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

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
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op vrijdag 7 januari 2011 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Tessa Nicole van den Kommer

geboren te Delft

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

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

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

Contents


Chapter 3

Classification models for early identification of persons at risk for dementia in primary care: an evaluation in a sample aged 80 years and older

Tessa N. van den Kommer
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Abstract

Aim: To evaluate previously developed classification models to make implementation in primary case possible and aid early identification of persons at risk for dementia.

Methods: Data were drawn from the OCTO-Twin Study. At baseline, 521 persons ≥ 80 years were non-demented, and for 387 a blood sample was available. Predictors of dementia were collected and analyzed in initially non-demented persons using generalized estimation equations and Cox survival analyses.

Results: In the basic model using predictors already known or easily obtained (basic set), the mean two-year predictive value increased from 6.9 to 28.8% in persons with memory complaints and an MMSE score ≤ 25. In the extended model, using both the basic set and an extended set of predictors requiring further assessment, the eight-year predictive value increased from 15.0 to 45.8% in persons with low cholesterol and an MMSE score ≤ 24.

Conclusion: Both models can contribute to an improved early identification of persons at risk for dementia in primary care.

Keywords: Incident dementia; Early identification; Classification models; Case finding.

Introduction

Early identification of persons at risk for dementia is an increasingly important issue, although currently no curative measures are available. However, management of modifiable risk factors may delay the onset and lower dementia risk (Alagiakrishnan et al., 2006; Haan and Wallace, 2004). Early pharmacological treatment of persons at high risk could result in delay of cognitive decline, preservation of functional independence and prevention of behavioral problems (Gauthier, 2005; Gauthier et al., 2006, 2008). Furthermore, identification of persons at high risk may promote timely recognition of dementia which may enable caregivers and patients to cope with problems associated with disease progression. Early person-tailored psychosocial interventions may promote adaptation to the disease, help maintain well-being (Sørensen et al., 2008), reduce caregiver strain and delay institutionalization (Mittelman et al., 2006; Spijker et al., 2008).

Many have stressed the key position of the general practitioner in detecting and diagnosing dementia as well as the accompanying difficulties (Bamford et al., 2007; Valcour et al., 2000; Vernooij-Dassen et al., 2005). In primary care there is a need for a more proactive approach to case-finding in which prediction models with multiple indicators are used to identify persons at the highest risk for dementia (Bäckman, 2008). Classification models, also called decision tree methods and classification and regression tree methodology (Allore et al., 2005; Breiman et al., 1984; Lemon et al., 2003), yield a clinical tool that addresses this need.

Two classification models for potential use in primary care were previously developed for the identification of persons at risk for developing persistent cognitive decline. It was shown that persons over 75, with memory complaints, low education and an MMSE score ≤ 24, as well as persons over 75, with low cholesterol (< 5.0 mmol/L) and an MMSE score ≤ 24 were at the highest risk of developing persistent cognitive decline, resulting in a substantial increase in predictive value from 4.0% to 43.5% and 30.0%, respectively (Van den Kommer et al., 2008). The aim of the present study is to construct these models in another independent longitudinal population-based study in which a formal dementia diagnosis is present in order to test whether congruent classification models would develop. Consequently this would make implementation in primary care possible and contribute to case-finding of persons at risk for developing dementia in a cost-effective way. The OCTO-Twin Study (Origins of Variance in the Old-Old: Octogenarian Twins) was selected for this purpose through the Integrative Analysis of Longitudinal Studies of Aging research network.

Methods

Study sample

Data were used from the OCTO-Twin Study, a longitudinal population-based study consisting of twins aged 80 and older, drawn from the Swedish twin registry (McClearn et al., 1997). Data collection started in 1991 (N = 702). Subjects were re-examined at two-year intervals over eight years of follow-up. Demographic characteristics including gender ratio, education,

housing, socioeconomic and marital status correspond to population statistics of this birth cohort (Simmons et al., 1997). Loss to follow-up during the second (14.2%), third (27.4%), fourth (27.2%) and fifth (28.9%) wave was mainly due to mortality. A small percentage declined participation at follow-ups (0.3, 0.3, 0.2, 0.6%). Subjects lost to follow-up were older (except those lost to follow-up at wave 4) ($p < 0.05$) and had a lower cognitive status ($p < 0.001$) at prior assessment. Blood samples were drawn during 1993-1995 and were available for 637 respondents at one occasion. Informed consent was obtained from all respondents in compliance with the Declaration of Helsinki.

For the present analyses, information on predictors had to be collected before dementia diagnosis. Five hundred and ninety five were free of dementia at baseline. For 74 of these respondents follow-up data were not available, resulting in a baseline sample of N = 521 (see Figure 1 for a flow chart of the study sample). In total, blood samples were available for 387 respondents without dementia during the time of blood drawing and with at least one wave of follow-up.

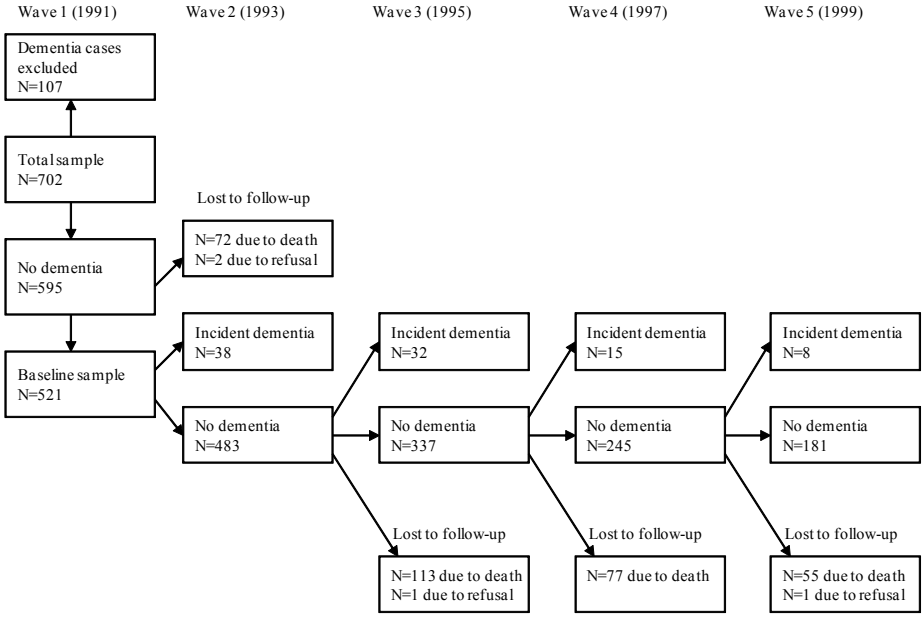

Figure 1 Flow chart of the study sample

Dementia diagnosis

Dementia diagnosis was made using DSM-III-R criteria (American Psychiatric Association, 1987), and based on a review of the performance on a battery of neuropsychological tests, informant interview, and medical records. Diagnostic procedures and neuropsychological tests have been described in detail elsewhere (Johansson and Zarit, 1991, 1995). As an indicator of the

DSM-III-R criterion impairment in social or occupational activities, impairment in instrumental activities of daily living was systematically assessed while taking sensory and motor impairment into account. Individuals suspected of dementia were presented and discussed in detail in a consensus meeting. Time of dementia diagnosis (incidence) was based on the best estimate of the age of dementia onset made during the consensus meeting using information from medical records and a supplement study partly investigating the same cases (Gatz et al., 2005).

Early predictors

Based on recent reviews and research on predictors of cognitive decline and dementia (Gauthier et al., 2006; Ownby et al., 2006; Panza et al., 2006; Razay et al., 2006; Róman, 2005; Stampfer, 2006; Van der Flier and Scheltens, 2005), a basic and extended set of predictors were selected. The basic set comprised variables in the person's medical chart or easily obtained in an interview. In addition, the MMSE (Folstein et al., 1975) was added to the basic set to assess the additive predictive value of a short cognitive screening instrument feasible in primary care, controlling for other significant predictors of dementia. The extended set consisted of variables that require further measurement, including laboratory tests. For the development of the classification models predictors were dichotomized as described below based on previous research.

Basic set of predictors

The basic set of predictors consisted of age (continuous), sex, education (≤ elementary school, > elementary school), as well as information on memory complaints, cardiovascular disease (CVD), diabetes mellitus, functional limitations, depressive symptoms, alcohol consumption, smoking and the MMSE score.

Memory complaints were assessed by self report (Do you think that you have any problems with your memory which make daily living more difficult?). Response categories 'no, not at all', 'no, hardly' were recoded to 'no'; categories 'hard to take a stand on', 'yes, to a certain degree' and 'yes, definitely' were recoded to 'yes'.

Diabetes mellitus and CVD were assessed by self report. CVD consisted of one or more of the following diseases: stroke, heart insufficiency, heart attack, angina pectoris, circulation disturbances, vascular spasm, thrombosis, and varicose ulcer in leg. Diabetes and/or CVD were combined into one dichotomous variable for comparison purposes.

Functional limitations were defined as experiencing difficulties on one or more of three items from a list of (instrumental) activities of daily living: climbing stairs, using transportation, bending down and picking up item from the floor.

Depressive symptoms were assessed with the Center for Epidemiologic Studies-Depression scale, a 20-item self-report scale (range, 0-60) (Radloff, 1977). The generally applied cutoff score ≥ 16 was used to define clinically relevant depressive symptoms (Lewinsohn et al., 1997). The Swedish translation has psychometric properties comparable to those found in previous studies (Gatz et al., 1993).

Alcohol consumption was assessed by asking the number of days on which alcohol was consumed, and was categorized as no and any alcohol use since no longitudinal information on amount of alcohol was available.

In order to detect the optimal cutoff, MMSE scores were dichotomized using three standard cutoffs (≤ 24, 25 and 26).

Extended set of predictors

The extended set of predictors consisted of hypertension, body mass index (BMI), total homocysteine (tHcy), vitamin B_{12}, total cholesterol, high-density lipoprotein (HDL) cholesterol, and Apolipoprotein E (APOE) genotype.

Hypertension was determined by high systolic blood pressure (≥ 160 mmHg) and/or the use of antihypertensive medication.

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

tHcy was analyzed by fluorescence polarization immunoassay using an IMX instrument (Abbott). The highest quartile values (≥ 19.95 μmol/L) were considered high tHcy.

Analysis of vitamin B_{12} was done by time-resolved fluoroimmunoassay using an Autodelfia instrument (Wallace). Low vitamin B_{12} was defined by the lower quartile values (≤ 181 pmol/L).

Total and HDL cholesterol were analyzed using routine methods with an AXON analyzer (Bayer). Both high and low cholesterol were included in the analyses, defined by respectively the upper (≥ 7.4 mmol/L) and lower (≤ 5.6 mmol/L) quartile values, respectively. Low HDL cholesterol levels were defined by the lower quartile values (≤ 1.20 mmol/L).

APOE genotyping was performed by examining single nucleotide polymorphisms (SNPs) (SNP000002328). The distribution of APOE genotypes was in Hardy-Weinberg equilibrium. APOE status was classified as ε4 carriers in persons with genotypes ε2/4 (2.4%), ε3/4 (26.5%) and ε4/4 (1.7%), and as ε4 non-carriers in persons with genotypes ε2/2 (1.1%), ε2/3 (14.8%) and ε3/3 (53.4%).

Data analysis

Basic classification model (basic set of predictors)

Predictors were lagged one occasion relative to dementia outcome. At each occasion, dementia outcome (yes/no) was predicted using data on predictors collected in the prior wave. Hence, predictors collected at baseline in the non-demented study sample were used to predict dementia outcome at wave 2, predictors from wave 2 collected in the remaining non-demented sample were used to predict dementia outcome at wave 3 and so forth. The odds ratio (OR) was computed for each of the predictors using univariate logistic longitudinal regression analyses based on generalized estimating equations (GEE). To predict dementia incidence, longitudinal logistic regression analyses based on GEE (method enter, exchangeable correlation structure) used the lagged predictors from the wave prior to dementia outcome. Predictors were added to

the model dichotomized as previously described. To examine the predictive value of age, continuous baseline age was added to the model. Years in study was added as a time variable. First, the strongest predictor of incident dementia was identified within the initially non-demented sample. Second, the sample was split into two subsamples based on the dichotomization of that particular predictor. This procedure was repeated in both subsamples until no more significant predictors were found, after which the dichotomized MMSE was added to the model. Since the use of the MMSE requires an additional action in clinical practice, the MMSE was added to the model only after no other significant predictors of dementia could be identified. The identification of the strongest predictor was based on the OR with a 95% confidence interval (CI) ($p < 0.05$). The remaining subsample size had to be sufficient for analysis ($N \geq 50$). Finally, the positive predictive value of each of the identified predictors (measured one wave before diagnosis) was computed, which was derived from four intervals (wave 1-2, wave 2-3, and so forth) and thus represents the mean percentage of persons who were identified with dementia each two years during the course of the study.

To test sensitivity, data were analyzed with Cox survival analyses using predictors from the non-demented study sample at wave 1 to predict any subsequent dementia (wave 2-5). Survival time was defined as (continuous) time to event. In persons who were not diagnosed with dementia during the study, time to event was equal to time in study. The same procedure described above, splitting into subsamples after each step, was used to develop the classification model. A predictor was selected based on the relative risk (RR).

Extended classification model (all predictors)

Since longitudinal blood data were not available, analyses were not based on GEE. Instead, only Cox survival analyses were used to predict dementia incidence during the study using both the basic and extended sets of wave 1 predictors (or closest wave to blood sampling in non-demented respondents). Survival time was defined as (continuous) time to dementia diagnosis (since blood drawing procedure). In persons who were not diagnosed with dementia during the study, time to event was equal to time in study (since blood drawing procedure). The RR was computed for each of the predictors using univariate Cox survival analyses. For the development of the extended classification model, the same procedure was used as described for the basic model. The predictive value of each of the identified predictors measured at baseline was computed, which represents the total percentage of persons who were identified with dementia during the study.

Results

Basic classification model

Within the study sample, 93 respondents developed dementia during the study (wave 2-5, 8 years), resulting in 17.9% (93/521) new dementia cases over 8 years of follow-up. The longitudinal analysis revealed an overall two-year rate of 6.9% new dementia cases derived from four

intervals (wave 1-2, wave 2-3, and so forth). The latter rate provides the reference against which the positive predictive values for dementia derived from GEE were evaluated.

Table 1 shows the characteristics and OR of the basic set of predictors measured in non-demented respondents one wave prior to dementia outcome, separately for persons who developed dementia during the study and who did not.

Table 1 Characteristics of the basic set of predictors lagged one wave to dementia outcome for persons who developed dementia and persons who did not

	Incident dementia (N = 93)	No dementia (N = 1,246)	OR	95% CI
Age, mean (SD), years	83.27 (3.03)	83.29 (2.80)	1.03	0.96 – 1.10
Female, % (N)	62.4 (58)	67.7 (844)	0.80	0.52 – 1.25
≤ elementary school, % (N)	78.5 (73)	70.1 (872)	1.55	0.93 – 2.60
Memory complaints, % (N)	25.8 (24)	9.7 (120)	3.26	2.00 – 5.31
Depressive symptoms, % (N)	15.8 (12)	11.6 (136)	1.40	0.73 – 2.67
Diabetes and/or CVD, % (N)	67.4 (62)	71.9 (888)	0.84	0.53 – 1.32
≥ 1 functional limitations, % (N)	86.0 (74)	72.7 (889)	2.49	1.33 – 4.68
Smoking, % (N)	6.5 (6)	5.9 (73)	1.04	0.44 – 2.50
No alcohol use, % (N)	47.8 (44)	32.6 (402)	1.96	1.28 – 2.98
MMSE ≤ 24, % (N)	56.0 (51)	14.8 (180)	7.45	4.71 – 11.78
MMSE ≤ 25, % (N)	62.6 (57)	20.5 (249)	6.67	4.23 – 10.53
MMSE ≤ 26, % (N)	71.4 (65)	28.8 (351)	6.26	3.88 – 10.09

ORs and CIs are based on univariate logistic generalized estimation equations. *OR* Odds Ratio; *CI* confidence interval; *SD* standard deviation; *CVD* cardiovascular disease; *MMSE* Mini-Mental State Examination.

The results show that persons with memory complaints were over three times more likely to receive a dementia diagnosis after one wave of follow-up. In addition, functional limitations, drinking no alcohol and lower MMSE score two years prior were significant predictors of dementia. With respect to the different cutoffs for the MMSE, the results show the highest OR for the MMSE ≤ 24. Persons who received a dementia diagnosis during the study had a mean MMSE of 23.76 (SD = 3.80) one wave prior to diagnosis. Persons who were not diagnosed with dementia had a mean MMSE of 27.20 (SD = 3.10) one wave prior to outcome.

Figure 2 shows the classification tree using the basic set of predictors one wave prior to diagnosis. Memory complaints were the strongest predictor of dementia (OR 3.26; 95% CI: 2.00 to 5.31). In the subsample of persons with memory complaints, an MMSE score ≤ 25 (OR 4.67; 95% CI: 1.70 to 12.85) resulted in an overall percentage of 28.8 classified with dementia two years later. In the subsample without memory complaints, drinking no alcohol (OR 2.32; 95% CI: 1.43 to 3.78) and an MMSE score ≤ 24 (OR 3.28; 95% CI: 1.54 to 7.02) resulted in a predictive value of 18.0%. In the subsample of persons consuming alcohol, having functional

limitations was the strongest predictor of dementia diagnosis two years later (OR 4.44: 95% CI: 1.32 to 14.94). In this subsample, an MMSE score ≤ 24 (OR 18.40; 95% CI: 7.57 to 44.75) resulted in a predictive value of 24.7%. The number of persons who developed dementia within the subsample without functional limitations was only three (positive predictive value of 1.3%).

Sensitivity analyses using Cox survival analyses to predict dementia incidence during the study (wave 2-5) using wave 1 predictors resulted in similar classification trees and a maximum increase from the initial eight-year rate of 17.9% newly identified dementia cases to a total positive predictive value for dementia of 52.6% (data not shown).

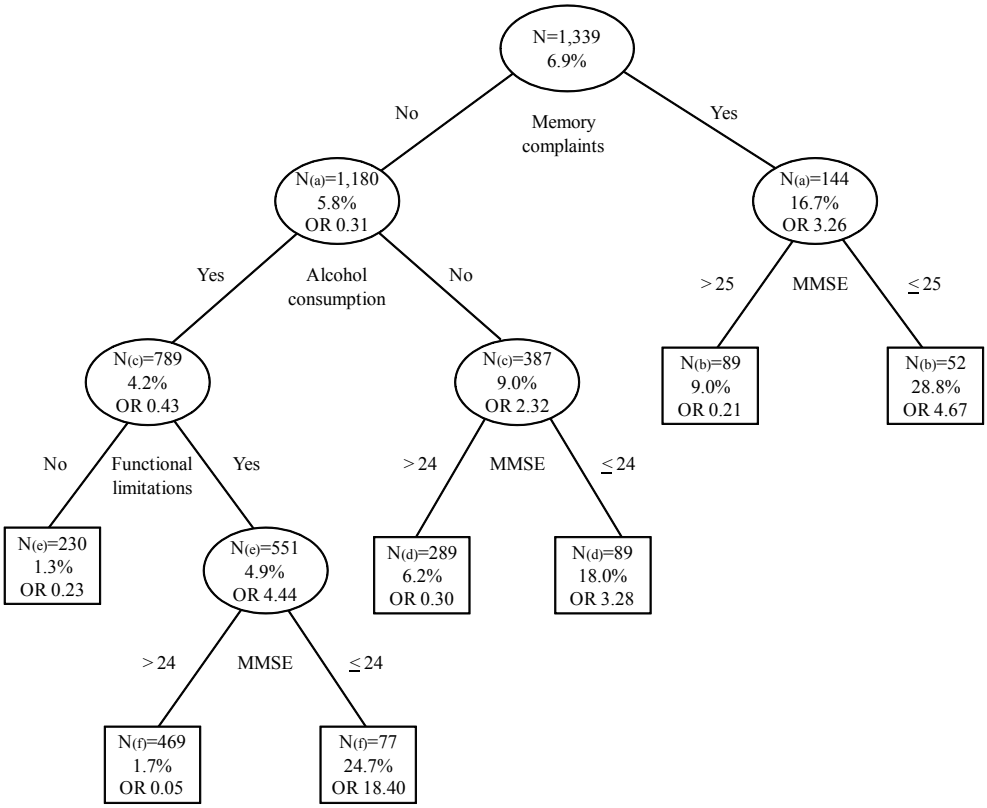

Figure 2 Basic classification model using the basic set of predictors one wave prior to diagnosis for the ascertainment of the risk of developing dementia using generalized estimating equations (GEE)

[a] Missing data on memory complaints, GEE was based on N = 1,324; [b] Missing data on the MMSE score, GEE was based on N = 141; [c] Missing data on alcohol consumption, GEE was based on N = 1,176; [d] Missing data on the MMSE score, GEE was based on N = 378; [e] Missing data on functional limitations, GEE was based on N = 781; [f] Missing data on the MMSE score, GEE was based on N = 546. *N* the number of persons who satisfied the set criterion; *%* the percentage of subjects who were diagnosed with dementia during the study; *OR* Odds Ratio; *MMSE* Mini-Mental State Examination.

Table 2 Characteristics of all predictors at the time of blood sampling measured in the non-demented study sample for persons who developed dementia during the study and persons who did not

	Incident dementia (N=58)	No dementia (N=329)	RR	95% CI
Age, mean (SD), years	84.79 (3.14)	84.52 (3.02)	1.07	0.98 – 1.16
Female, % (N)	56.9 (33)	65.7 (216)	0.61	0.36 – 1.03
≤ elementary school, % (N)	79.3 (46)	68.0 (223)	1.66	0.88 – 3.13
Memory complaints, % (N)	12.1 (7)	6.8 (22)	1.87	0.85 – 4.12
Depressive symptoms, % (N)	7.5 (4)	10.7 (33)	0.71	0.26 – 1.97
Diabetes and/or CVD, % (N)	66.7 (38)	72.2 (236)	0.86	0.50 – 1.49
≥ 1 functional limitations, % (N)	76.4 (42)	68.6 (223)	1.61	0.87 – 3.01
Smoking, % (N)	6.9 (4)	5.8 (19)	1.28	0.46 – 3.52
No alcohol use, % (N)	43.1 (25)	24.5 (80)	2.06	1.23 – 3.47
Vitamin B_{12}, low, % (N)	33.3 (18)	23.7 (75)	1.52	0.86 – 2.68
Homocysteine, high, % (N)	33.9 (19)	23.3 (73)	1.75	1.01 – 3.05
Total cholesterol, low, % (N)	46.3 (25)	24.0 (76)	2.79	1.63 – 4.78
Total cholesterol, high, % (N)	13.0 (7)	28.1 (89)	0.41	0.19 – 0.91
HDL cholesterol, low, % (N)	37.0 (20)	26.2 (83)	1.68	0.97 – 2.93
BMI, low, % (N)	15.4 (8)	17.9 (55)	0.80	0.38 – 1.70
BMI, high, % (N)	44.2 (23)	37.5 (115)	1.12	0.65 – 1.94
Hypertension, % (N)	60.0 (33)	63.8 (203)	0.81	0.47 – 1.40
APOE ε4 carriers, % (N)	43.6 (24)	22.9 (72)	2.43	1.43 – 4.15
MMSE ≤ 24, % (N)	43.9 (25)	14.0 (45)	5.13	3.02 – 8.71
MMSE ≤ 25, % (N)	49.1 (28)	19.9 (64)	4.40	2.61 – 7.42
MMSE ≤ 26, % (N)	57.9 (33)	26.8 (86)	4.02	2.37 – 6.82

RRs and CIs are based on univariate Cox survival analysis. *RR* Relative Risk; *CI* confidence interval; *SD* standard deviation; *CVD* cardiovascular disease; *HDL* high-density lipoprotein; *BMI* body mass index; *APOE* Apolipoprotein E; *MMSE* Mini-Mental State Examination.

Extended classification model

During the course of the study, 58 (of 387 in the total study sample) were diagnosed with dementia resulting in an initial percentage of 15.0% newly identified dementia cases. This rate provides the reference against which the computed positive predictive values for dementia were evaluated.

Table 2 shows the characteristics of both sets of predictors measured in non-demented respondents, separately for persons who developed dementia during the study and those who did not, as well as the RR of each predictor of dementia. The results show that low cholesterol, APOE ε4 and high homocysteine were significant predictors of dementia, while high cholesterol reduced the risk of becoming demented during the study. In addition, drinking no alcohol

and lower MMSE score were significant predictors of dementia. With respect to the different cutoffs used for dichotomization of the MMSE, again the highest RR was found for the cutoff score ≤ 24 in the total non-demented study sample. Persons who were diagnosed with dementia during the study had a mean MMSE of 24.93 (SD = 3.77). The mean MMSE of persons who did not develop dementia during the study was 27.42 (SD = 2.87).

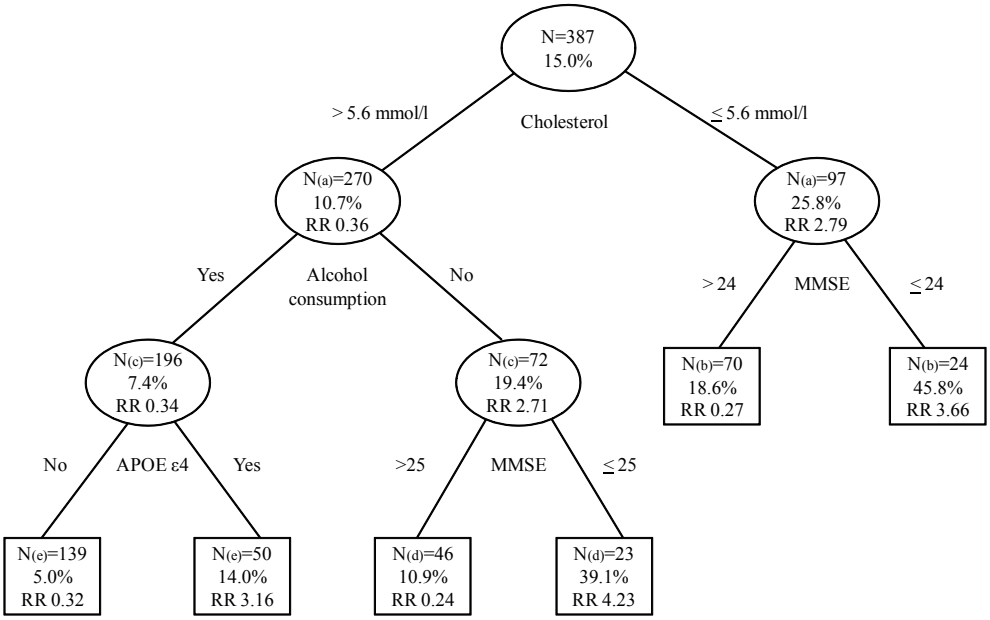

Figure 3 Extended classification model using all predictors for the ascertainment of the risk of developing dementia during the duration of the study using Cox survival analyses

[a] Missing data on cholesterol, Cox survival analysis was based on N = 367; [b] Missing data on the MMSE score, Cox survival analysis was based on N = 94; [c] Missing data on alcohol consumption, Cox survival analysis was based on N = 268; [d] Missing data on the MMSE score, Cox survival analysis was based on N = 69; [e] Missing data on APOE ε4, Cox survival analysis was based on N = 189; *N* number of persons who satisfied the set criterion; *%* the percentage of subjects who were diagnosed with dementia during the study; *RR* Relative Risk; *MMSE* Mini-Mental State Examination; *APOE* Apolipoprotein E.

Figure 3 shows the extended classification tree using all predictors. Low cholesterol (≤ 5.6 mmol/L) was the strongest predictor of dementia. In persons with low cholesterol (RR 2.79; 95% CI: 1.63 to 4.78), an MMSE score ≤ 24 (RR 3.66; 95% CI: 1.60 to 8.34) resulted in a total predictive value of 45.8%. In persons with a cholesterol level > 5.6 mmol/L, drinking no alcohol (RR 2.71; 95% CI: 1.31 to 5.63) and an MMSE score ≤ 25 (RR 4.23; 95% CI: 1.42 to 12.66) resulted in 39.1% diagnosed with dementia during the study. In the subsample of persons with cholesterol > 5.6 mmol/L who consumed alcohol, APOE ε4 (RR 3.16; 95% CI: 1.11 to 9.03) was a significant predictor of dementia. However, the final predictive value of 14.0% did not exceed the initial percentage of new dementia cases (15.0%). In this subsample the number

of dementia cases (N = 7) was insufficient for further analysis. In the subsample of persons with cholesterol > 5.6 mmol/L, drinking alcohol, not carrying the APOE ε4 allele, the positive predictive value for dementia was 5.0% (7 developed dementia during the study).

A comparison between persons at the highest risk for dementia identified with the basic classification model based on GEE (subsample with memory complaints and MMSE score ≤ 25) and the extended model based on Cox survival analyses (subsample with low cholesterol and MMSE ≤ 24) showed an overlap of 8.3% (N = 2/24). A comparison within the group of persons for whom a cholesterol level was defined, showed an overlap of 12.5% (N = 2/16).

Discussion

The aim of the present study was to evaluate previously proposed classification models for early identification of persons at risk for dementia by constructing these models in a population-based longitudinal sample in which a formal dementia diagnosis was present to test whether congruent models would develop. The underlying objective was to provide cost-effective guidance for early detection of persons at risk for subsequent dementia in primary care.

It was shown that the basic classification model produced an overall two-year positive predictive value of 28.8%, to be compared with the corresponding two-year initial rate of 6.9% new dementia cases. The eight-year cumulative predictive value for dementia over the course of the study of the basic model increased from 17.9% to 52.6%. The extended classification model produced an increase in the cumulative predictive value for dementia over the course of the study from 15.0% to 45.8%. In addition, it was found that the classification models identified mostly different persons, i.e. a low overlap. The univariate analyses showed that memory complaints were not a significant predictor in the sample used for the extended classification model. However, persons with low cholesterol who became demented were not complaining about memory problems some years before diagnosis. Therefore, the two sets of markers with the highest predictive value (memory complaints and MMSE ≤ 25; low cholesterol and MMSE ≤ 24) could be used complementary to each other during case-finding of persons at risk for dementia. At the same time, research efforts should focus on understanding why these models identify different persons to be at risk.

A comparison of models of persistent cognitive decline previously developed in the Longitudinal Aging Study Amsterdam (LASA) with the current models of dementia incidence indicates a fairly similar combination of predictors. Similar to findings in the LASA, memory complaints, drinking no alcohol, functional limitations and lower MMSE score were also significant predictors of dementia in the basic classification model developed in the present study. With respect to the extended model, consistent with the model developed in the LASA, low cholesterol, APOE ε4 and lower MMSE score were also significant predictors of dementia.

Some differences from prior findings need to be noted. In the current study, neither age nor education were significant predictors in the basic classification model. Also, the predictive utility of functional limitations in the model was different. In the extended model, again age was

not a significant predictor. Furthermore, alcohol abstinence was a stronger predictor of dementia than APOE ε4. Finally, in some instances adding the dichotomized MMSE to the models suggested different optimal cutoffs for the best prediction of being at risk for dementia. These differences are likely due to differences in characteristics between the two samples. The baseline age range in the current study was 79 to 97 (mean = 83.3, SD = 3.0), while the baseline age range in the LASA sample was 57 to 88 (mean = 71.6, SD = 8.3). Age dichotomized at 75 years was most predictive of persistent cognitive decline in the LASA. The relatively high mean age and small variance in the current sample is likely to account for the fact that age, as might be expected, was not a significant predictor of dementia in this cohort. Previous research has shown that prevalence and incidence of dementia increases with age (Fratiglioni et al., 2000). This is in contrast with our finding that the percentage of newly identified dementia cases initially increased from 7.3% (wave 1 to 2) to 8.7% (wave 2 to 3) but started decreasing after wave 3 to 5.8% (wave 3 to 4) and 4.2% (wave 4 to 5). Possibly, the longer a person survived and remained healthy enough to continue in the study, the more the risk of becoming demented decreased, and the likelihood of a hardy phenotype increased. However, the longitudinal regression analysis did not show a protective effect of the variable time in study. Nonetheless, it may be hypothesized that the oldest-old (85+) included in the current study were especially hardy, since both twins had to be alive and able to participate in order to be included in the OCTO-Twin Study at baseline. Therefore, a genetic protective effect may still be plausible.

In addition, of the relatively older participants in the present study sample 71.2% had an education level less than or equal to elementary school compared to 39.8% in the younger study sample derived from the LASA. Failure to replicate low education as a significant risk factor is likely due to the restricted range of education in current Swedish older cohorts, and especially in those older than 80 (Johansson and Zarit, 1995). In the early 20th century, only six years of education was mandatory in Sweden and the vast majority of the population stopped school thereafter (Gatz et al., 2001).

In the present study, having functional limitations was a significant risk factor of dementia in alcohol-consuming persons without memory complaints, while in the model developed in the LASA it was a significant predictor only for persons 75 years and younger. The fact that functional limitations were not a significant risk factor in alcohol-consuming persons over 75 without memory complaints is likely due to power, only 13 persons developed persistent cognitive decline in that subsample.

In the extended model, no alcohol consumption was a stronger predictor of dementia than APOE ε4. The results from a study by Sando et al. (2008) show that the risk of APOE ε4 is weaker with increasing age. They showed that the frequency of the APOE ε4 allele decreased in patients with Alzheimer's disease onset after the age of 80 (Sando et al., 2008). In addition, alcohol abstinence may be a strong marker for frailty in this older sample (Woo et al., 2005). A study by Hajat et al. (2004) showed that non-drinkers were less likely to have a sociable lifestyle and more likely to have a poor general health perception, difficulty with everyday activities and

suffer from cognitive impairment compared to drinkers. Further research into potential benefits of light alcohol consumption is needed.

Some limitations of the present study need to be addressed. As expected, mortality rate in this old cohort of persons 80 years and older was relatively high compared to younger cohorts. For comparison, mortality rate in subjects 80 years and older participating in the LASA was around 30%, therefore similar to the OCTO-Twin Study. Mortality may have led to an underestimation of the strength of memory complaints, functional limitations and the MMSE score as significant predictors of future dementia, since these predictors were associated with loss to follow up. Furthermore, for the purpose of the present study, we have combined diabetes and CVD into one dichotomous variable. However, some components of this cardiovascular risk factor such as circulation disturbances may be less predictive of dementia risk compared to other components such as stroke. This may have diluted the impact of this predictor for subsequent dementia. A limitation with respect to the evaluation of the extended classification model was that blood was drawn on only one occasion. Therefore, in contrast with the basic model, we were only able to use predictors measured in the non-demented study sample during the wave of (or closest to) blood collection to predict incident dementia during the study. This resulted in a lower power to detect significant predictors. However, the sensitivity analyses of the basic model revealed similar results, which makes it less likely that we have missed predictors using Cox regression instead of GEE. Also, low-density lipoprotein cholesterol and C-reactive protein were not available within the OCTO-Twin data set. Furthermore, although we have based our selection of the basic and extended sets of predictors of dementia on recent reviews and research and feasibility in primary care, we may have missed potential predictors of dementia risk during the initial selection process for our previous study. One potential predictor we had not included in our previous study is hypotension (Moretti et al., 2008; Yap et al., 2008). Post hoc analyses showed that hypotension, defined as systolic blood pressure below 120 mmHg or diastolic blood pressure below 70 mmHg, was not a significant predictor of subsequent dementia risk in the current study. Finally, a potential limitation of the current study is that generalizability of the results to a group of non-Caucasian elderly is not known due to the highly homogeneous ethnic and cultural background of the participants in the OCTO-Twin Study.

Strengths of the present study are the presence of a formal dementia diagnosis based on DSM-III-R criteria and the fact that we could increase power by focusing on predicting dementia incidence during the total study period. Furthermore, two methods of analyses were used for the development of the basic classification tree. Both methods revealed the same set of variables predictive of a higher risk of developing dementia over the course of the study. Finally, given our previous finding that age (> 75 years) was by far the strongest predictor of future persistent cognitive decline, a strength of the current study is that we evaluated both models in a sample already at a higher risk for dementia, i.e. in participants 80 years and older.

In conclusion, both classification models developed in the present study in which a formal dementia diagnosis was available, led to a substantial increase of the predictive value for

dementia. In the basic model using predictors easily enquired by the general practitioner, the initial two-year percentage of new dementia cases increased from 6.9 to 28.8% while the eight-year cumulative predictive value increased from 17.9 to 52.6%. In the extended classification model including markers determined in blood, the predictive value increased from 15.0 to 45.8%. Finally, the sets of markers with the highest predictive value in each model largely identified different persons and thus may be used complementary in primary care to further maximize early detection of persons at risk for dementia in a feasible and cost-effective way. Practical use of the models will be investigated in primary practice by implementation of a short and simple questionnaire (decision tree) for identification of persons at high risk for future dementia, based on findings of the present study as well as the classification models developed in the LASA (Van den Kommer et al., 2008).

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