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Prevalence and natural course of aging-associated cognitive decline in a population-based sample of "young-old" subjects

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Article abstract

Objective: The term “mild cognitive impairment” refers to cognitive deficits in the older age which exceed age-related cognitive decline but do not fullfill criteria of dementia. Affected subjects are assumed to be at higher risk for the development of dementia such as Alzheimer’s disease (AD). However, little is known about the group of “young-old” subjects with respect to prevalence and natural course of cognitive decline.

Methods: Within the population-based Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE), neuropsychological functioning was assessed in 500 community-dwelling “young-old” subjects (mean age at baseline: 62.4±2.4 years) of two German urban regions born between 1930 and 1932. Participants were carefully screened for physical and mental health and reexamined four years later. The concept of „aging-associated cognitive decline“ (AACD) was applied.

Results: At baseline, 13.4% of the subjects fulfilled the AACD criteria. Four years later, AACD prevalence rates rose to 24.1%. 52.3% of the subjects initially classified as AACD retained the diagnosis at follow-up. While AACD subjects showed a reduced performance in all neuropsychological domains addressed, a significant ($p<0.05$) decline was confined to delayed verbal memory test performance during the 4-year follow-up period when compared to the controls. AACD did not predict conversion to dementia during the follow-up intervall.

Conclusions: In “young-old” community-dwelling individuals, AACD is a frequent condition with a high temporal stability. During a 4-year follow-up period, AACD subjects deteriorated specifically in measures of episodic memory underscoring the value of the respective deficits in characterizing “mild cognitive impairment”.

Key words: mild cognitive impairment, AACD, AD

Introduction

Mild cognitive impairment refers to cognitive deficits which exceed age-related cognitive decline but do not fullfill criteria of dementia. Clinical and epidemiological evidence indicate that patients with Alzheimer's disease (AD) undergo a longstanding preclinical phase where the cognitive deficits remain subtle over a longstanding phase before the threshold of dementia is reached.[1] Since it has been postulated that elderly subjects with mild cognitive impairment are at increased risk of developing dementia a reliable identification of those preclinical stages is important for successful preventive strategies and early therapeutic interventions.

Recent studies reported age-dependent prevalence rates of mild cognitive impairment in the elderly population.[2,3] Taking into account that older age is the most important risk factor for AD and mild cognitive impairment preceds AD in a considerable proportion of the affected individuals it is conceivable that not only prevalence rates of mild cognitive impairment but also conversion rates to AD differ with respect to selective age ranges within the elderly population (e.g. the "young-old", the "old-old", and the "oldest-old").[4] To date, studies investigating prevalence and course of mild cognitive impairment mainly focused on subjects in their seventies and older.

Furthermore, the majority of studies did not address mild cognitive impairment due to significant somatic comorbidity. This is of particular importance since diabetes mellitus, heart disease, and hypertension were recently found to be more prevalent among subjects with mild cognitive impairment than otherwise healthy participants of a longitudinal study.[5] This effect could clearly be addressed more thoroughly by the prospective investigation of "young-old" subjects in whom these conditions are still less frequent.

To date, various research diagnostic criteria as well as clinical manuals have been proposed in order to further define mild cognitive impairment.[2,6,7] Those include age-associated memory impairment (AAMI)[8] and its modifications age-consistent memory impairment (ACMI)[9] and late-life forgetfulness (LLF)[9], the amnestic variant of mild cognitive impairment introduced by Petersen and colleagues (MCI amnestic)[10] as well as the ICD-

10 criteria of 'mild cognitive disorder'[11]. In order to meet some of the limitations afflicted with earlier attempts to define mild cognitive impairment a working party of the International Psychogeriatric Association (IPA) introduced the concept of 'aging-associated cognitive decline' (AACD)[12]. In contrast to most previous concepts, AACD not only uses age and educational adjusted norms to define a cognitive deficit but also considers decline in a broader potential range of cognitive domains, namely memory and learning, attention and concentration, thinking, language, and visuospatial functioning. This is in accordance with the hypothesis that not only mnestic but also language deficits such as verbal fluency impairment might indicate further cognitive decline.[13]

Use of norm values adjusted for educational levels constitutes another advantage of the AACD concept since higher education might be associated with increased cognitive reserve capacity leading to delayed onset of cognitive decline. Thus, it has been postulated that AACD has an improved potential to identify individuals who experience cognitive decline that falls short of dementia.[12]

Up to now, three longitudinal population-based studies were performed to establish prevalence rates of AACD in the elderly population and to assess its predictive validity.[14,15,16] Notably, all three studies found similar prevalence rates for AACD in the investigated populations (20-27%). Furthermore, AACD proved to be superior to other concepts of mild cognitive impairment with respect to temporal stability and prediction of dementia yielding conversion rates of 28-47% within a 2-3 year period. Although these results indeed support the notion that AACD is of high utility for the identification of preclinical stages of AD they are not necessarily generalizable to the elderly population as a whole. While previous studies mainly focused on the group of the "old-old" little is known about AACD prevalence and conversion rates for individuals in their sixties. However, the latter age-group does not only constitute a major proportion of those individuals asking for advice in outpatient memory clinics but might also represent a promising target population for early preventive interventions. This holds particularly true considering that most of these so-

called "young-old" individuals are still independently living in the community.

Accordingly, the aims of the present study were two-folded: 1. Establishing prevalence rates of mild cognitive impairment according to the AACD criteria within a population-based sample of "young-old" individuals, and 2. investigating the longitudinal course of this condition, particularly with respect to its temporal stability, neuropsychological test performance, and conversion to dementia.

Methods

Subjects and psychometric instruments

Subjects were participants of the Interdisciplinary Longitudinal Study on Adult Development (ILSE) born between 1930 and 1932. ILSE is a prospective study on adult development in Germany, based on two birth cohorts born 1930-32 and 1950-52.[17] Subjects were randomly identified and recruited according to the community registers. These registers are regularly up-dated for changes of address and marietal status. Since it is compulsory for each resident in Germany aged 16 and above to be registered, this recruitment procedure yielded an almost representative sample for the respective communities.

All 500 participants of the elderly birth cohort living in the urban regions of Leipzig (Saxony) and Heidelberg/Mannheim (Palatine) were included in the present study. The study was approved by the ethical committee of the University of Heidelberg, Germany. After complete description of the study to the subjects, written informed consent was obtained.

Participants were carefully screened for physical and mental health by extensive interview, physical examination, and laboratory testing. In addition, potential psychiatric disorders were assessed by using the German version of the Structured Clinical Interview for the DSM-III-R.[18]

Most of the neuropsychological instruments applied for the assessment of cognitive performance were subtests of the 'Nürnberger-Alters-Inventar' (NAI)[19] and the 'Leistungsprüfsystem' (LPS 50+)[20], both of which are well established and commonly used test batteries in Germany. In

particular, the following instruments were used for the investigation of the respective cognitive domains: a) memory and learning: immediate word list recall and delayed word list recognition: (NAI), b) attention and concentration: 'Aufmerksamkeits-Belastungs-Test' (d2-test)[21], c) abstract thinking: subtest 'Gemeinsamkeiten finden' (HAWIE-R)[22], d) Language: subtest verbal fluency (LPS 50+), (e) Visuospatial functioning: subtest visual imagination ('Räumliche Vorstellung' LPS 50+)

Subjective cognitive complaints were assessed by interviewing and applying the appropriate items of the 'Nürnberger Selbsteinschätzungsliste' (NSL)[23]. The NSL is a self-assessment questionaire on general functioning in the elderly and contains four items with a direct relation to cognitive functioning. Subjective complaints were explored on a "yes or no" basis. In addition, the self rating depression scale (SDS) was applied.

To date, the first two waves of ILSE are completed and served as the database for the present study. Examinations took place between December 1993 and January 1995 (t1) and between December 1997 and January 2000 (t2). Mean age was 62.4±2.4 years at baseline (t1) and 66.7±1.1 years at 4-years-follow-up (t2), respectively. The sample had a balanced gender distribution (249 female and 251 male participants).

Definition of diagnostic categories

AACD was diagnosed according to the criteria of the IPA working party.[12] Those include: 1. subjective impairment: a report by the individual (or a reliable informant) that cognitive function has declined, and 2. objective impairment: difficulties in any of the following cognitive domains as indicated by a neuropsychological test performance of at least one standard deviation (SD) below age and education norms: memory and learning, attention and concentration, abstract thinking (problem solving, abstraction), language, and visuospatial functioning. Age-adjusted norm values were available for all psychometric instruments administered but norm values adjusted for educational level were missing for the tests addressing verbal fluency and visuospatial functioning. In these cases, results of the entire age cohort were differentiated according to high (secondary school) and low educational (primary school) levels. In the latter

cases, the test results of the entire age cohort 1930-1932 were differentiated according to high (secondary school) and low (primary school) educational levels and each of the resulting distributions used as a reference. The same differentiation was applied for the remaining tests on basis of the norms reported in the literature. 3. Exclusion criteria: none of the abnormalities listed above is of a sufficient degree for a diagnosis of dementia or can be attributed to a clinically significant psychiatric disorder (in particular depression, substance abuse, psychosis). Furthermore, there should be no objective evidence from physical and neurological examination or laboratory tests and no history of cerebral disease, damage or dysfunction, or of systemic physical disorder known to cause cognitive dysfunction.

As pointed out in the IPA consensus paper[12] the differential diagnosis between AACD, dementia, and ICD-10 'mild cognitive disorder' (MCD) should be considered as the most important. In our investigation, dementia was defined in line with the DSM IV criteria. In short, this includes the development of multiple cognitive deficits, severe enough to cause significant impairment in social or occupational functioning. The diagnosis of MCD was assigned if a mild cognitive deficit according to the 1. and 2. AACD criteria was present, but history and/or objective examination revealed evidence for a cerebral and/or systemic disorder sufficient to cause cerebral dysfunction (AACD exclusion criteria).

Data analysis

Complete data sets were available in 485 out of the 500 investigated subjects. For each time point of the investigation, prevalence rates for AACD, MCD, and dementia were determined according to the criteria described above. Furthermore, conversion rates from one to another diagnostic category were calculated. Repeated measure ANOVA was used to analyze the time course of cognitive deficits across diagnostic groups with respect to different cognitive domains.

Results

At t1, subjective complaints about cognitive decline were found in 226 subjects (46.6%), and 200 subjects (41.2%) scored below one SD of age

and education adjusted norm values in at least one of the cognitive tests applied. Ninety two subjects (19.0%) of the total sample suffered from medical and/or neurological conditions with a potential causative relation to cognitive decline. When diagnostic criteria were applied to these findings, 65 subjects (13.4%) fulfilled the AACD criteria. Additionally, 28 subjects (5.8%) had evidence of subjective and objective cognitive impairment but simultaneously met the exclusion criteria of AACD. Those were classified as suffering from MCD. None of the investigated participants was diagnosed as suffering from dementia according to the DSM IV criteria.

At t2, 449 subjects or 89.8% of the original sample could be reexamined after the follow-up period of 4 years. Twenty subjects had deceased. Other reasons for dropout (n=31) were severe physical handicaps which would make the investigation too troublesome, lost of interest/motivation, move to other places in the country, or no reason was given for refusal. Drop out rates were highest in subjects with AACD, followed by those fulfilling ICD-10 criteria for MCD and controls (15.4%, 14.3%, and 7.6%, respectively), however, these differences did not reach statistical significance (χ^2=3.2 df=2, p=n.sig.). Among the subjects who were reexamined at t2, prevalence rate of AACD increased to 24.1% (n=106). An additional 8.0% of the subjects (n = 35) fulfilled the ICD-10 criteria for MCD. None of the reexamined subjects had developed dementia during the 4-year follow-up.

Out of the subjects diagnosed with AACD at t1, 34 (52.3%) retained the diagnosis at follow-up (Figure 1). Two subjects (3.1%) did not complain any longer about cognitive decline, and in another 3 subjects (4.6%) a severe medical condition sufficient to cause cognitive dysfunction had become apparent during the follow-up period. Both conditions led to an exclusion from the AACD group. In contrast, 15 subjects (23.1%) of the original AACD group performed normal (within 1 SD) on cognitive testing at follow-up, despite persisting complaints about cognitive decline. Another subject classified as AACD at t1 presented without any subjective or objective cognitive deficits (1.5%). 10 subjects (15.4%) initially diagnosed with AACD dropped out and could not be reexamined at t2. Out of the 207

subjects with subjective complaints at baseline 172 reproduced their complaints at follow-up.

While four of the 28 subjects, who initially fulfilled MCD criteria could not be reexamined, 7 of them did no longer demonstrate cognitive impairment at follow up. Among those, 2 subjects did no longer report subjective complaints, while 5 performed normal in all tests applied.

At t2, 72 new cases of AACD were identified (Figure 2). Among those, 17 had been found to be unimpaired on cognitive testing at t1, although 20 of them had already complained about cognitive decline at the time of the first examination. Further 35 incidence cases of AACD had already previously been impaired on cognitive testing, but did not fulfill the subjective criteria at t1.

At t1, the vast majority of AACD subjects demonstrated cognitive deficits in one (58.8%) or two (23.5%) neuropsychological tests, respectively; whereas deficits in three (14.7%) or four (2.9%) domains were less frequent. At t2, the proportion of AACD subjects impaired in one (47.1%) or two (17.7%) tests had declined while more subjects showed deficits in three and more domains (three: 14.7%, four: 11.8%, and five: 8.8%; χ^2=2.7 df=1 p=0.09). In addition, at t2 the vast majority of subjects demonstrated deficits in those domains which were already impaired at t1. The respective figures for the different neuropsychological tests were: memory and learning: 85.3%, attention and concentration: 88.2%, abstract thinking: 97%, language: 91,1%, and visuospatial functioning 94.1%.

Prevalence of isolated mnestic deficits according to "MCI amnestic"[10] was rather low. The respective criteria applied for 4.1% at t1 and 4.2% at t2, respectively. 35.7% of subjects who fulfilled "MCI amnestic" criteria at t1 could be reclassified accordingly at t2.

In a further step, development of performance across different cognitive domains during the follow-up period was compared between subjects who retained the AACD diagnosis from t1 to t2 (n=34) and controls who were cognitively unimpaired both at t1 and t2 (n=39) (table 1). According to the ANOVAs calculated, AACD subjects were significantly impaired in all cognitive tests applied when compared with controls (word list immediate recall: $F_{diagnosis}$=39.2 df=1,71 p<0.0005, F_{time}=0.3 df=1,71

p=0.6; word list delayed recognition: $F_{diagnosis}$=16.8 df=1,71 p<0.0005, F_{time}=0.5 df=1,71 p=0.5; d2-test (attention and concentration): $F_{diagnosis}$=16.1 df=1,69 p<0.0005, F_{time}=0.2 df=1,69 p=0.6; HAWIE-R subtest (abstract thinking): $F_{diagnosis}$=24.8 df=1.71 p<0.0005, F_{time}=4.6 df=1,71 p<0.05; verbal fluency: $F_{diagnosis}$=36.8 df=1,71 p<0.0005, F_{time}=3.5 df=1,71 p=0.06; visual imagination: $F_{diagnosis}$=19.8 df=1.71 p<0.0005, F_{time}=14.2 df=1,71 p<0.0005). Additionally, AACD subjects showed a significant decline in performance for the delayed word recognition task compared to controls during follow-up as demonstrated by a significant diagnosis by time interaction (word list delayed recognition: $F_{diagnosis\ x\ time}$=4.25 df=1,71 p<0.05). The respective interaction for verbal fluency also reached significance level (verbal fluency: $F_{diagnosis\ x\ time}$=4.4 df=1,71 p<0.05). However, this effect resulted from an increased performance in the controls while AACD subjects showed rather stables values. None of the other interactions for the remaining neuropsychological test scores addressing immediate recall, attention and concentration, abstract thinking, and visuospatial functioning reached significance level ($0.1<F_{1,71}<2.9$).

Compared with the controls AACD subjects demonstrated significantly (p<0.05) more mild depressive symptoms at t1 (SDS score: AACD subjects: 37.7 ± 7.8; controls: 30.3 ± 5.6) and t2 (SDS score: AACD subjects: 38.0 ± 7.5; controls: 30.4 ± 5.7). Similar results were obtained when all subjects diagnosed with AACD at t2 (n=106) were compared with all cognitively unimpaired controls at t2 (n=245).

Discussion

According to our findings, AACD represents a frequent condition affecting 13.4% of the 60-64 year old population. In addition, prevalence of AACD showed an age-related increase rising to 24.1% within a 4-year follow-up period. The established prevalence rates are in line with the results from previous population-based studies which applied AACD criteria.[14,15,16] However, while previous investigations mainly focused on subjects in their seventies and eighties, our study for the first time indicates that AACD is also common in the population of the “young-old”. Since all subjects underwent a thorough physical examination prevalence rates of

AACD in the present study may not be attributed to early effects of severe systemic or neurological disorders.

Furthermore, the diagnosis of AACD was characterized by a relatively high temporal stability. This finding emphasizes the existence of a distinct diagnostic entity such as mild cognitive impairment which has been challenged recently.[24,25] It has been argued that mild cognitive impairments might considerably fluctuate over time and would not be suitable to define a circumscribed diagnostic category. Indeed, several population-based studies revealed that in particular the amnestic form of mild cognitive impairment (MCI-amnestic)[10] was rather unstable over time in that only about 7% of the affected subjects were still classified under this category after 2 to 3 years, while more than 40% reverted to normal.[15,25] This is in contrast to our finding that 52.3% of the subjects with a baseline diagnosis of AACD retained the diagnosis at follow-up. Further 6.2% had persisting deficits in cognitive tests although they had to be excluded from the AACD group for other reasons (lack of subjective complaints; severe medical conditions). Only 23.1% of the original AACD subjects improved with respect to cognitive testing. A single one (1.5%) of them reverted to normal in so far as he was neither subjectively nor objectively impaired at follow-up. Similar figures were reported by Ritchie et al.[15] who found that 50-60% of subjects classified as AACD retained this diagnosis when they were reexamined after a period of 1 year. Taken together, these findings indicate that in contrast to other concepts of mild cognitive impairment AACD defines a distinct syndrome which is reproducable over time in a considerable proportion of elderly subjects.

Compared to controls a significantly larger percentage of AACD subjects suffered from mild depressive symptoms. Since patients with manifest depression were excluded from the AACD group cognitive impairment due to affective disorders did not contribute to this finding. Otherwise, in patients with manifest dementia depressive symptoms and apathy often overlap making it difficult to differentiate depressive disorder comorbidity in dementia. Thus, mild depressive symptoms in AACD might represent an epiphenomenon of increasing cognitive decline.

In our population of the "young-old", AACD did not predict the conversion to dementia within a 4-year follow-up period. Ritchie et al.[15] and Busse et al.[16] determined conversion rates of 28% and 47% within a comparable time interval. However, the investigated population in the these studies was considerably older. Drop out rates were highest in subjects with AACD, followed by those fulfilling ICD-10 criteria for MCD and controls and it is likely that at least some of the AACD subjects might have converted into dementia. However, we could not definitely prove this assumption. Nevertheless, other factors have to be considered in order to explain this discrepancy. In particular, length of the follow-up intervall has to be weighed against the age of the subjects. Previous studies on cognitive deficits in preclinical AD had revealed some empirical evidence that deficits across multiple cognitive domains are apparent not only years but even decades before the diagnosis of dementia can be made,[26] and that the magnitude of those preclinical cognitive deficits appear to be relatively stable until a few years before clinical diagnosis.[1] Consequently, the likelyhood of observing accelerated changes in cognitive performance among incident AD increases as time before eventual diagnosis decreases. Taking into account that incidence and prevalence of dementia are relatively low during the seventh decade of life but increase exponentially from the age of 70, the divergent results with respect to conversion rates might mainly be explained by age differences between the studied populations. Accordingly, our results suggest that age and length of follow-up interval are of crucial relevance when the predicitve validity of different concepts of mild cognitive impairment is assessed.

Longitudinal analysis of our data nonetheless indicates that the respective neuropsychological deficits follow a progressive course. At t2, AACD subjects were in significantly more neuropsychological tests impaired than at t1. This observation is in line with the assumption that the putative pathological process involved a broader range of cognitive domains during the follow-up period. Compared to controls AACD subjects deteriorated significantly during follow-up in the test on delayed word recognition. In contrast, performance in immediate recall remained rather stable in the AACD subjects or improved slightly in the controls. Obviously,

the slight performance gains observed in the control group in this cognitive domain as well as with respect to delayed recognition and verbal fluency may refer to an increased awareness of the participants of the study towards their neuropsychological performance. Moreover, the double dissociation found between between immediate and delayed verbal memory argues against an effect of other conditions such as depressive syndroms which should affect both recall conditions simultaniously.

Several previous studies had addressed the question whether deficits in specific cognitive domains are predictive for the development of AD.[26,27,28,29,30,31] They all agreed that in particular deficits with respect to episodic memory tasks are associated with an increased risk of further cognitive decline. Notably, Palmer et al.[30] also found that specifically tests of word recall and verbal fluency had positive predictive value for dementia. These findings are paralleled by the results of recent neuroimaging studies. Pantel et al.[32] demonstrated in a subsample of the AACD subjects investigated here atrophic changes of medial temporal lobe structures which are specifically involved in episodic memory function. Similar findings were obtained in a variety of previous neuroimaging studies in patients with manifest AD (for review: see [33,34]).

In conclusion, we could show that AACD is a frequent condition in community-dwelling "young-old" subjects. AACD prevalence increased with age and diagnosis of AACD was characterized by a rather high temporal stability. Although in this particular sample of "young-old" subjects AACD did not predict dementia during a 4 year follow-up period AACD subjects were characterized by a selective further decline of episodic memory which occured independently from physical comorbiditiy.

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References

1. Small BJ, Mobly JL, Laukka EJ, Jones S, Backman L: Cognitive deficits in preclinical Alzheimer's disease. Acta Neurol Scand Suppl 2003;179:29-33
2. Bischkopf J, Busse A, Angermeyer MC: Mild cognitive impairment – a review of prevalence, incidence and outcome according to current approaches. Acta Psychiatr Scand 2002;106:403-414.
3. Tervo S, Kivipelto M, Hänninen T, Vanhanen Matti, Hellikainen M, Mannermaa A, Soininen H: Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement Geriatr Cogn Disord 2004;17:196-203.
4. Riley MW, Riley JW: Long-livity and social structure: the potential of the added years. In:Pifer A, Bronte L (Eds.):Our aging society: paradox and promise. Norton, New York,London,1986;53-77.
5. Lopez OL, Jagust WL, Dulberg C, Becker JT, DeKosky ST, Fitzpatrick A, Breitner J, Lyketsos C, Jones B, Kawas C, Carlson, Kuller LH: Risk factors for mild cognitive impairment in the cardiovacular health study cognition study: Part 2. Arch Neurol 2003;60:1394-1399.
6. Schröder J, Kratz B, Pantel J, Minnemann E, Lehr U, Sauer H: Prevalence of mild cognitive impairment in an elderly community sample. J Neural Transm 1998;54:51-59
7. Ritchie K, Touchon J: Mild cognitive impairment: conceptual basis and current nosological status. Lancet 2000;335:225–228.
8. Crook T, Bartus RT, Ferris SH, Whitehouse P, Cohen GD, Gershon S : Age associated memory impairment: proposed diagnostic criteria and measures of clinical change: report of a National Institute of Mental Health Work Group. Dev Neuropsychol 1986;2:261–276
9. Blackford RC, La Rue A: Criteria for diagnosing age-associated memory impairment: proposed improvements from the field. Develop Neuropsychol 1989;5:295-306

10. Petersen CP, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B: Current concepts in mild cognitive impairment. Arch Neurol 2001;58;1985-1992
11. World Health Organization: The ICD-10 Classification of mental and Behavioural Disorders. Diagnostic criteria for research. World Health Organization 1992,Geneva
12. Levy R. Aging-associated cognitive decline. Int Psychogeriatr 1994;6:63–68
13. Bondi MW, Salmon DP, Monsch AU, Galasko D, Butters N, Klauber MR, Thal LJ, Saitoh T: Episodic memory changes are associated with the APOE-epsilon 4 allele in nondemented older adults. Neurology 1995;45:2203-2206
14. Hänninen T, Koivisto K, Reinikainen KJ, Helkala EL, Soininen H, Mykkänen L, Laakso M, Riekkinen PJ: Prevalence of ageing-associated cognitive decline in an elderly population. Age and Ageing 1996;25:201-205
15. Ritchie K, Arteron S, Touchon J: Classification criteria for mild cognitive impairment - a population-based validation study. Neurology 2001;56:37-42
16. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC: Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria. Br J Psychiatry 2003;182:449-454
17. Martin P, Martin M: Design und Methodik der Interdisziplinären Längsschnittstudie des Erwachsenenalters. In: Martin, P, Etrich KU, Lehr U, Roether D, Fischer-Cyrulies A (Eds.): Aspekte der Entwicklung im mittleren und höheren Erwachsenenalter: Ergebnisse der Interdisziplinären Längsstudie des Erwachsenenalters (ILSE). Darmstadt Steinkopf 2000:17-27
18. Wittchen HU, Zaudig M, Schramm E, Spengler P, Mombour W, Klug J, Horn R: Strukturiertes klinisches Interview für DSM-III-R. Beltz-Test 1991,Göttingen
19. Oswald WD, Fleischmann VM: Nürnberger-Alters-Inventar. Universität Erlangen-Nürnberg 1991,Erlangen-Nürnberg
20. Horn WC: Leistungsprüfsystem. Hogrefe 1983,Göttingen

21. Brickenkamp R: Test d2. Aufmerksamkeits-Belastungs-Test. Hogrefe 1978, Göttingen
22. Tewes W: HAWIE-R. Hamburg-Wechsler-Intelligenztest für Erwachsene. Revision. Huber 1991, Bern
23. Oswald WD, Fleischmann VM: Nürnberger Selbsteinschätzungsliste (NSL). Universität Erlangen-Nürnberg 1986, Erlangen-Nürnberg
24. Milwain E: Mild cognitive impairment: further caution. Lancet 2000; 355:1018
25. Larrieu S, Letenneur L, Orgogozo JM, Fabrigoule C, Amieva H, Le Carret N, Barberger-Gateau P, Dartigues JF : Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002;59:1594-1599
26. Tierney MC, Szalai JP, Snow WG, Fisher RH, Nores A, Nadon G, Dunn E, St George-Hyslop PH: Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. Neurology 1996;46:661-665
27. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB: The preclinical phase of Alzheimer disease. A 22-year prospective study of the Framingham cohort. Arch Neurol 2000;57: 808-813.
28. Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M: Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. Arch Gen Psychiatry 2001;58:853-858
29. Tian J, Bucks RS, Haworth J, Wilcock G: Neuropsychological prediction of conversion to dementia from questionable dementia: statistically significant but not yet clinically useful. J Neurol Neurosurg Psychiatry 2003;74:433-438
30. Palmer K, Backman L, Winblad B, Fratiglioni L: Detection of Alzheimer's disease and dementia in the preclinical phase: population based cohort study. BMJ 2003;326:245
31. Backman L, Small BJ, Fratiglioni L: Stability of the preclinical episodic memory deficit in Alzheimer's disease. Brain 2001;124:96-102

32. Pantel J, Kratz B, Essig M, Schröder J. Parahippocampal volume deficits in subjects with aging-associated cognitive decline. Am J Psychiatry 2003;160:379-382.
33. Pantel J, Schönknecht P, Essig M, Schröder J. Distribution of cerebral atrophy assessed by magnetic resonance imaging reflects patterns of neuropsychological deficits in Alzheimer's dementia. Neurosci Lett 2004;361:17-20.
34. Schröder J, Buchsbaum MS, Shihabuddin L, Tang C, Wei T, Spiegel-Cohen J, Hazlett EA, Abel L, Luu-Hsia C, Ciaravolo TM, Marin D, Davis KL. Patterns of cortical activity and memory performance in Alzheimer's disease. Biol Psychiatry 2001;49:426-436.

Figure 1: Diagnostic classification of AACD subjects (t1) at follow-up (t1: n=485; t2: n=449).

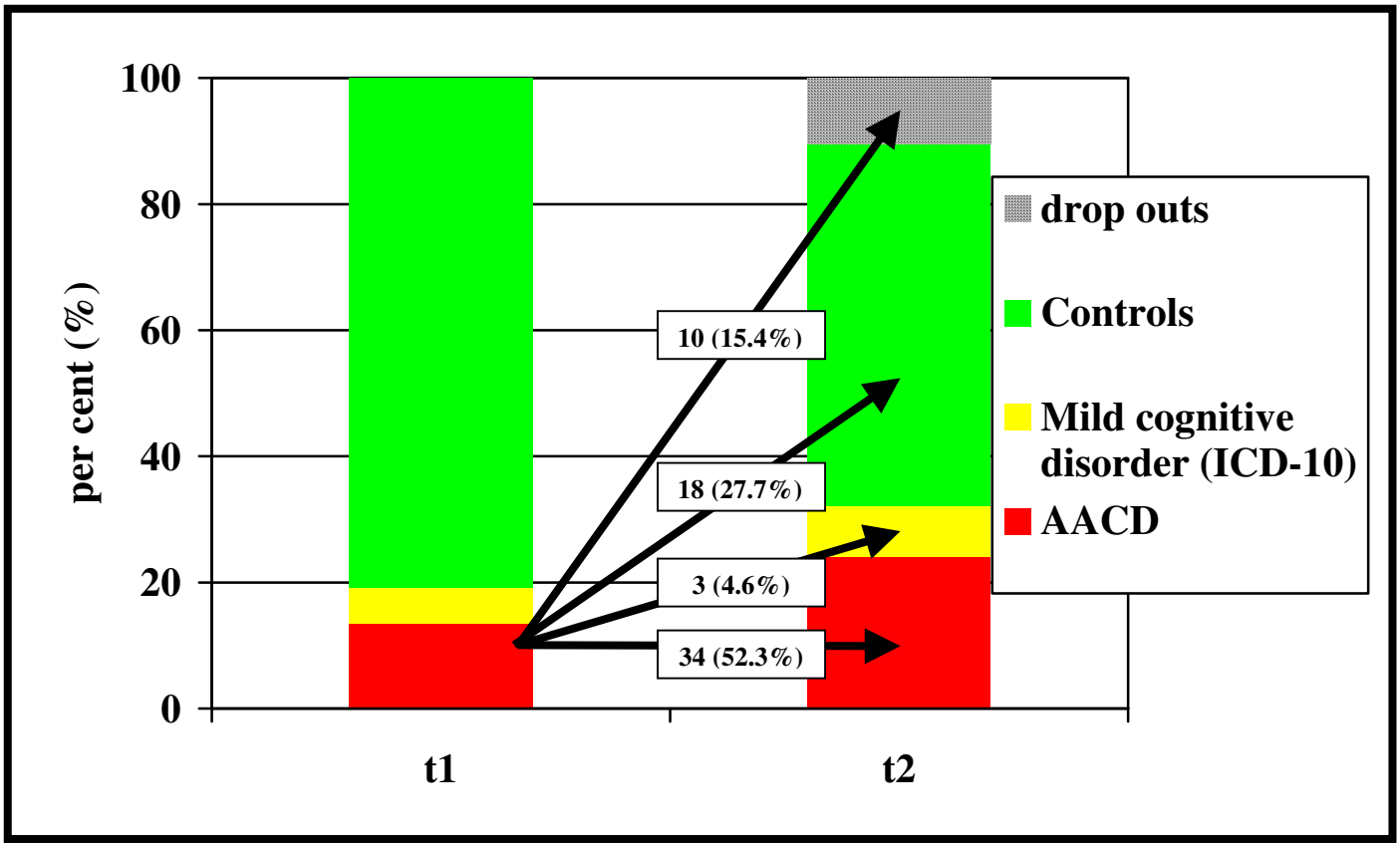

Figure 2: Initial diagnostic classification of subjects diagnosed with AACD at t2 (t1: n=485; t2: n=449).

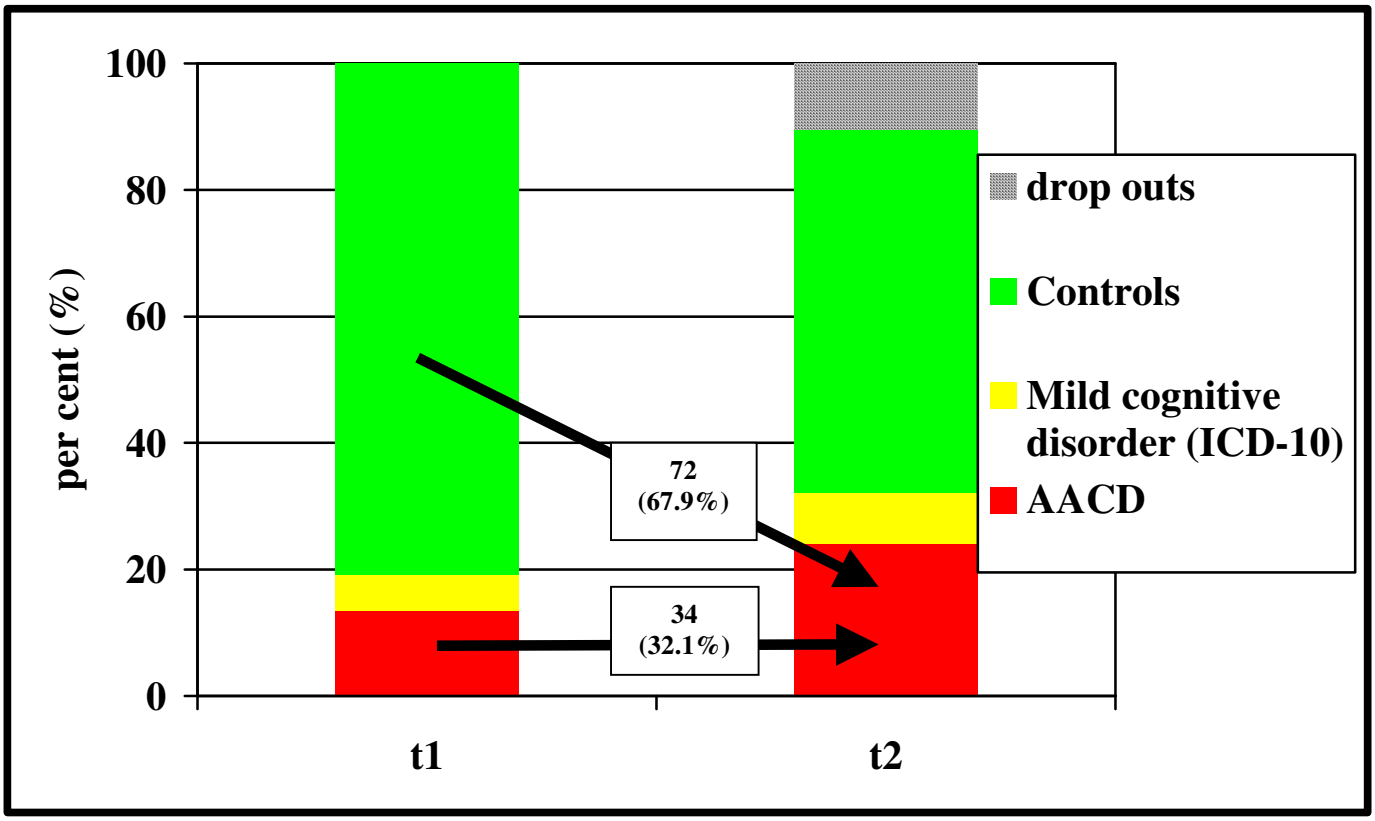

Table 1. Neuropsychological test performance in AACD subjects (n=34) and controls (n=39)

Cognitive domain	Neuropsychological test	t1 AACD (mean ± SD)	t1 controls (mean ± SD)	t2 AACD (mean ± SD)	t2 controls (mean ± SD)
Episodic memory	Word list immediate recall (NAI)[1]	4.4 ± 1.3	5.7 ± 1.1	4.2 ± 1.2	6.0 ± 1.4
	Word list delayed recognition (NAI) [1,3a]	5.2 ± 2.5	6.3 ± 2.0	4.2 ± 2.9	6.7 ± 2.1
Attention and concentration	d2-Test [1]	334.8 ± 84.4	408.0 ± 72.6	333.7 ± 88.6	403.9 ± 70.7
Abstract thinking	HAWIE-R subtest [1, 2a]	21.7 ± 7.2	27.1 ± 2.8	19.8 ± 8.1	26.7 ± 3.5
Language	Verbal fluency (LPS 50+)[1,3b]	24.8 ± 7.0	32.4 ± 7.3	24.6 ± 8.0	35.7 ± 7.5
Visuospatial functioning	visual imagination (LPS 50+)[1,2b]	18.5 ± 7.4	24.3 ± 4.9	16.2 ± 7.8	22.7 ± 4.6

[1]main effect "diagnosis": $16.1<F_{(1,71)}<36.8$, $p<0.05$; [2a]main effect "time": $F_{(1,71)}= 4.6$, $p<0.05$; [2b]main effect "time": $F_{(1,71)}=14.2$, $p<0.0005$; [3a]interaction "diagnosis*time": $F_{(1,71)}=4.3$, $p<0.05$ [3b]interaction "diagnosis*time": $F_{(1,71)}=4.4$, $p<0.05$

NAI Nürnberger-Alters-Inventar, *HAWIE-R* Hamburg-Wechsler-Intelligenztest für Erwachsene (Revision), *LPS+50* Leistungsprüfsystem, *d2-Test* Aufmerksamkeits-Belastungs-Test, *SD* standard deviation