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

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Tessa Nicole van den Kommer

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

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
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in het openbaar te verdedigen
ten overstaan van de promotiecommissie
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door

Tessa Nicole van den Kommer

geboren te Delft

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

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

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

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Development of classification models for early identification of persons at risk for persistent cognitive decline

Tessa N. van den Kommer
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Miranda G. Dik
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Abstract

Objective: To develop two classification models for use in primary care to aid early identification of persons at risk for persistent cognitive decline.

Methods: Data were used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing population-based study. The study sample consisted of 2,021 non-demented men and women aged 58-88 years. Data on relevant predictors of persistent cognitive decline were collected at baseline.

Results: The incidence of persistent cognitive decline after three years of follow-up was 4.0%. In the first model, in which predictors already known or otherwise easily assessed (first set) were included, age was the strongest predictor of persistent cognitive decline, with an increased risk for persons > 75. In addition, having memory problems, low education, and an MMSE score of ≤ 24, resulted in a predictive value for persistent cognitive decline of 43.5%. In the second classification model, in addition to the first set, predictors requiring additional measurement (e.g. markers determined in blood) were included in the analyses. Age was again the strongest predictor of persistent cognitive decline. In persons > 75 years, having a low total cholesterol level (< 5.0 mmol/L) and an MMSE score of ≤ 24 resulted in a predictive value of 30.0%.

Conclusions: Both models lead to a substantial increase of the predictive value for persistent cognitive decline, that is from 4.0% to 43.5% and 30.0%, and may identify to a large extent a different subsample of persons who are at risk for persistent cognitive decline. The developed classification trees could be useful for case-finding of persons at risk for future persistent cognitive decline who are therefore at risk for dementia, in a feasible and cost-effective manner.

Keywords: Early identification; Dementia; Case-finding; Cognitive decline; Classification models.

Introduction

Early identification of persons at risk for dementia is an increasingly important issue. Although no cure for dementia is available yet, early detection is crucial for several reasons. Pharmacological treatment of populations at high risk could result in preservation of cognitive abilities, functional independence, and prevention of behavioural problems for as long as possible (Gauthier, 2005), as well as economic benefits (Gauthier et al., 2006). Control of risk factors of dementia is possible and may prove useful in preventing dementia (Alagiakrishnan et al., 2006; Gauthier et al., 2006; Róman, 2005). Furthermore, it could be of importance for both patients and caregivers to know the diagnosis of dementia in an early phase of the disease to be able to anticipate future difficulties. Early psychosocial interventions may alleviate caregiver strain and reduce the rate of institutionalization (Mittelman et al., 1996; Moniz-Cook and Woods, 1997).

Older persons with subjective memory problems and their concerned relatives usually first turn to primary care. However, early detection of dementia in primary care is not a simple task, and as a result dementia is regularly unrecognized (Bamford et al., 2007; Valcourt et al., 2000). Therefore, a more proactive approach to case-finding is desirable (Bamford et al., 2007). Moreover, as dementia is often characterized by persistent cognitive decline, case-finding should be directed at cognitive decline at an early stage. To be able to accurately predict persistent cognitive decline, it is necessary to look for a combination of predictors with a sufficient prognostic value. In the present study two classification models were developed for the identification of persons who are at risk for persistent cognitive decline using sets of markers which are relatively easy to determine. The use of such a model in primary care could help to identify the most vulnerable group in a simple and cost-effective manner.

Methods

Study sample

Data for the present study were collected in the Longitudinal Aging Study Amsterdam (LASA), an ongoing population-based study (Deeg and Westendorp-de Serière, 1994; Van den Heuvel et al., 1996). Procedures regarding sampling and data collection have been previously described in detail (Van den Heuvel et al., 1996). In short, a random sample of men and women aged 55 to 85, stratified by age and sex according to expected five-year mortality, was drawn from the population registries of eleven municipalities in three areas of the Netherlands. Figure 1 shows a flow chart of the study sample. Data collection started in 1992/1993 (T_1) in 3,107 participants, of whom 3,091 had a valid score on the Mini-Mental State Examination (MMSE), and included follow-up measurements every three years. For the early identification of persons at risk for developing persistent cognitive decline, data on relevant predictors have to be collected some years before the detection of clinically relevant cognitive decline. In the present study, data collected during the second data collection (T_2), which was considered the baseline measurement were used for the development of the classification models. Respondents were included in the study sample at baseline if they fulfilled the following criteria: 1) to ensure that persons were not

demented at baseline they had to have an MMSE ≥ 19, and show no persistent cognitive decline (T_1 to T_2, based on MMSE scores as described below); 2) to be able to identify persistent cognitive decline over the subsequent years cognitive data had to be available at follow-up measurements (T_3 and T_4). This resulted in a study sample of 2,021 persons. Within the study sample, blood samples were available for 1,133 respondents. In the LASA study, the blood drawing procedure was restricted to respondents who were 65 years and older. The respondents who refused to take part in the blood drawing procedure, were significantly older ($p < 0.001$) and had lower scores on cognitive performance tests ($p < 0.001$) compared with those who agreed to give blood. All interviews were conducted in the homes of the respondents by specially trained and intensively supervised interviewers. Informed consent was obtained from all respondents, and the study was approved by the Ethical Review Board of the VU University medical center (VUmc).

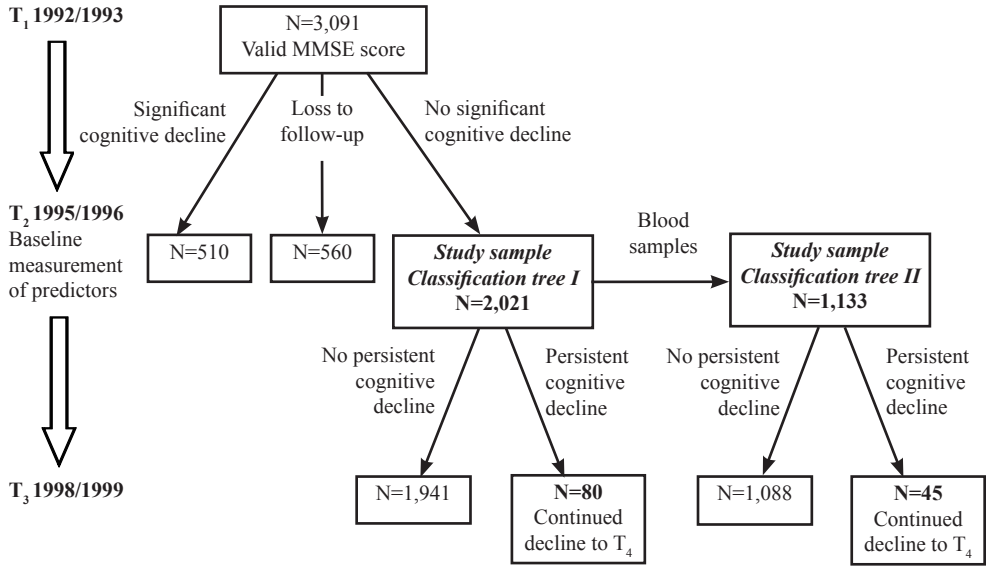

Figure 1 Flow Chart of the study sample

Loss to follow-up during the second, third and fourth data collection was mainly due to mortality (13.4%, 13.5%, 13.9%). A smaller percentage of respondents lost to follow-up refused to participate (2.9%, 2.8%, 3.0%) or was ineligible (1.2%, 1.7%, 1.5%). Respondents lost to follow-up were older ($p < 0.001$), had lower scores on cognitive performance tests ($p < 0.001$), and were more likely to be men ($p < 0.001$). Within the study sample, a complete MMSE score was available for N = 1,895, N = 1,855 and N = 1,454 at respectively T_2, T_3 and T_4. Respondents who refused or were no longer able to participate in the complete interview, were asked to participate in a brief interview by telephone. In second instance, if persons were not able or refused to complete the telephone interview, a close relative was asked to take part in a brief telephone interview after consent was given by the respondent.

Cognitive measurements

The MMSE was administered during the baseline measurement and during all follow-up measurements (Folstein et al., 1975). The MMSE is widely used as a tool for monitoring change in global cognitive functioning, with satisfactory reliability and construct validity (Tombaugh and McIntyre, 1992). The score on the MMSE was compared with the MMSE score on subsequent interviews. Significant cognitive decline was defined as more than two standard deviations below the average decline of the total sample (Altman, 1999).

Persons who were not able or refused to participate in the complete follow-up interview were asked to participate in a telephone interview in which an abbreviated version of the MMSE was administered. The abbreviated version of the MMSE included the following items: year; day of the week; month; two streets in the neighbourhood; address; repeating three words; the highest score on either subtracting (100-7) or spelling backwards; remembering three words. Subsequently, the score on the abbreviated version of the MMSE was compared with the score on the abbreviated MMSE derived from the complete score on the MMSE obtained in a previous interview. Again, significant cognitive decline was defined as more than two standard deviations below the average cognitive decline of the total sample.

For persons who were not able or refused to complete the telephone interview, an abbreviated version of the IQCODE was administered (Jorm and Korten, 1988). This instrument has been shown to be valid and reliable for measuring cognitive decline (Jorm, 2004). Furthermore, the short version of the IQCODE has been shown to measure cognitive change in everyday activities of elderly persons and may be used as an efficient rating scale for clinical assessment of dementia (De Jonghe et al., 1997). The following six items in which decline over the past ten years was enquired are included in the short version of the IQCODE: remembering conversations a few days later; remembering his or her address and telephone number; knowing how to work familiar machines around the house; making decisions on everyday matters; handling money for shopping; handling financial matters. The items are scored on a 5-point scale: 1 (much better), 3 (no change), 5 (much worse). Scores range from 6 to 30, a higher score indicating more decline. Significant cognitive decline was defined by a minimum score of 28 (i.e. the maximum score of 5 on at least four areas, and a score of 4 on the remaining two areas).

Persistent cognitive decline

To be able to determine whether a subject was at risk of developing dementia, respondents with 'persistent cognitive decline' were identified. Persistent cognitive decline was defined as 1) significant cognitive decline over at least three years (T_2 to T_3) and 2) continued cognitive decline over the subsequent years (T_3 to T_4).

Longitudinal measurements of the (abbreviated) MMSE and the IQCODE were applied to determine whether the criteria set for persistent cognitive decline were met. Finally, if applicable, the interviewers recorded the reason for loss-to-follow-up, in which 'dementia' was one of the response categories.

Respondents who did not fulfil the set criteria for persistent cognitive decline, were characterized as showing 'no persistent cognitive decline'.

Early predictors

The selection of predictors was based on recent reviews and research on predictors of cognitive decline and (early) dementia (Gauthier et al., 2006; Ownby et al., 2006; Panza et al., 2006; Razay et al., 2006; Róman, 2005; Stampfer, 2006; Van der Flier and Scheltens, 2005). Subsequently, those predictors which are relatively easy to determine were selected to ensure feasibility in primary care, leading to the selection of two sets of predictors.

First set of predictors

The first set consisted of variables already known or otherwise easily enquired: age (> 75, ≤ 75 years old), sex, level of education (≤ elementary school, > elementary school), memory complaints (yes, no) (Geerlings et al., 1999; Schofield et al., 1997), diabetes mellitus, cardiovascular disease, functional limitations, depressive symptoms, alcohol use, smoking (yes, no), and the baseline MMSE score. For the present study, the MMSE was dichotomized using three different cutoff points: 24, 25, and 26.

Cardiovascular disease (cardiac disease and stroke) and diabetes mellitus were assessed by self-report, which has been shown to display moderate to nearly perfect agreement with general practitioner information ($\kappa = 0.50\text{-}0.85$) (Kriegsman et al., 1996). In the present study cardiovascular disease and diabetes mellitus were combined into one dichotomous variable.

Functional limitations were measured with a questionnaire which was previously validated in the Netherlands (Smits et al., 1997; Van Sonsbeek, 1988), concerning the degree of difficulty with activities of daily living (ADL).

Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale (range, 0 to 60) designed to measure depressive symptoms in the general population (Radloff, 1977). The generally applied cutoff score validated for both men and women of ≥ 16 was used to identify clinically relevant depressive persons (Beekman et al., 1997).

Alcohol consumption was assessed by asking for the number of days per week that alcohol was consumed and the number of alcoholic units consumed on a drinking day (Garretsen and Knibbe, 1983), and was thereafter classified as no, light, and moderate to excessive consumption. In the present study light alcohol use was considered the reference category (Lang et al., 2007). Both no and moderate to excessive alcohol use were included in the analyses. Moderate to excessive alcohol use was defined as ≥ 6 drinks ≥ 1 days per month, ≥ 4 drinks ≥ 1 days per week, and ≥ 2 drinks ≥ 3 days per week.

Second set of predictors

The second set of variables consisted of predictors that require additional measurement, although feasible in primary care: hypertension, body mass index (BMI), and several blood parameters, namely homocysteine, vitamin B_{12}, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, C-reactive protein (CRP), and Apolipoprotein E (ApoE) phenotype.

Hypertension was determined by high systolic blood pressure (≥ 160 mmHg) or use of anti-hypertensive drugs, based on the practical guideline 'Cardiovascular risk management' developed by the Dutch College of General Practitioners (DCGP) (Burgers et al., 2007).

BMI was calculated as (weight (kg) /(height (m))^2). Both high BMI (> 25) and low BMI (< 21) were included as predictors in the present study (Razay et al., 2006; Róman, 2005).

Serum levels of total homocysteine (tHcy) were determined at the Laboratory of Clinical Chemistry of the VUmc with an Abbott Imx analyzer using fluorescence polarization immunoassay (FPIA) technology. In the present study, the highest quartile values (> 16.93 µmol/L) were considered high tHcy.

Serum levels of vitamin B_{12} were determined at the Endocrine Laboratory of the VUmc with a competitive immunoassay luminescence on the automated CS 180 System (Bayer Diagnostics, Mijdrecht, The Netherlands). The lower quartile values (< 214 pmol/L) were considered low vitamin B_{12} in the present sample. A shortage of vitamin B_{12} is known to cause an increase in tHcy concentrations (Mooijaart et al., 2005).

Total cholesterol and HDL cholesterol were measured with a Hitachi 747 analyzer (VUmc) using enzymatic colorimetry assay (Roche diagnostics, Mannheim, Germany). LDL cholesterol was calculated using the following formula (total cholesterol - HDL cholesterol - VLDL cholesterol). VLDL cholesterol was calculated as (0.456 x total triglyceride concentration) expressed in mmol/L (Friedewald et al., 1972). LDL cholesterol could only be calculated if triglycerides were < 5.0 mmol/L, since the Friedewald formula is known to be less reliable as triglyceride concentration increases (Rifai et al., 1992). Both high (upper quartile > 6.2 mmol/L) and low total cholesterol (lower quartile < 5.0 mmol/L) were included in the analyses (Evans et al., 2000; Solfrizzi et al., 2002). Also, high LDL cholesterol (upper quartile > 4.2 mmol/L) and low HDL cholesterol (lower quartile < 1.03 mmol/L) were studied.

CRP levels were measured with a sandwich-type enzyme linked immunosorbent assay (ELISA). The upper quartile values (≥ 5.0 µg/mL) were regarded as high CRP in the present study.

The ApoE phenotype was determined by isoelectric focusing of delipidated serum samples, followed by immunoblotting (Havekes et al., 1987). Obtained serum samples were frozen at -80°C until actual ascertainment. The distribution of ApoE phenotypes was in Hardy-Weinberg equilibrium (ApoE e2/2: 0.7%; e2/3: 11.7%; e3/3: 60.5%; e2/4: 3.0%; e3/4: 21.3%; e4/4: 2.9%).

ApoE status was classified as e4 carriers for persons with the ApoE e4 isoform (phenotypes e2/4, e3/4, e4/4) and as e4 non-carriers for persons without the ApoE e4 isoform (phenotypes e2/2, e2/3, e3/3).

Data analysis

Differences in characteristics were evaluated between respondents who did not show persistent cognitive decline and those who were identified with persistent cognitive decline, using either Mann-Whitney U tests for independent samples (continuous variables) or Chi-Square tests (dichotomous variables). The Odds Ratio (OR) was computed for each of the predictors using univariate regression analyses.

Development of the classification models

Stepwise logistic regression analysis was used for the development of the classification models. First of all, the strongest predictor of persistent cognitive decline was identified in the total study sample. Secondly, the sample was split into two subsamples on the basis of that particular predictor, dichotomized according to the optimal cutoff point determined for each predictor. The strongest predictor of persistent cognitive decline was then identified within each subsample, after which the subsample was divided again. This procedure was repeated until no more significant predictors could be found. In addition, the remaining subsample size had to be sufficient for further analysis ($N \geq 50$).The decision to add a predictor in the classification tree was made with logistic regression analysis and was based on the Odds Ratio (OR) with a 95% confidence interval ($p < 0.05$).

Two classification trees were constructed. The first one with the first set of predictors, which are already known or relatively easy to determine in primary care, the second including all predictors (first and second set of predictors). Since the use of the MMSE requires an additional action in clinical practice and takes an average of seven minutes, the dichotomized MMSE score was added to both models only after no other significant predictors could be identified.

The predictive value of all predictors was computed, which represents the percentage of persons who were identified with persistent cognitive decline after the subsequent three years. In addition, the Relative Risk (RR) (95% confidence interval), which is a more accurate risk estimation than the OR as the cumulative predictive value increases, was computed using Cox regression survival analyses with equal survival time for all participants.

Results

Classification tree I using the first set of predictors

Within the study sample significant cognitive decline was observed in 101 respondents between T_2 and T_3, of whom 78 continued to decline. In two respondents the reason for lost to follow up was recorded ‘dementia’. In total, 4.0% (N = 80/2,021) of the respondents were identified with persistent cognitive decline after three years of follow-up.

Table 1 shows the characteristics of the first set of predictors, separately for persons who developed persistent cognitive decline and who did not. The mean age of the respondents who developed persistent cognitive decline was 81.05 (SD = 5.63) at baseline. The mean age of respondents who developed no persistent cognitive decline was 71.19 (SD = 8.16).

Table 1 Characteristics of the first set of predictors separately for subjects who showed persistent cognitive decline and subjects who did not

	Persistent cognitive decline (N=80) (% (N))	No persistent decline (N=1,941) (% (N))	Odds ratio	95% Confidence interval
Age > 75 years	83.8 (67)	30.3 (589)	11.83	6.48 – 21.60
Women	56.3 (45)	55.3 (1,073)	1.04	0.66 – 1.63
≤ Elementary school	53.2 (42)	39.2 (761)	1.76	1.12 – 2.76
Memory complaints	42.9 (30)	23.2 (423)	2.49	1.53 – 4.04
Depressive symptoms, CES-D ≥ 16	16.3 (13)	11.9 (231)	1.44	0.78 – 2.64
Diabetes mellitus and/or CVD	47.1 (33)	25.5 (465)	2.61	1.62 – 4.23
≥ 1 functional limitation	81.5 (53)	44.5 (804)	5.50	2.92 – 10.36
Smoking [1]	17.2 (10)	17.9 (209)	0.96	0.48 – 1.92
No alcohol use [1,2]	43.1 (25)	23.8 (278)	2.71	1.48 – 4.96
Moderate or excessive alcohol use [1,2]	22.4 (13)	24.7 (289)	1.35	0.66 – 2.76
MMSE ≤ 24	51.3 (41)	15.6 (302)	5.71	3.62 – 9.00
MMSE ≤ 25	60.0 (48)	21.3 (413)	5.55	3.50 – 8.79
MMSE ≤ 26	67.5 (54)	31.2 (605)	4.59	2.85 – 7.39

The Odds Ratios (of the first set of predictors of persistent cognitive decline) are based on univariate regression analysis [1] smoking and alcohol use were determined during the medical interview within LASA (≥ 65 years old; N=1,509). [2] light alcohol use = reference category. *MMSE* Mini-Mental State Examination; *CES-D* Center for Epidemiologic Studies Depression Scale; *CVD* cardiovascular disease.

The OR of each predictor of persistent cognitive decline in the first set is shown in Table 1. The results show that persons older than 75 years were nearly 12 times more likely to show persistent cognitive decline compared with persons younger than 75 years. Other significant predictors were lower education, memory complaints, presence of cardiovascular disease and/or diabetes mellitus, functional impairments, no alcohol use (reference category: light alcohol use) and a lower score on the MMSE at baseline. The mean baseline MMSE score of subjects who developed persistent cognitive decline was 24.74 (SD = 3.07). The mean MMSE score of the respondents who did not develop persistent cognitive decline was 27.38 (SD = 2.42) at baseline.

Figure 2 shows the classification tree using the first set of predictors. Age was the strongest predictor of persistent cognitive decline. Persons over 75 years old had a substantially increased risk (RR: 10.72; 95% confidence interval (CI): 5.92 to 19.42) of developing persistent cognitive decline over the subsequent years. In the age group > 75 years old, having memory complaints

(RR: 2.02; 95% CI: 1.21 to 3.38), low education (≤ elementary school) (RR: 2.29; 95% CI: 1.06 to 4.96), and an MMSE score of ≤ 24 (RR: 3.70; 95% CI: 1.16 to 11.78), resulted in a percentage of 43.5 classified with persistent cognitive decline three years later. In the subsample of persons reporting no memory problems (age > 75 years old), drinking no alcohol (RR: 2.31; 95% CI: 1.06 to 5.02), and an MMSE score of ≤ 24 (RR: 3.07; 95% CI: 1.69 to 8.63) resulted in a predictive value for persistent cognitive decline of 22.0%. In the subsample of persons ≤ 75 years old, reporting one or more functional limitations was the most significant predictor of persistent cognitive decline (RR: 8.52; 95% CI: 1.89 to 39.44). However, within this subsample the number of persons who showed persistent cognitive decline was only 11, resulting in a low predictive value for persistent cognitive decline (2.0%) and a wide confidence interval. In the age group ≤ 75 years old without any reported functional limitations, no other significant predictors could be found. The predictive value for persistent cognitive decline in this subsample was only 0.2%.

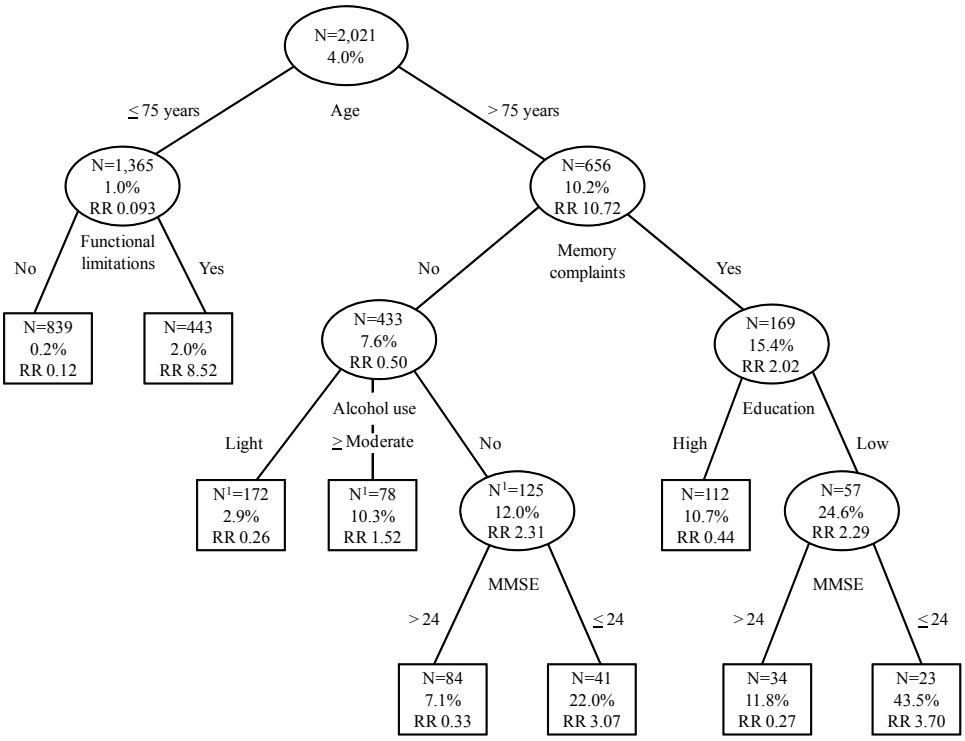

Figure 2 Classification tree I using the first set of predictors for the ascertainment of the risk of developing persistent cognitive decline

[1] Alcohol use was determined during the medical interview within LASA and was available for 375 respondents in this subsample; *N* the number of persons who satisfied the set criterion; *%* the percentage of subjects who showed persistent cognitive decline after three years of follow-up; *RR* relative risk.

Table 2 Characteristics of all predictors separately for subjects who showed persistent cognitive decline and subjects who did not

	Persistent cognitive decline (N^1=45) (% (N))	No persistent decline (N^2= 1,088) (% (N))	Odds ratio	95% Confidence interval
Age > 75 years	88.9 (40)	40.2 (437)	11.91	4.67 – 30.44
Women	48.9 (22)	54.2 (590)	0.81	0.45 – 1.47
≤ Elementary school	51.1 (23)	39.4 (429)	1.61	0.88 – 2.92
Memory complaints	42.2 (19)	25.2 (274)	2.17	1.18 – 3.98
Depressive symptoms, CES-D ≥ 16	13.3 (6)	14.0 (152)	0.95	0.39 – 2.28
Diabetes mellitus and/or CVD	48.9 (22)	27.0 (293)	2.59	1.42 – 4.72
≥ 1 functional limitation	76.2 (32)	51.1 (549)	3.06	1.49 – 6.29
Smoking [1]	11.1 (5)	17.5 (190)	0.59	0.23 – 1.52
No alcohol use [1,2]	42.2 (19)	22.2 (10)	2.66	1.35 – 5.27
Moderate or excessive alcohol use [1,2]	22.2 (10)	25.1 (273)	1.29	0.58 – 2.88
Vitamin B_{12}, low	34.1 (14)	24.1 (248)	1.64	0.84 – 3.17
Homocysteine, high	34.9 (15)	20.8 (219)	2.04	1.07 – 3.88
Total cholesterol, high	16.7 (7)	29.9 (313)	0.47	0.21 – 1.07
Total cholesterol, low	47.6 (20)	21.2 (222)	3.38	1.81 – 6.30
LDL cholesterol, high	22.0 (9)	26.6 (277)	0.78	0.37 – 1.65
HDL cholesterol, low	38.1 (16)	23.0 (241)	2.06	1.09 – 3.90
BMI, high	66.7 (26)	65.2 (660)	1.07	0.54 – 2.11
BMI, low	7.7 (3)	2.5 (25)	3.29	0.95 – 11.41
CRP, high	45.2 (19)	32.6 (339)	1.71	0.92 – 3.18
Hypertension	40.5 (17)	37.9 (409)	1.11	0.59 – 2.09
ApoE e4 carriers	36.4 (16)	25.9 (277)	1.64	0.87 – 3.07
MMSE ≤ 24	42.2 (19)	11.0 (120)	5.90	3.17 – 10.97
MMSE ≤ 25	53.3 (24)	17.0 (185)	5.58	3.04 – 10.23
MMSE ≤ 26	62.2 (28)	28.8 (313)	4.08	2.20 – 7.56

The Odds Ratios (of all predictors of persistent cognitive decline) are based on univariate regression analysis. *N^1* total number of persons with persistent cognitive decline of whom blood samples were available. *N^2* total number of persons with no persistent cognitive decline of whom blood samples were available. [1] smoking and alcohol use were determined during the medical interview within LASA (≥ 65 years old; N = 1,509). [2] light alcohol use = reference category. *MMSE* Mini-Mental State Examination; *CES-D* Center for Epidemiologic Studies Depression Scale; *CVD* cardiovascular disease; *LDL* low density lipoprotein; *HDL* high-density lipoprotein; *BMI* body mass index; *CRP* C-reactive protein; *APOE* Apolipoprotein.

Classification tree II using all predictors

For the development of the second classification model, in addition to the first set, the second set of predictors, containing among others markers determined in blood was included in the

analyses. Within this study sample significant cognitive decline was observed in 60 respondents between T_2 and T_3, of whom 44 continued to decline. In one respondent the reason for lost to follow up was recorded 'dementia'. In total, 4.0% (N = 45/1,133) of the respondents were identified with persistent cognitive decline after three years of follow-up.

Table 2 shows the characteristics of all predictors (first and second set), separately for persons who developed persistent cognitive decline over the subsequent years and those who did not. The mean age of the respondents who developed persistent cognitive decline was 81.97 (SD = 5.06) at baseline. The mean age of respondents who did not develop persistent cognitive decline was 74.65 (SD = 6.29).

The OR of each predictor of persistent cognitive decline is shown in Table 2. The results show that high homocysteine level, low total cholesterol level, and low HDL cholesterol level were significant predictors of persistent cognitive decline, in addition to age, memory complaints, presence of cardiovascular disease and/or diabetes, functional limitations, no alcohol consumption (reference category: light alcohol use) and a lower MMSE score at baseline. The mean baseline MMSE score of the subjects who showed persistent cognitive decline was 24.93 (SD = 3.06). The mean MMSE score of the respondents who showed no persistent cognitive decline was 27.25 (SD = 2.40) at baseline.

Figure 3 shows the classification tree using all predictors. The results show that age was again the most significant predictor of persistent cognitive decline (RR 11.0; 95% CI: 4.34 to 27.88), resulting in a predictive value of 8.4%. In the age group > 75 years with a low total cholesterol level (RR 2.23; 95% CI: 1.16 to 4.27) and an MMSE score of ≤ 24 (RR 3.73; 95% CI: 1.39 to 10.01), 30.0% developed persistent cognitive decline over the subsequent years. In the subsample of persons with a total serum cholesterol level ≥ 5.0 mmol/L (age > 75 years old), carrying the ApoE e4 allele was the strongest predictor of persistent cognitive decline (RR 3.21; 95% CI: 1.35 to 7.63). In this subsample the incidence of persistent cognitive decline increased to a final 12.0%. In the age group ≤ 75 years, no other significant predictor was found. The predictive value within this subsample was only 0.8%.

From both classification models developed in the present study a subgroup comprising persons at high risk for persistent cognitive decline was deduced. An arbitrary chosen predictive value of ≥ 12.0%, which is at least three times the incidence rate of persistent cognitive decline in the total study sample, was used to classify persons in this subgroup. Consequently, subjects > 75 years old without memory complaints, consuming no alcohol with an MMSE score of ≤ 24 at baseline, as well as subjects > 75 years old with memory complaints, low education, and an MMSE of ≤ 24 at baseline would be regarded at high risk for persistent cognitive decline. In addition, subjects over 75 years old with a cholesterol level of ≥ 5.0 mmol/L who carried the ApoE e4 allele, as well as subjects > 75 years with a cholesterol level < 5.0 mmol/L and an MMSE score of ≤ 24 at baseline were considered at high risk.

A comparison between persons at risk for persistent cognitive decline identified with the first and second classification model showed an overlap of 5.0% (N = 1/20).

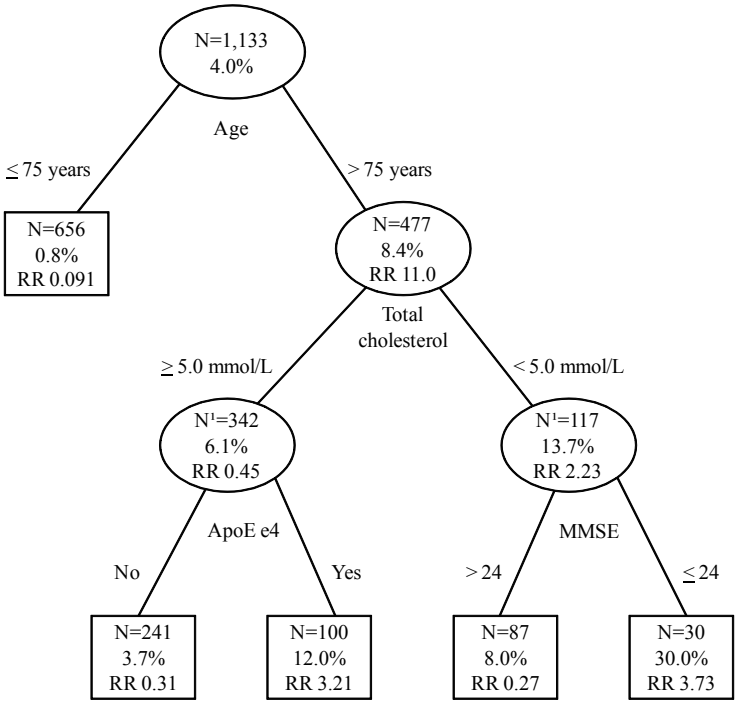

Figure 3 Classification tree II using all predictors for the ascertainment of the risk of developing persistent cognitive decline

[1] Cholesterol was available for 459 respondents in this age group (> 75 years old); *N* the number of persons who satisfied the set criterion; *%* the percentage of subjects who showed persistent cognitive decline after three years of follow-up; *RR* relative risk.

Discussion

In the present study two simple classification models were developed that could facilitate the early identification of persons at risk for persistent cognitive decline. Although it is very likely that the persons with persistent cognitive decline in our sample have dementia, no formal dementia diagnosis was available. Therefore, these findings need to be validated in another large population-based study in which a formal dementia diagnosis and data on all predictors is present, before the models can be implemented in clinical practice. These classification models could contribute to case-finding of frail older persons at risk for dementia in primary care in a cost-effective way. The identification of persons at risk in an early phase when cognitive disorders and functional limitations are less obvious and are not yet interfering with daily living is important in order to create the opportunity to start dementia-care at an early stage of the disease.

A major strength of the present study is that longitudinal data from a large population-based study were used, including data on many relevant predictors of cognitive decline and dementia, such as demographic variables, lifestyle factors, cardiovascular risk factors, and biological

markers, measured before persistent cognitive decline started. It was shown that age was the strongest predictor of persistent cognitive decline in both classification models. In the first classification tree in which predictors requiring additional measurement such as biological markers were not included, the predictive value increased from 4.0% to 43.5% and 22.0%, respectively. In the second classification tree, in which all relevant predictors were included the predictive value for persistent cognitive decline increased from 4.0% to 30.0 % and 12%, respectively. Both classification models mostly identified different persons. Therefore, both models could be complementary to each other during case-finding of older persons at risk for persistent cognitive decline.

The importance of the distinguished predictors in the classification trees has been stressed before. Subjective memory complaints have been shown to be a relatively strong predictor of dementia in older persons in whom cognitive impairment is not yet apparent (Geerlings et al., 1999; Jonker et al., 2000). With respect to the role of alcohol intake, previous studies showed an U-shaped relationship between alcohol consumption and cognitive decline and dementia (Lang et al., 2007; Stampfer, 2006). Furthermore, alcohol abstinence has been associated with increased frailty (Woo et al., 2005). It has been suggested that older persons may abstain from alcohol in response to worsening health (Pringle et al., 2006). With respect to the role of cholesterol, previous studies have suggested that low cholesterol in later life may be viewed as a frailty marker (Schalk et al., 2004; Spada et al., 2007; Van den Kommer et al., 2009), as opposed to midlife where high cholesterol is considered to be a risk factor for dementia (Jarvik et al., 1995; Kivipelto et al., 2001). Furthermore, the APOE ε4 allele is a known risk factor for cognitive decline and Alzheimer's disease (AD) (Strittmatter and Roses, 1995).

A few limitations should also be mentioned. In the present study the outcome measure was persistent cognitive decline as identified by repeated measurements of the MMSE and the IQCODE. Unfortunately, a formal dementia diagnosis satisfying the criteria as posed by the DSM-IV (American Psychiatric Association, 1994) or the NINCDS-ADRDA (McKhann et al., 1984) could not be made. However, those identified with persistent cognitive decline showed clinically significant cognitive decline in the first three years of follow-up, satisfying the rather strict criterion of more than two standard deviations below the average cognitive decline observed in the total study sample, and continued to decline during the subsequent three years. Therefore, it seems likely that most of the subjects identified with persistent cognitive decline will have developed dementia. The remaining 96% of the sample not identified with persistent cognitive decline is likely to be a heterogeneous group, some of whom may develop dementia at some point. It seems possible that persons with a slower rate of cognitive decline were unjustly classified as showing no persistent cognitive decline (false negatives) and therefore as not being at risk for dementia. Moreover, because of the strict criteria for persistent cognitive decline it is likely that we have misclassified some cases, which may have resulted in an underestimation of the relative risk. In the age group ≤ 75 years, only 1.0% (first model) respectively 0.8% (second model) was identified with persistent cognitive decline. Only in the first classification

tree could a significant predictor of future persistent cognitive decline, namely the presence of functional limitations, be determined, increasing the relative risk to 8.52. No other significant predictors were found in the analyses. It is possible that we did not have the right predictors at our disposal or enough power to identify a larger percentage of persons aged ≤ 75 years at risk for persistent cognitive decline. Furthermore, especially within this age group, persons at risk for fronto-temporal dementia could have been missed since for example changes in personality and behaviour were not taken into account. However, with respect to the development of the classification trees, prevention of false positives was even more essential because persons unjustly identified with persistent cognitive decline would have had considerably more influence on the results. Furthermore, persons, of whom blood samples were not available and therefore could not be included in the second classification model, were the most frail and cognitively poorest functioning older persons. Therefore an underestimation of the predictive value of this model may be likely.

The Dutch College of General Practitioners (DCGP) has developed a dementia standard, in which the use of the MMSE to objectify memory problems and other cognitive disorders is recommended (Wind et al., 2003). In the Netherlands, use of the MMSE should therefore produce few practical objections besides time investment, since this instrument should be available in most general practices. However, variations in dementia guidelines exist across countries because of differences in system resources, service provision, and professional cultures within the primary care system (Vernooij-Dassen et al., 2005).

The mean MMSE score at baseline was significantly lower in persons who were identified with persistent cognitive decline, which may suggest that they were already demented at baseline. However, no significant cognitive decline was established in those persons during three years before the baseline measurement. In addition, the age of the persons with persistent cognitive decline was significantly higher and their educational level was significantly lower compared with the persons who did not decline, which could explain the observed differences with respect to the MMSE score at baseline (Freidl et al., 1996; Ishizaki et al., 1998).

In conclusion, the classification models developed in the current study both lead to a substantial increase of the predictive value for persistent cognitive decline, that is from 4.0% to 43.5% and 30.0%, and identify to a large extent a different subsample of persons who are at risk for persistent cognitive decline. The developed classification trees could be useful for case-finding of persons at risk for future persistent cognitive decline who are therefore at risk for dementia in a feasible and cost-effective way.

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References

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

Alagiakrishnan, K., McCracken, P., Feldman, H., 2006. Treating vascular risk factors and maintaining vascular health: is this the way towards successful cognitive ageing and preventing cognitive decline? Postgrad. Med. J. 82, 101-105.

Altman, D., 1999. Practical Statistics for Medical Research. Chapman & Hall, London.

Bamford, C., Eccles, M., Steen, N., Robinson, L., 2007. Can primary care record review facilitate earlier diagnosis of dementia? Fam. Pract. 12, 183-192

Beekman, A.T.F., Deeg, D.J.H., van Limbeek, J., Braam, A.W., de Vries, M.Z., van Tilburg, W., 1997. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in the Netherlands. Psychol. Med. 27, 231-235.

Burgers, J.S., Simoons, M.L., Hoes, A.W., Stehouwer, C.D., Stalman, W.A., 2007. Guideline cardiovascular risk management. Ned. Tijdschr. Geneeskd. 151, 1068-1074 (in Dutch).

De Jonghe, J.F., Schmand, B., Ooms, M.E., Ribbe, M.W., 1997. Abbreviated form of the Informant Questionnaire on cognitive decline in the elderly. Tijdschr. Gerontol. Geriatr. 28, 224-229.

Deeg, D.J.H., Westendorp-de Serière, M., eds., 1994. Autonomy and well-being in the aging population I: report from the Longitudinal Aging Study Amsterdam 1992-1993. VU University Press, Amsterdam, The Netherlands.

Evans, R.M., Emsley, C.L., Gao, S., Sahota, A., Hall, K.S., Farlow, M.R., Hendrie, H., 2000. Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. Neurology 54, 240-242.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-Mental State. A practical method for grading cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189-198.

Freidl, W., Schmidt, R., Stronegger, W.J., Irmler, A., Reinhart, B., Koch, M., 1996. Mini Mental State Examination: influence of sociodemographic, environmental and behavioral factors, and vascular risk factors. J. Clin. Epidemiol. 49, 73-78.

Friedewald, W.T., Levy, R.I., Frederickson, D.S., 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. Clin. Chem. 18, 499-502.

Garretsen, H.F.L., Knibbe RA (1983) Alcohol prevalence study Rotterdam/Limburg, national final report Ministry of Welfare, Health and Culture, Leidschendam (in Dutch).

Gauthier, S.G., 2005. Alzheimer's disease: the benefits of early treatment. Eur. J. Neurol. 12, 11-16.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R.C., Ritchie, K., Broich, K., Belleville, S., Brodaty, H., Bennett, D., Chertkow, H., Cummings, J.L., de Leon, M., Feldman, H., Ganguli, M., Hampel, H., Scheltens, P., Tierney, M.C., Whitehouse, P., Winblad, B., 2006. Mild cognitive impairment. Lancet 367, 1262-1270.

Geerlings, M.I., Jonker, C., Bouter, L.M., Ader, H.J., Schmand, B., 1999. Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. Am. J. Psychiatry 156, 531-537.

Havekes, L.M., de Knijff, P., Beisiegel, U., Havinga, J., Smit, M., Klasen, E., 1987. A rapid micromethod for apolipoprotein E phenotyping directly in serum. J. Lipid Res. 28, 455-463.

Ishizaki, J., Meguro, K., Ambo, H., Shimada, M., Yamaguchi, S., Hayasaka, C., Komatsu, H., Sekita, Y., Yamadori, A., 1998. A normative, community-based study of Mini-Mental State in elderly adults: the effect of age and educational level. J. Gerontol. B Psychol. Sci. Soc. Sci. 53, 359-363.

Jarvik, G.P., Wijsman, E.M., Kukull, W.A., Schellenberg, G.D., Yu, C., Larson, E.B., 1995. Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: a case-control study. Neurology 45, 1092-1096.

Jonker, C., Geerlings, M.I., Schmand, B., 2000. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int. J. Geriatr. Psychiatry 15, 983-991

Jorm, A.F., Korten, A.E., 1988. Assessment of cognitive decline in the elderly by informant interview. Br. J. Psychiatry 152, 209-213.

Jorm, A.F., 2004. The informant questionnaire on cognitive decline in the elderly (IQCODE): a review. Int. Psychogeriatr. 16, 275-293

Kivipelto, M., Helkala, E.L., Laakso, M.P., Hänninen, T., Hallikainen, M., Alhainen, K., Soininen, H., Tuomilehto, J., Nissinen, A., 2001. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 322, 1447-1451.

Kriegsman, D.M.W., Penninx, B.W.J.H., van Eijk, J., Boeke, A.J.P., Deeg, D.J.H., 1996. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinations of inaccuracy. J. Clin. Epidemiol. 49, 1407-1417.

Lang, I., Wallace, R.B., Huppert, F.A., Melzer, D., 2007. Moderate alcohol consumption in older adults is associated with better cognition and well-being than abstinence. Age Ageing 36, 256-261.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34, 939-944

Mittelman, M.S., Ferris, S.H., Shulman, E., Steinberg, G., Levin, B., 1996. A family intervention to delay nursing home placement of patients with Alzheimer disease. A randomized controlled trial. JAMA. 276, 1725-1731.

Moniz-Cook, E., Woods, R.T., 1997. The role of memory clinics and psychosocial intervention in the early stages of dementia. Int. J. Geriatr. Psychiatry 12, 1143-1145.

Mooijaart, S.P., Gussekloo, J., Fr□lich, M., Jolles, J., Stott, D.J., Westendorp, R.G.J., de Craen, A.J.M., 2005. Homocysteine, vitamin B-12, and folic acid and the risk of cognitive decline in old age: the Leiden 85-Plus Study. Am. J. Clin. Nutr. 82, 866-871.

Ownby, R.L., Crocco, E., Acevedo, A., John, V., Loewenstein, D., 2006. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch. Gen. Psychiatry 63, 530-538.

Panza, F., D'Introno, A., Colacicco, A.M., Capurso, C., Pichichero, G., Capurso, S.A., Capurso, A., Solfrizzi, V., 2006. Lipid metabolism in cognitive decline and dementia. Brain Res. Rev. 51, 275-292.

Pringle, K.E., Heller, D.A., Ahern, F.M., Gold, C.H., Brown, T.V., 2006. The role of medication use and health on the decision to quit drinking among older adults. J. Aging Health 18, 837-851

Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas 1, 385-401.

Razay, G., Vreugdenhil, A., Wilcock, G., 2006. Obesity, abdominal obesity and Alzheimer disease. Dement. Geriatr. Cogn. Disord. 22, 173-176.

Rifai, N., Warnick, G.R., McNamara, J.R., Belcher, J.D., Grinstead, G.F., Frantz, I.D. Jr., 1992. Measurement of low-density-lipoprotein cholesterol in serum: a status report. Clin. Chem. 38, 150-160.

Róman, G.C., 2005. Vascular dementia prevention: a risk factor analysis. Cerebrovasc. Dis. 20 (Suppl 2), 91-100.

Schalk, B.W.M., Visser, M., Deeg, D.J.H., Bouter, L.M., 2004. Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: the Longitudinal Aging Study Amsterdam. Age Ageing 33, 266-272.

Schofield, P.W., Marder, M., Dooneief, G., Jacobs, D.M., Sano, M., Stern, Y., 1997. Association of subjective memory complaints with subsequent cognitive decline in community-dwelling elderly individuals with baseline cognitive impairment. Am. J. Psychiatry 154, 609-615.

Smits, C.H.M., Deeg, D.J.H., Jonker, C., 1997. Cognitive and emotional predictors of disablement in older adults. J. Aging Health 9, 204-221.

Solfrizzi, V., Panza, F., D'Introno, A., Colacicco, A.M., Capurso, C., Basile, A.M., Capurso, A., 2002. Lipoprotein(a), apolipoprotein E genotype, and risk of Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 72, 732-736.

Spada, R.S., Toscano, G., Cosentino, F.I., Iero, I., Lanuzza, B., Tripodi, M., Ferri, R., 2007. Low total cholesterol predicts mortality in the nondemented oldest old. Arch. Gerontol. Geriatr. 44 (Suppl. 1), 381-384.

Stampfer, M.J., 2006. Cardiovascular disease and Alzheimer's disease: common links. J. Intern. Med. 260, 211-223.

Strittmatter, W.J., Roses, A.D., 1995. Apolipoprotein E and Alzheimer Disease. Proc. Natl. Acad. Sci. USA. 92, 4725-4727.

Tombaugh, T.N., McIntyre, N.J., 1992. The Mini-Mental State Examination: a comprehensive review. J. Am. Geriatr. Soc. 40, 922-935.

Valcour, V.G., Masaki, K.H., Curb, J.D., Blanchette, P.L., 2000. The detection of dementia in the primary care setting. Arch. Intern. Med. 160, 2964-2968.

Van den Heuvel, N., Smits, C.H.M., Deeg, D.J.H., Beekman, A.T.F., 1996. Personality: a moderator of the relation between cognitive functioning and depression in adults aged 55-85? J. Affect. Disord. 41, 229-240.

Van den Kommer, T.N., Dik, M.G., Comijs, H.C., Fassbender, K., Lütjohann, D., Jonker, C., 2009. Total cholesterol and oxysterols: early markers for cognitive decline in elderly? Neurobiol. Aging 30, 534-545.

Van der Flier, W.M., Scheltens, P., 2005. Epidemiology and risk factors of dementia. J. Neurol. Neurosurg. Psychiatry 76 (Suppl 5), v2-v7.

Van Sonsbeek, J.L.A., 1988. Methodological and substantial aspects of the OECD indicator of chronic functional limitations. Maandbericht Gezondheid (CBS) 88, 4-17 (in Dutch).

Vernooij-Dassen, M.J., Moniz-Cook, E.D., Woods, R.T., De Lepeleire, J., Leuschner, A., Zanetti, O., de Rotrou, J., Kenny, G., Franco, M., Peters, V., Iliffe, S., 2005. Factors affecting timely recognition and diagnosis of dementia across Europe: from awareness to stigma. Int. J. Geriatr. Psychiatry 20, 377-386.

Wind, A.W., Gussekloo, J., Vernooij-Dassen, M.J.F.J., Bouma, M., Boomsma, L.J., Boukes, F.S., 2003. NHG-Standard Dementia (revised version). Huisarts Wetenschap 46, 754-767 (in Dutch).

Woo, J., Goggins, W., Sham, A., Ho, S.C., 2005. Social determinants of frailty. Gerontology 51, 402-408.