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ORIGINAL PAPER

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Risk factors and early signs of Alzheimer's disease in a family study sample

Risk of AD

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Abstract *Objective* Several predictors of Alzheimer's disease (AD) have been identified. However, the relevance and independent contribution of risk factors and of possible early signs such as mild cognitive impairment and subjective memory impairment on the development of AD has not been investigated prospectively in a cohort of non-demented elderly including first-degree relatives of AD subjects. *Method* The development of AD was investigated in 757 non-demented elderly. Initial diagnoses were made from personal interviews. Information on 633 subjects after 4.7 ± 1.2 years (mean ± SD) was obtained either from personal or family history interviews. Using forward logistic regression analysis, predictors were identified by comparing their presence in 38 subjects who developed AD and 577 subjects who remained non-demented. *Results* The most important predictors of later Alzheimer's disease were increased age (Odds ratio OR = 1.086/additional year, $p < 0.001$), initial subjective memory complaints (OR = 2.68, $p = 0.019$), initial mild cognitive impairment (OR = 2.51, $p = 0.032$) and female gender (OR = 2.84, $p = 0.069$). Exploratory analysis revealed that previous depression after the age of 60 years (OR = 2.37, $p = 0.033$) and the presence of the apolipoprotein E4 allele (OR = 2.49, $p = 0.043$) individually predicted new AD during follow-up. A positive family history of AD (i. e. being a first degree relative of a subject suffering from AD) did not significantly influence the development of AD ($p > 0.2$). *Conclusions* Increased age, the presence of mild cognitive impairment, subjective memory impairment and gender are the most relevant independent predictors of later Alzheimer's disease that may be used in combination for clinical prediction of AD.

Key words Alzheimer's disease · risk factors · mild cognitive impairment · subjective memory impairment · depression

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Even though several treatment options are available, treatment is most often started too late, i. e. when considerable neuropathological changes have already occurred (Hulette et al. 1998). However, a prerequisite for early intervention is to discriminate subjects who will later develop AD and those who will not (Soininen et al. 1998). This discrimination might be improved by a better knowledge of the relevance of putative risk factors and early signs of AD.

Several risk factors for AD have been observed, the most relevant being increased age (Andersen et al. 1999a, 1999b; Gao et al. 1998; Kawas et al. 2000) and female gender (Fratiglioni et al. 1997; Geerlings et al. 1999; Letenneur et al. 1999; Small 1995). A gender effect, however, has not been found by all authors (Andersen et al. 1999b; Rocca et al. 1998), or was only present in specific age groups (Ruitenberg et al. 2001). Genetic risk factors, such as the apolipoprotein E 4 genotype, are also known to increase the risk of AD (Albert et al. 1996; Gomez-Isla et al. 1996; Petersen et al. 1997; Roses 1998; Slooter et al. 1998; Steffens et al. 1997; Weiner et al. 1999), but their contribution in high-risk samples is less clear. A positive family history of AD might indicate the relevance of genetic risk factors, even if these are not yet identified (Breitner and Folstein 1984; Heun et al. 2001; Mohs et al. 1987; Payami et al. 1997; Silverman et al. 1994). Other authors, however, did not find a positive family history of AD to be a sufficient predictor of the development of AD (Launer et al. 1999; Small et al. 1995). These differences might be partially explained by the variance in the defi-

nitions of a positive family history of AD, i. e. such as having one relative with AD in variable numbers of relatives of different age.

Early signs of AD might be the presence of mild cognitive impairment (Almkvist et al. 1998; Bozoki et al. 2001; Daly et al. 2000; Devanand et al. 1997; Doody et al. 2001; Flicker et al. 1991; Geerlings et al. 1999; Morris et al. 2001; Petersen et al. 1999; Petersen et al. 2001; Sramek et al. 2001), or of subjective memory impairment (Geerlings et al. 1999). Most of these studies examined a limited set of risk factors and did not look at possible interactions. Consequently, it is not clear whether subjective memory impairment is relevant for the prediction of AD in addition to the effect of mild cognitive impairment on the risk. Subjective memory impairment has been assumed to be more characteristic of depression and pseudodementia than of dementia; the major clinical impact of depressive episodes on later development of AD has only rarely been examined (Steffens et al. 1997; Geerlings et al. 2000). Consequently, it is of major interest whether mild cognitive impairment, subjective memory impairment as well as a history of previous depression independently predict the development of AD.

The relevance of these risk factors or early signs might be different for clinical and population samples (Jorm et al. 1997; Ritchie et al. 2001). However, the relevance of different risk factors has not yet been confirmed in an elderly cohort that included first-degree relatives of carefully examined AD subjects. Consequently, we examined the relevance of risk factors and early signs in a prospective cohort of non-demented elderly including first-degree relatives of AD subjects. Being identified as a first-degree relative of an examined AD patient is a more precise and less questionable indicator of a positive family history of AD than the history of dementia in family member.

Risk factors and initial signs of AD selected for the present study were age, female gender, a positive family history for AD (i. e. the subject being a first-degree relative of a subject suffering from AD), the presence of an apolipoprotein E4 allele, the presence of mild cognitive impairment, of subjective memory complaints and a history of geriatric depression (age at onset > 60 years). The comparison of the initial characteristics of subjects with new AD at follow-up with subjects who had remained non-demented allowed the evaluation of the predictive validity of initially assessed risk factors and early signs of AD.

Subjects and methods

Subject recruitment

All non-demented subjects (defined by the absence of dementia according to DSM-III-R criteria (American Psychiatric Association 1987) above the age of 55 years, who had been carefully examined for possible initial signs of dementia and for the presence of possible risk factors during a previous comprehensive family study, were selected for the present prospective cohort study. The study has been performed in agreement with the declaration of Helsinki, the design was approved by the ethics committees of the Universities of Mainz and Bonn, all patients and relatives gave full written consent for participation after having been completely informed on the study procedures.

Recruitment strategies and results of the initial family study sample including possible selection bias have already been published (Heun et al. 1995, 2001). Briefly, patients with Alzheimer's disease (AD) and/or major depression (according to DSM-III-R criteria, APA 1987 39) over 60 years had been consecutively recruited from the Inpatient Departments of Psychiatry of the University of Mainz (recruitment from 1992 to 1995) and of the University of Bonn (recruitment from 1996 to 1998). Control subjects who were group-matched to the patient sample for age, gender, and educational background had been recruited with the support of the cities' census agencies. The patients and controls had been asked to provide names and addresses of all first-degree relatives. For the purpose of the family study, patients and controls had to have at least one first-degree relative aged 55 or older who was available for an interview. The initial family study sample included 78 subjects with AD, 78 with early-onset depression, 74 with late-onset depression (onset age > 60 years), 53 with histories of both AD and depression (co-morbid patients) and 162 control subjects from the general population (including 22 subjects with AD and 17 subjects with a lifetime diagnosis of major depression). The 445 personally interviewed study subjects had had 3002 first-degree relatives. Information on 210 (7 %) of these relatives was unavailable. Of the remaining 2792 relatives, 1236 (44.3 %) were deceased (Table 1); 775 (49.8 %) of the remaining relatives could be interviewed.

To assess the relevance of possible predictors of AD for the present study, all 757 initially non-demented and personally interviewed subjects of the family study sample aged above 55 years (out of 775 interviewed family members and 162 interviewed subjects from the general population) were selected for the present prospective cohort study. Subjects either with a MMSE score below 24, a Hachinski Ischemic score above 2, a history of dementia or other major medical disorder possible to cause depression or depression were excluded from this follow-up study. The follow-up study was performed between 1999 and 2001 in Bonn and Mainz. To cover a large time span for survival analyses, those examined last during the initial family study were examined first during follow-up, and vice versa. Thus, the time span between both examinations ranged from 2 up to 10 years, the mean follow-up period was 4.7 ± 1.2 years.

Diagnostic assessment during the initial assessment

All first-degree relatives and control subjects were assessed using the Composite International Diagnostic Interview (CIDI, World Health Organization 1990) to assign lifetime DSM-III-R diagnoses for major psychiatric disorders (American Psychiatric Association 1987). To detect and diagnose dementia, patients, controls and their relatives were interviewed using the Structured Interview for Diagnosis of Dementia of the Alzheimer Type, Multi-infarct Dementia, and Dementia of other Aetiology (SIDAM, Zaudig et al. 1991), which includes the Mini Mental State Examination (MMSE, Folstein et al. 1975) and the Hachinski Ischemia Scale (Hachinski et al. 1975).

To detect depression and dementia in relatives, we additionally used the Family History Questionnaire (Andreasen et al. 1977) and the Family Dementia Risk Questionnaire (Breitner and Folstein 1984; Silverman et al. 1986). Family history information from spouses as well as from all interviewed relatives was obtained, if possible. The interviewers were carefully trained medical students in their final year of training or junior physicians.

After reviewing all available information, final diagnoses and age-at-onset for the initial family study and again, independently, for the follow-up study were assigned according to the consensus judgement of two experienced psychiatrists who remained blind to the identity of all probands and relatives using the best-estimate procedure (Leckman et al. 1982).

Interrater reliability of the direct interview data and of family history information were good for AD (Cohen's $\kappa = 1.0$, CI 0.78–1.0 and $\kappa = 0.82$, CI 0.61–1.0, respectively, independent interviews in both cases; Heun et al. 1998, Ptok et al. 2001).

Table 1 Description of the initial family study sample of 757 initially non-demented personally interviewed subjects by recruitment and interview results during follow-up

	Status at initial examination	Status at follow-up examination			
	All non-demented subjects at first assessment	Living subjects	Deceased subjects	Unavailable subjects	Unadjusted comparison of living, deceased and unavailable subjects
Number of subjects	757 (100%)	550 (100%)	83 (100%)	124 (100%)	
Female subjects [n (% of all)]	456 (60.2%)	337 (61.3%)	42 (50.6%)	77 (62.1%)	$Chi^2 = 3.64$, df = 2, p = 0.162
Age at first assessment [years, mean ± SD (range)]	68.19 ± 8.45 (56–97)	67.23 ± 7.87 (56–97)	74.70 ± 9.04 (57–94)	68.09 ± 8.66 (56–96)	F = 30.36, df = 2, p < 0.001
Age at second assessment or death [years, mean ± SD (range)]	73.03 ± 8.84 (57–97)	72.32 ± 8.10 (57–97)	78.49 ± 8.65 (61–96)	Not applicable	F = 41.15, df = 1, p < 0.001
Information obtained at follow-up					$Chi^2 = 1006.1$, df = 6, p < 0.001
Personal interview	306 (40.4%)	306 (55.6%)	0	0	
Telephone interview	128 (16.9%)	128 (23.3%)	0	0	
Family history	199 (26.3%)	116 (21.1%)	83 (100%)	0	
No information	124 (16.4%)	0	0	124 (100%)	

Specific definitions of independent variables

Mild cognitive impairment (MCI) was assessed according to the criteria outlined by Petersen et al. (1999). Most MCI subjects scored between 24 and 28 points in the MMSE. A score of 23 and below is often used as the conventional threshold for dementia (Anthony et al. 1982; Blessed et al. 1991; Clarke et al. 1991; Grut et al. 1993). Healthy subjects usually score 28 or above in the MMSE (Heun et al. 1998). All subjects with a MMSE score below 24 and or a history of dementia were excluded from the follow-up.

Subjective memory complaints were not used in these criteria to allow an independent evaluation of the predictive validity of these symptoms. The presence of subjective memory complaints was assumed (Hulette et al. 1998) when the subjects spontaneously reported memory problems after being asked for their general problems at the beginning of the semi-structured SIDAM interview, or (Kawas et al. 2000) when the SIDAM question "Do you have trouble remembering things?" was positively answered.

A positive family history was defined as being a first-degree relative of an AD patient or AD subject from the general population.

DNA-analysis

Leukocyte DNA was isolated with the Qiagen® blood isolation kit according to the instructions of the manufacturer (Qiagen, Hilden, Germany). The apolipoprotein E genotype was studied as described before (Hixson and Vernier 1990).

Diagnostic assessment during follow-up

The interviews and diagnostic procedures including the CIDI, the SIDAM and the structure investigation of family history information were independently repeated during follow-up. The available information on the 757 eligible initially non-demented subjects was limited at follow-up as given in Table 1. However, unavailable subjects were comparable according to age and gender to the rest of the sample ($p > 0.2$).

Final diagnoses for the follow-up study were assigned according to the consensus judgement of two experienced psychiatrists using the best-estimate procedure (Leckman et al. 1982). At this stage, they were blind to the diagnoses of the initial assessments.

Inter-informant reliability of family history-based diagnoses of AD was good to moderate ($\kappa = 0.58$, CI 0.48–0.68; Heun et al. 1998). Compared with direct interview results, family history data showed limited sensitivity, but good specificity for AD, i. e. 20.8% and 98.4%, respectively. The sensitivity of family history interviews was quite low in subjects with early dementia diagnosed using psychometric assessments including the MMSE; however, sensitivity increased substantially with severity and duration of illness, e. g. it reached nearly 70% for subjects with a MMSE score below 19 points and is well above 90% in subjects with moderate AD (e. g. with a MMSE score below 15 and five or more years of dementia Heun et al. 1997, 2001). According to our studies, a subject with severe AD, who suffered from AD between 7 to 10 years before he died and declined by an average MMSE score of 3–4 points/year is very unlikely to have its dementia undetected by family history information. Consequently, the sensitivity on study results should be acceptable in subjects who suffered for several years or even died from AD. However, to control for a reduced sensitivity of family history information, we included the source of information (direct assessment with or without family history versus family history data only during follow-up) as a covariate in-group comparison.

Statistical analysis

Since we were interested in prediction of AD, 18 subjects who developed other dementing disorders according to personal or family history information (predominantly vascular dementia, n = 9) were excluded from analysis. Group comparisons used the chi-square statistic, t-tests and ANOVA. Forward logistic regression analysis was used to identify significant predictors (see Table 2) of the outcome, i. e. the presence of AD at follow-up in initially non-demented subjects. To account for possible confounding the duration of individual follow-up and the source of information during the follow-up investigation (i. e. personal interview versus family history information only) were included in the model as covariates in addition to the possible predictors, i. e. age, gender, the presence of mild cognitive impairment, the presence of subjective memory impairment, a previous geriatric depression (age at onset above 60 years), a positive family history for AD, and the presence of an apolipoprotein E4 allele. Survival analysis using the Cox proportional hazard model also allows for several variables to be included in the model but was not used for data presentation since the proportionality of effects assumed in the model was not very likely. However, both methods led to identical results. The conventional threshold for statistical significance (α) $p < 0.05$ was used.

To allow comparison with other publications, exploratory analyses investigated the effects of individual risk factors on the outcome, i. e. the development of new AD. In these exploratory logistic regression analyses, only the individual factors and age (i. e. the most significant covariate) were included.

Table 2 Comparison of demographic information and possible predictors of AD in subjects who developed new AD and those who remained non-demented during follow-up. 18 subjects who developed other dementing disorders, i. e. vascular dementia (n = 9) or severe cognitive disorders (n = 9) were excluded from the comparisons

	Subjects who remained non-demented at follow up	Subjects who developed AD	Unadjusted group comparisons[a]
Number of subjects	577 (100%)	38 (100%)	
Gender of subjects [% female][b]	337 (58.4%)	31 (81.6%)	$Chi^2 = 7.97$, df = 1, $p < 0.01$
Age at first assessment[b] [years, mean ± SD (range)]	67.70±8.16 (56–96)	74.39±9.00 (58–90)	T = 4.98, df = 613, $p < 0.001$
Age at second assessment or death [years, mean ± SD (range)]	72.44±8.58 (58–97)	79.82±8.82 (62–95)	T = 5.32 df = 613, $p < 0.001$
Mild cognitive impairment at initial assessment (MMS = 24–27) [n (%)][b]	192 (33.3%)	25 (65.8%)	$chi^2 = 19.38$, df = 1, $p < 0.001$
Subjective memory complaints at initial assessment [n (%)][b]	286 (49.6%)	24 (66.7%)	$chi^2 = 3.96$, df = 1, $p < 0.05$
Previous history of geriatric depression at initial assessment (onset ≥ 60) [n (%)][b]	60 (10.4%)	10 (26.3%)	$chi^2 = 8.96$, df = 1, $p < 0.01$
Positive family history of AD [n (%)][b]	153 (26.5%)	10 (26.3%)	$chi^2 = 0.001$, df = 1, $p = 0.98$
Presence of an apolipoprotein E4 allele [n (%)][b]	152 (26.3%)	16 (42.1%)	$chi^2 = 4.46$, df = 1, $p < 0.05$
Source of information available at follow-up assessment [n (%)][b]			$Chi^2 = 14.6$, df = 2, $p < 0.001$
Personal interview	279 (48.4%)	18 (47.4%)	
Telephone interview	128 (22.2%)	–	
Family history information	170 (29.5%)	20 (52.6%)	
Numbers of subjects deceased during follow-up [n (%)]	71 (12.3%)	9 (23.7%)	$Chi^2 = 4.08$, df = 1, $p < 0.05$
Causes of death during follow-up as reported by relatives [n (%)]			$Chi^2 = 20.4$, df = 9, $p = 0.016$
Cardiovascular	12 (16.9%)	1 (11.1%)	
Stroke	5 (7%)	1 (11.1%)	
Cancer	17 (23.9%)	1 (11.1%)	
Lung disease	4 (5.6%)	–	
Gastrointestinal disease	1 (1.4%)	–	
Renal disease	2 (2.8%)	–	
Suicide	4 (5.6%)	–	
Old age and infirmity	10 (14.1%)	3 (33.3%)	
Dementia	–	2 (22.2%)	
Others	16 (22.5%)	1 (11.1%)	

[a] Group comparisons were based on the data of the present table; consequently, we did not adjust for age, gender, or source of information here. This was done in the forward logistic regression analysis used for evaluation of the combined effects of risk factors, early signs and possible confounding variables, see Methods and Results
[b] Possible predictors and covariates used in forward logistic regression analysis

Results

Subject recruitment during follow-up

Sufficient follow-up information was available on 633 of 757 initially non-demented subjects (83.6%), see Table 1. A total of 550 subjects (72.7%) were still living at the time of the follow-up investigation; 83 subjects (11%) had died between the initial and the follow-up investigation. Relevant information on their medical and psychiatric history was obtained from at least one informant. Causes of death included cardiovascular disease, stroke, cancer, lung disease, gastrointestinal disease, renal failure, suicide, old age and infirmity, and severe dementia (see Table 2). 124 subjects (16.4%) could not be contacted for follow-up; we were unable to obtain sufficient personal information on these subjects to allow any valid decision on the development of medical or psychiatric disorders or cognitive deficits during follow-up. Since these subjects were comparable according to age and gender to the living subjects, but less so to the deceased subjects, it is likely that most of these subjects had moved without leaving their addresses, and that only some of them had deceased. Consequently, a reduction of statistical power, but no significant attrition bias may be expected. For a detailed description of the study sample and recruitment success, see Table 1.

Of 550 living subjects, 306 (55.6%) could be personally interviewed, 128 other subjects (23.3%) provided detailed personal information over the telephone to an experienced psychiatrist, but did not allow a face-to-face re-interview, while 116 subjects (21.1%) allowed other relatives to provide detailed medical and psychiatric information, but were not willing or unable to be personally interviewed. The reasons for not allowing personal interviews in the latter two samples were poor medical condition, acute depression, dementia, feeling uncomfortable at the first interview, not understanding the reason for the second interview, not wanting to be reminded of previous psychiatric disorders, lack of time, not remembering the first interview, and no interest. A minority did not give any reason for refusal.

Risk factors and initial signs of AD

During the follow-up period, 38 of 633 initially non-demented subjects developed new AD, and 18 subjects developed other types of dementia. Since the aim of the study was to identify risk factors of AD, the latter subjects were excluded from further analysis. The comparison of the initial characteristics of the newly diseased AD subjects with the 577 subjects who had remained non-demented at follow-up allowed the prognostic value of risk factors and initial signs to be evaluated (see Table 2). Using forward logistic regression analyses, we observed that increased age (Odds ratio OR = 1.086/additional years, 95 %-confidence interval (CI) = 1.040–1.135, $p < 0.001$), the presence of subjective memory complaints (OR = 2.68, CI = 1.11–6.46, $p = 0.019$) and of mild cognitive impairment (OR = 2.51. CI = 1.08–5.81, $p = 0.032$) significantly predicted the development of new AD during follow-up. There was a trend towards an increased AD risk for females (OR = 2.84, CI = 0.92–8.76, $p = 0.069$) in this analysis. An additional exploratory analysis accounting for age differences revealed that a previous depression after the age of 60 years (OR = 2.37, CI = 1.072–5.23, $p = 0.033$) and the presence of the apolipoprotein E4 allele (OR = 2.49, CI = 1.020–7.05, $p = 0.043$) individually predicted the development of new AD. A positive family history of AD, the source of information and duration of follow-up interval were no significant predictors of new AD ($p = 0.89$, $p = 0.26$, and $p = 0.53$, respectively).

Discussion

Increased age, the initial presence of subjective memory impairment, of mild cognitive impairment and female gender were the most relevant independent predictors for the development of AD. The history of late-onset depression and the presence of the apolipoprotein E 4 allele were of reduced importance. Both significantly predicted AD independently from all other variables, but did not add to the prediction when the above-mentioned variables were already accounted for. The presence of a positive family history of AD did not significantly predict the development of new AD in this sample, which is most likely due to a lack of statistical power. Our study supports the observation that age is the most relevant risk factor for AD (Andersen et al. 1999a, 1999b; Copeland et al. 1999; Fratiglioni et al. 1997; Gao et al. 1998; Geerlings et al. 1999; Kawas et al. 2000; Letenneur et al. 1999).

In agreement with others (Geerlings et al. 1999; Jorm et al. 2001; Schmand et al. 1997; Schofield et al. 1997), subjective memory complaints were significant predictors of later AD. In contrast, Carr et al. (2000) observed that self-reported memory complaint did not correlate with memory impairment or prognosis. Wang et al. (2000) found that subjective memory impairment was associated with poorer objective memory performance even after controlling for the effect of depression and demographic data, but subjective memory impairment did not predict faster cognitive decline or dementia over 3 years. In a review on subjective memory impairment, Jonker et al. (2000) reported that memory complaints predicted dementia after a follow-up of at least 2 years, in particular in those with mild cognitive impairment, defined as MMSE score above 23. Memory complaints in highly educated elderly subjects may be predictive of dementia even when there is no indication of cognitive impairment on short cognitive screening tests. Schofield et al. (1997) claimed that new memory complaints might suggest the presence of significant impairment of memory or cognition if reported by individuals who were recently non-demented and denied subjective memory impairment.

In agreement with other studies, the presence of mild cognitive impairment (Bozoki et al. 2001; Daly et al. 2000; Devanand et al. 1997; Doody et al. 2001; Flicker et al. 1991; Geerlings et al. 1999; Morris et al. 2001; Petersen et al. 1997, 1999, 2001; Small et al. 1997; Tierney et al. 2000) significantly predicted later AD. In the present study, there was a trend towards females having a greater risk of developing new AD during the follow-up. This equivocal finding reflects the controversy over the relevance of female gender on the incidence of AD. Several authors reported significant gender effects (Andersen et al. 1999a; Copeland et al. 1999; Fratiglioni et al. 1997; Gao et al. 1998; Geerlings et al. 1999; Letenneur et al. 1999; Seshadri et al. 1997; Small et al. 1995), while other in equally large studies could not find significant effects (Andersen et al. 1999b; Hebert et al. 2001; Kawas et al. 2000; Rocca et al. 1998). Some authors suggest that the effect of gender varies by age stratum (Letenneur et al. 1999; Ruitenberg et al. 2001) or by educational level (Letenneur et al. 2000), which may account for the controversial findings. To assess the relevance of the many possible interactions of gender, educational level, age strata and other factors for the risk of AD much larger samples are still needed.

Our observation that late onset depression represents a risk factor for AD has been supported by Berger et al. (1999). However, the temporal relationship between depression and later dementia indicated that depression is often an early symptom rather than a true risk factor (Berger et al. 1999; Steffens et al. 1997; Wetherell et al. 1999).

Our data support the view that apolipoprotein E 4 allele increases the risk of AD (Albert 1996; Gomez-Isla 1996; Murphy et al. 1997; Payami et al. 1997; Petersen et al. 1997; Steffens et al. 1997) even if genetic factors may only explain parts of the risk in the general population (Slooter et al. 1998). Bondi et al. (1999) revealed that apolipoprotein E4 allele status and measures of recall performance were significant and independent predictors of conversion to AD. In contrast, Tierney et al. (1996b) found a predictive validity of the apolipoprotein E4 allele only in combination with the presence of memory impairment.

In agreement with others (Launer et al. 1999; Small et al. 1995), we did not find a family history of AD to be a good predictor of the development of AD. In contrast, Payami et al. (1997) observed that a family history of AD significantly predicted the development of AD in a prospective study. However, the effect of a positive family history might be smaller than previously reported (Silverman et al. 2000). Thus, it might not have been strong enough to be observed in the present prospective study over a limited period less than 5 years.

Conclusion

The lack of significant effects of the latter variables might be explained by limited numbers of new AD subjects, even though study duration, numbers of investigated subjects and effort were considerable.

A possible delay of a few years in detecting AD in some subjects by family history due to its low sensitivity in early stages might have led to a reduction of the number of detected AD subjects and thus to a reduction of statistical power, but this effect should not change our results to a major extent, and most importantly should not lead to false positive associations.

Extensive interactions of different variables might be another reason to explain a lack of significant differences: e. g., the awareness of subjective memory impairment might well be influenced by age, gender, the presence of mild cognitive impairment, and of depression (Jonker et al. 2000; Jorm et al. 2001; Small et al. 1999; Stewart et al. 2001). Stewart et al. (2001) reported that depression, self-reported physical impairment and presence of an apolipoprotein E4 allele were associated with subjective memory impairment. According to Small et al. (1999), subjective memory impairment was associated with an apolipoprotein E4 allele. Bartres-Faz et al. (2001) observed an increased rate of memory impairment and an increased prevalence of apolipoprotein E4 alleles in mild cognitive impairment versus age-associated memory impairment. Jonker et al. (2000) found that high age, female gender and low level of education are generally associated with a high prevalence of memory complaints. In community-based samples of elderly subjects, an association has been found between memory complaints and memory impairment, after adjustment for depressive symptomatology. Using structural equation modelling, Jorm et al. (2001) reported that memory complaints do reflect perceptions of past memory performance and are also an early manifestation of memory impairment; however, current symptoms of depression were also associated with memory complaints. It should be mentioned that both mild cognitive and subjective memory impairment were independent predictors of AD in the present study.

The sample size of the present study does not allow the investigation of further interactions of potential predictors. Consequently, it does not provide a comprehensive understanding of the many possible interactions between age, gender, subjective and objective memory impairment, mild cognitive impairment, depression and genotype. It should also not be forgotten that other genetic or biochemical risk factors might influence the risk of AD (Doran and Larner 2004; Hampel at al. 2004). They might influence and thus weaken the associations between AD and different types of risk factors.

However, the study was designed to identify the most important predictors for the development of new AD and it served this purpose well, even though the type of statistical analysis may be criticised for two reasons: (i) One might argue that logistic regression analysis is less appropriate than survival analysis since the former does not account for the duration of the follow-up period. We preferred logistic regression analysis instead of survival analysis, since logistic regression allows the use of many covariates, but makes fewer assumptions on the model than the Cox proportional hazard analysis. (ii) Since some of the subjects were members of the same family, the assumption of independence of the units of observation does not hold. However, survival analyses as well as analyses using one subject per family led to identical results. Consequently, we applied the more robust logistic regression analysis and included all subjects.

It should be stressed that our study investigated AD as an outcome measure; thus, we can neither confirm nor deny if the identified risk factors are specific to AD, or if they would also apply to other types of dementia as well. An exploratory analysis using dementia in general as an outcome variable (data not given) expectedly revealed identical results, which is the consequence of the high impact of the majority suffering from AD. Another analysis with the small group of subjects with different types of dementias only did not result in any significant predictors. This can be explained (1) by the fact that the power for such an analysis is low and (2) by the fact that at least some different risk factors are likely to be relevant in different dementing disorders. However, the specificity of predictors for different types of dementia is an important issue for future studies.

In summary, the paper confirms previously identified predictors, but adds to the knowledge by using a prospective approach in a high-risk sample finding that age, gender, mild cognitive impairment as well as subjective memory impairment are independent, better predictors of AD than the knowledge of the apolipoprotein E4 genotype or a family history of AD or history of depression. This information might be most useful in the counselling of family members of AD patients.

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