur (DHA) (afkomstig uit vis en andere producten) en de daaropvolgende 5-jaars cognitieve achteruitgang. Deze studie is uitgevoerd bij 210 mannen van het Nederlandse cohort van de FINE Studie, de Zutphen Elderly Study, die in 1990 70-90 jaar waren. Mannen die vis aten hadden in de vijf jaren die daarop volgden een cognitieve achteruitgang die kleiner was dan bij mannen die geen vis aten (p=0,01). Tevens werd een lineaire trend gevonden tussen de inname van EPA + DHA en cognitieve achteruitgang (p=0,01). Een gemiddeld verschil in de inname van EPA + DHA van ongeveer 380 milligram per dag was geassocieerd met een verschil in cognitieve achteruitgang van 1,1 punt (p=0,01). Deze resultaten laten zien dat het eten van vis en een lage inname van EPA + DHA de cognitieve achteruitgang bij oudere mannen kan vertragen. Echter, onze resultaten zullen eerst in andere studies bevestigd moeten worden voordat definitieve uitspraken over deze associaties gedaan kunnen worden.

In hoofdstuk 7 werd de associatie tussen 5-jaars *veranderingen* in het cognitief functioneren en de sterfte in de daarop volgende vijf jaar bij 493 Italiaanse en Nederlandse mannen bestudeerd. Mannen waarvan de cognitie afnam met meer dan 1 SD (2,8 punten) op de MMSE tussen 1990 en 1995 hadden een twee keer grotere kans op sterfte in de daarop volgende vijf jaar dan mannen waarvan het cognitief functioneren stabiel bleef (Hazard Ratio $(HR)_{gecorrigeerd}$=1,9; 95% BI: [1,3;2,7]). De kans op sterfte voor mannen waarvan de cognitie tussen 1995 en 2000 verbeterde verschilde

niet van de mannen met een stabiele cognitie ($HR_{gecorrigeerd}$=1,1; 95% BI: [0,7;1,9]). In deze analyses is geadjusteerd voor leeftijd, opleiding, land, leefstijl factoren, het voorkomen van chronische ziektes en voor cognitief functioneren in 1990. Concluderend laten onze resultaten zien dat een afname in het cognitief functioneren geassocieerd is met een grotere kans op sterfte.

In hoofdstuk 8 zijn onze belangrijkste bevindingen samengevat, enkele methodologische aspecten (zoals de interne en externe validiteit van de resultaten) besproken en de sterkte van de associaties geëvalueerd. Tenslotte hebben we de implicaties van onze resultaten voor de volksgezondheid bediscussieerd.

De resultaten met betrekking tot burgerlijke staat, leefsituatie en lichamelijke activiteit leveren met de bevestiging ervan in de literatuur voldoende bewijs om volksgezondheidsaanbevelingen voor de preventie van cognitieve achteruitgang te doen. Omdat oudere alleenstaande mannen een kwetsbare groep vormen die speciale aandacht nodig hebben, bevelen we programma's aan gericht op een beter cognitief functioneren van deze mannen. Tevens is het van belang dat oudere mannen lichamelijk actief zijn met een minstens matige intensiteit en actief blijven of zelfs actiever worden (qua duur en intensiteit). Ook hiervoor bestaan al verschillende programma's met het doel oudere mensen te stimuleren lichamelijk actief bezig te zijn.
Onze bevindingen met betrekking tot koffie - en visconsumptie en de inname van de n-3 vetzuren EPA + DHA in relatie met het cognitief functioneren hebben eerst bevestiging van andere studies nodig voordat aanbevelingen gericht op het voorkómen van cognitieve achteruitgang gedaan kunnen worden. Echter, een matige koffie en regelmatige visconsumptie zijn ook goed voor andere aspecten van de gezondheid.

Wij concluderen dan ook dat een sociale en lichamelijk actieve leefstijl en een gezonde voeding zoals een matige koffie- en regelmatige visconsumptie en een lage EPA + DHA inname van belang zijn voor het behoud van een goede cognitie. Daarom raden we ouderen aan een sociale *en* lichamelijk actieve leefstijl te hebben *en* een gezonde voeding te consumeren om hun kwaliteit van leven, lichamelijke en psychische gezondheid te bevorderen. Ouderen moeten zelf beslissen of ze deze aanbevelingen willen opvolgen. Echter, huisartsen, verzorgers en verzorgingshuizen dienen over voldoende kennis te beschikken om ouderen te kunnen informeren en stimuleren een sociaal en lichamelijk actief leven te leiden en gezond te eten.

Samengevat kunnen we zeggen dat cognitieve achteruitgang een groot gezondheidsprobleem is dat niet te genezen is en geassocieerd is met een grotere kans op sterfte. Echter, de resultaten

van dit proefschrift laten zien dat een sociale en lichamelijk actieve leefstijl en een gezonde voeding cognitieve achteruitgang mogelijk kan uitstellen.

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Boukje

About the author

Boukje Maria van Gelder was born on May 25th, 1976 in Leiderdorp, the Netherlands. In 1994, she completed secondary school (VWO) at the Adelbert College in Wassenaar. From 1994 to 1996 she studied Psychology at the Leiden University and from 1996 to 2000 she continued her study at the University of Amsterdam (UvA). As part of this study she did a six months internship at the Neuropsychology department of the Leiden University Medical Center in Leiden. Furthermore, she conducted a research project on the clinical diagnostic value of the Dutch version of the California Verbal Learning Test for patients with a neurological disorder and she wrote her master thesis on intervention possibilities for patients with an unilateral neglect. In September 2000, she obtained her Master of Arts in Psychology, with majors in Clinical Psychology, Psychonomics and Clinical Neuropsychology. Furthermore she obtained the psychodiagnostic registration.

In April 2001 she started working at the Centre for Prevention and Health Services Research of the National Institute for Public Health and the Environment in Bilthoven. During this period she worked at the research described in this thesis and participated in the 'Healthy Ageing: Longitudinal study in Europe (HALE)' project for which she attended several international conferences. In 2003 she obtained her Master of Science in Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam. In 2005 she continued to work as an epidemiologic researcher at the Centre for Prevention and Health Services Research of the National Institute for Public Health and the Environment in Bilthoven.

List of publications

van Gelder BM, Tijhuis M, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Physical activity in relation to cognitive decline in elderly men: the FINE Study. *Neurology 2004;63(12):2316-2321*.

van Gelder BM, Tijhuis M, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Marital status and living situation during a 5-year period are associated with a subsequent 10-year cognitive decline in older men: the FINE Study. *J Gerontol B Psychol Sci Soc Sci 2006;61(4):213-219*.

van Gelder BM, Buijsse B, Tijhuis M, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study*. Eur J Clin Nutr 2007;61(2):226-232.*

van Gelder BM, Tijhuis MAR, Kalmijn S, Giampaoli S, Kromhout D. Decline in cognitive functioning is associated with a higher mortality risk. *Neuroepidemiology 2007;28(2):93-100.*

van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *Am J Clin Nutr 2007; 85(4):1142-1147.*

van Gelder BM, Tijhuis M, Kalmijn S, Boshuizen HC, Giampaoli S, Nissinen A, Kromhout D. *Changes* in cognitive functioning among European elderly men during 10 years: age, period and cohort effects. The FINE Study. *Submitted*.

Bogers RP, Tijhuis MAR, van Gelder BM, Kromhout D. Final report of the HALE (Healthy Ageing: a Longitudinal study in Europe) Project (RIVM report number 260853003). Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu, 2005.

Wendel-Vos GCW, Picavet HSJ, van Gelder BM, Tijhuis MAR, Droomers M. Meervoudig ongezond gedrag in Nederland. Een exploratie van risicogroepen en samenhang met omgeving, gezondheid en zorggebruik (RIVM rapport nummer 260301008). Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu, 2007.

Vijgen S, van Gelder BM, van Baal P, van Zutphen M, Hoogenveen R, Feenstra T. Kosten en effecten van tabaksontmoediging (RIVM rapport nummer 260601004). Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu, 2007.

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