Cognitive Performance and Cerebrospinal Fluid Markers in Preclinical Alzheimer's Disease: Results from the Gothenburg H70 Birth Cohort Studies

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Abstract

Background: We have previously shown that older adults with preclinical Alzheimer's disease (AD) pathology in cerebrospinal fluid (CSF) had slightly worse performance in Mini-Mental State Examination (MMSE) than participants without preclinical AD pathology.

Objective: We therefore aimed to compare performance on neurocognitive tests in a population-based sample of 70-year-olds with and without CSF AD pathology.

Methods: The sample was derived from the population-based Gothenburg H70 Birth Cohort Studies in Sweden. Participants (n = 316, 70 years old) underwent comprehensive cognitive examinations, and CSF Aβ-42, Aβ-40, T-tau, and P-tau concentrations were measured. Participants were classified according to the ATN system, and according to their Clinical Dementia Rating (CDR) score. Cognitive performance was examined in the CSF amyloid, tau, and neurodegeneration (ATN) categories.

Results: Among participants with CDR 0 (n = 259), those with amyloid (A+) and/or tau pathology (T+, N+) showed similar performance on most cognitive tests compared to participants with A-T-N-. Participants with A-T-N+ performed worse in memory (Supra span ($p = 0.003$), object Delayed ($p = 0.042$) and Immediate recall ($p = 0.033$)). Among participants with CDR 0.5 (n = 57), those with amyloid pathology (A+) scored worse in category fluency ($p = 0.003$).

Conclusion: Cognitively normal participants with amyloid and/or tau pathology performed similarly to those without any biomarker evidence of preclinical AD in most cognitive domains, with the exception of slightly poorer memory performance in A-T-N+. Our study suggests that preclinical AD biomarkers are altered before cognitive decline.

Keywords: Biomarkers in early Alzheimer's disease; cerebrospinal fluid; cognition; population-based.

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Introduction

Alzheimer's disease (AD) pathology starts about 10-20 years before the onset of cognitive symptoms. According to the "amyloid cascade hypothesis", the starting event of AD pathology is the deposition of aggregated amyloid β (Aβ) plaques.[1] These Aβ plaques then start a cascade that results in neuronal and synaptic degeneration and dementia. Many longitudinal population-based studies have shown that the trajectory of cognitive performance before onset of a clinical AD diagnosis can be up to a decade or more;[2-4] with cognitive symptoms appearing late during this process. Preclinical AD pathology characterized by low Aβ42, high T-tau and high P-tau levels is very common in cognitively unimpaired older adults.[5]

Many studies applying the different criteria of preclinical AD (using CSF and amyloid PET) have shown that high amyloid burden as measured on Amyloid PET and in CSF[6-10] and/or tau pathology in CSF[11-13] and/or neurodegenerations markers[14-17] are related to cognitive decline, mild cognitive impairment (MCI) or dementia. Many of these studies showing a relationship between CSF/PET markers and decrease in cognitive function are clinical.[9,17] Population-based studies [6,8,11-16] have given disparate results, some showing a relationship between amyloid positivity on PET and subtle cognitive differences in otherwise cognitively unimpaired individuals[6,14,15] while others show no such relationship.[18-20] Population-based studies using CSF are rare and have shown that cognitively normal participants with positive AD biomarkers have an increased risk of developing cognitive decline compared to those without AD biomarkers.[8,11,16] Using CSF, we have previously shown that cognitively healthy participants with amyloid and tau pathology had slightly worse performance on global cognitive function (MMSE) than participants without underlying preclinical AD pathology.[5] It is however less clear if this group shows subtle cognitive decline in other domains.

Therefore, we sought to investigate if participants from the general population with Clinical Dementia Rating (CDR) 0 and underlying AD pathology differ in cognitive performance from those without AD pathology, and investigate as well the group of older adults with already established cognitive decline operationalized as Clinical Dementia Rating (CDR) 0.5 with the same cognitive battery.

Method

The sample was systematically obtained and derived from the 2014-2016 examinations of the H70 Gothenburg Birth Cohort Studies in Gothenburg, Sweden, and included people living in private households and in residential care[21] obtained from the Swedish population registry.

Every 70-year old living in Gothenburg, Sweden, born 1944 on predetermined birth dates was eligible to participate in the examinations during 2014 to 2016. 1203 participants took part (response rate 72.2%), and 430 (35.8%) consented to a lumbar puncture (LP). Of these individuals, 108 had contraindications such as immune modulated therapy, anticoagulant therapy and cancer therapy, leaving 322 (26.8%) participants who underwent LP. A CDR score was assigned to every participant and participants with dementia (n=5) were excluded. 259 had a CDR score of 0 and 59 had a CDR score of 0.5.[5]

Standard Protocol Approvals, Registrations, and Patient Consents

All participants and/or their close relatives provided written informed consent. The study was approved by the Regional Ethical Review Board in Gothenburg.[5]

Assessments

Participants were examined at the Neuropsychiatric memory clinic at Sahlgrenska University Hospital in Gothenburg or in their homes. The neuropsychiatric examinations were performed by experienced psychiatric research nurses, and comprised ratings of psychiatric symptoms and signs, tests of mental functioning, including assessments of episodic memory (short-term, long-term), aphasia, apraxia, agnosia, executive functioning and personality changes,[22-25] and key informant interviews performed by a psychologist and research nurses as described previously.[5,21] Additional cognitive assessments were performed by a research nurse, psychiatrist or medical doctor using a neuropsychological battery including the following cognitive tests: (1) memory (Immediate recall 10 words, delayed recall 10 words, word memory 10 word list, Supra span (BUSII), Thurstone's picture memory test, Short term memory), (2) language (word fluency animals, FAS), (3) executive function (Figure logic (SRB2), Backward digit span) (4) visuospatial (Block design, (SRB3)) and (5) mental speed (Psif).[21,22,26] Global cognitive function was assessed by MMSE and the assigning of a CDR score.

Dementia was diagnosed according to the DSM-III-R criteria as these criteria have been used in the Gothenburg Birth Cohort studies since more than 30 years. Education (defined as years of education) and stroke and TIA information was acquired from self-reports and close informants. The participants also underwent comprehensive somatic examinations.[5]

Apolipoprotein E (APOEε4) genotyping

The SNPs rs7412 and rs429358 in *APOE* (gene map locus 19q13.2) were genotyped, using KASPar® PCR SNP genotyping system (LGC Genomics, Hoddesdon, Herts, UK). Genotype-data for these two SNPs were used to define ε2, ε3, and ε4 alleles.[5] Data on genotypes were lacking for 5 individuals.

Cerebrospinal fluid sampling and biomarker analyses

As previously published,[5] lumbar punctures (LP) to collect CSF samples were performed in the morning, in the L3/L4 or L4/L5 inter-space. The first 10 mL of CSF were collected in a polypropylene tube and immediately transported to the laboratory and centrifuged at 1800 g in 20°C for 10 min. The supernatant was gently mixed to avoid possible gradient effects, aliquoted in polypropylene tubes and stored at –70°C.

CSF total tau and tau phosphorylated at threonine 181 (P-tau) concentrations were measured using a sandwich enzyme-linked-immunosorbent-assay (ELISA) (INNOTEST® htau Ag and PHOSPHO_TAU (181P), Fujirebio (formerly Innogenetics.[27,28]) CSF Aβ42 concentration was measured using a sandwich ELISA (INNOTEST® β-amyloid$_{1-42}$), specifically constructed to measure Aβ starting at amino acid 1 and ending at amino acid 42.[29] All assays are included in the panel of clinical routine analyses at the Mölndal Clinical Neurochemistry lab. Analytical runs had to pass quality control criteria for the calibrators and internal quality control samples had to be approved. In this study we used the following CSF cut-offs to determine amyloid, T-tau and P-tau pathology and the ATN groups:[30] CSF Aβ42 levels $\leq$ 530 pg/mL (the A criterion), P-tau levels of $\geq$ 80 pg/mL (T) and CSF T-tau levels $\geq$ 350 pg/mL (N).[31]

Statistical Analyses

Differences in means of cognitive test scores and the sample characteristics age and education were tested with unpaired Student's T-tests, and the null hypothesis was that there was no

differences in means between the groups. When variances were not equal according to Levene's test, Satterthwaite's T-test was used. Proportions for the variables sex, stroke, depression and *APOE* ε4 carriership were tested with Fischer's exact test.

We further investigated if there was an association between AD pathology and *APOE* ε4 carriership, and if this association depended on sex, using a Chi Square Test. A two-tailed level of significance was used for all analyses ($p<0.05$). Statistical analyses were completed using SPSS for Windows (v. 22, SPSS, Chicago, Il).

Results

Characteristics of the 259 participants with CDR0 and the 57 participants with CDR0.5 who participated in the lumbar puncture are given in table 1. In the CDR0 group, mean age was 70.55 (SD 0.25) years, 129 (49.8 %) were female and 87 (34.1 %) had the *APOE* ε4 allele (table1). In the CDR0.5 group, mean age was 70.56 (0.23), 23 (40.4%) were female and 27 (48.2%) were *APOE* ε4 carriers. The participants with CDR0.5 had lower education (11.30 years vs 13.04 years, $p=0.002$) and had more often had stroke (12.3 % versus 3.5%, $p= 0.013$) than participants with CDR0. They also had lower global cognitive function (MMSE) (27.61 vs 29.25, ($p<0.001$) (table 1). Participants with CDR0 and with and without CSF pathology were similar regarding a number of factors (*e.g.*, education) but had more often the *APOE* ε4 allele (supplementary table 1 and supplementary table 2) as previously published.[5]

We then compared the cognitive test performance between participants with CDR0 and CDR 0.5 (table 2). Cognitive test performance was better in all cognitive domains for the CDR0 group compared to the CDR0.5 group (table 2).

Pathology and cognitive tests in 70-year olds with CDR 0

In participants with CDR 0, 60 (23.2%) had amyloid pathology, 87 (33.6%) had T-tau pathology and 18 (6.9%) had P-tau pathology, as previously published.[5] Participants with amyloid and tau pathology and neurodegeneration were similar regarding cognitive tests of general cognitive function (MMSE), memory, language, executive function, visuospatial function and mental speed (table 3).

Pathology and cognitive tests in 70-year olds with CDR 0.5

We then investigated participants with CDR 0.5 according to their CSF biomarker status, divided into three groups (amyloid pathology, T-tau pathology and P-tau pathology). In participants with CDR 0.5 (n=57), 13 (22.8%) had amyloid pathology, 18 (31.6 %) had T-tau pathology and 2 (3.5 %) had P-tau pathology. Participants with amyloid pathology had worse performance in language (word fluency) (17.38 vs 22.84, p = 0.003) than those with no pathology (table 4). Participants with P-tau pathology had worse performance in word memory (3.0 vs 3.70, p=0.001), but there were only 2 participants in this group (table 4).

ATN classification system and cognitive performance in 70-year olds with CDR 0

Participants with CDR 0 and A+T+N+ had lower scores on general cognitive function (MMSE) than the group without pathology (28.5 vs 29.28, p=0.043) as previously published.[5] In addition, participants with A-T-N+ had lower scores on the memory tests Delayed recall (7.33 vs 7.91, p=0.042) and Supra span (7.07 vs 7.82, p= 0.003) and immediate recall (7.79 vs 8.38, p=0.033). A+T+N+ had better score in language (word fluency) (30.33 vs 25.33, p=0.003) than the group without pathology.

There were no differences in the other ATN groups compared to the group without pathology (A-T-N- group) regarding test of general cognitive function, executive function, visuospatial and mental speed (table 5).

ATN classification system and cognitive performance in70-year olds with CDR0.5

We then divided the group with CDR0.5 according to the ATN system for preclinical AD.

There were no participants with CDR0.5 in the A-T+N+, A-T+N- and A+T+N- group.

Participants with CDR0.5 and A+T-N- had worse mean score in visuospatial test (SRB3) (10.8 vs 17.06, p=0.007) as compared to the A-T-N- group.

The A+T-N+ group showed worse performance in language (word fluency) (16.83 vs 22.84, p=0.011) compared to participants without pathology. A+T+N+ had worse score in memory (word memory), (3.0 vs 3.7, p=0.020) (table 6).

Sex difference in prevalence of pathology in individuals with CDR0

There was a sex-difference in prevalence of T-tau pathology, although men had a higher proportion with T-tau pathology (40% vs 27.1% in women, p=0.035) as previously published[5] (relative risk 1.48).

Discussion

This study investigated the neurocognitive test performance of healthy older individuals from the population with underlying CSF biomarker signs of Alzheimer pathology in comparison to healthy older individuals without AD pathology. Besides subtle differences we demonstrated that cognitively healthy older adults from the general population performed almost similar in all cognitive tests compared to healthy older adults without underlying preclinical AD pathology. This finding is in line with previous studies using PET.[18-20,32] A study using amyloid PET in cognitively unimpaired older individuals from the community (mean age 74.4 years) showed that participants with underlying amyloid pathology were similar to participants without amyloid pathology regarding performance on a number of different cognitive tests examining all the different domains.[18] Another study examined episodic memory in cognitively normal elderly with amyloid beta positivity on PET from the Alzheimer's disease neuroimaging initiative (ADNI) and the Berkeley aging cohort (BAC). The study could not detect any differences in test performance to participants without amyloid beta positivity in the BAC (mean age 72.1).[32] In contrast to our study, there are a few population-based studies which found cognitive differences between healthy elderly with amyloid pathology on PET and CSF compared to healthy elderly without preclinical AD.[6,8,11,13-15] One possible explanation is that participants in some of these studies[8,10,14,15] had a higher mean age which may be related to worse cognitive performance.

Another possible explanation for the lack of findings in our study may be due to that participants with preclinical AD in our study are examined so early in their disease process that differences cannot be detected yet, a suggestion which is strengthened by the high mean test scores in the different cognitive domains. Our study is therefore in line with Jacks hypothetical model of the development of AD,[30] where CSF biomarkers are altered long before the onset of cognitive symptoms. Another possible explanation for the lack of findings is that cognitively normal participants with CDR 0 and both amyloid and tau pathology have a

higher cognitive reserve which may have allowed them to display AD pathology without manifesting any cognitive impairment. In line with this theory, one study in cognitively normal older adults with amyloid pathology showed that older adults with high cognitive reserve had normal test results on a variety of cognitive tests.[33] However, participants with and without AD pathology in our study were similar regarding a number of factors such as education which may indicate similar premorbid function. Further, it is possible that more demanding tests are needed to detect cognitive changes early in preclinical AD.[34] In line with this suggestion is a study which showed that amyloid related memory impairment could be detected with a difficult face-name associative memory test in a sample of older adults with CDR0 who performed otherwise normally on less demanding neuropsychological tests.[34]

Although cognitively healthy participants with and without AD pathology were similar on a number of tests, we found subtle differences on three memory tests. Participants with CDR0 and A-T-N+ performed worse on memory tests (immediate recall, delayed recall and supra span). The finding of slightly worse memory performance in participants with T-tau pathology is in line with findings from a community based study of older adults enrolled in St. Louis, where cognitively normal elderly with SNAP (solely T-tau pathology, suspected non-AD pathophysiology) performed worse on episodic memory tests and global cognition (MMSE).[11] Participants displaying A-T-N+ have previously been classified in the NIA-AA criteria as SNAP (suspected non-Alzheimer disease pathology), reflecting that this is a heterogenous group who may have a variety of other health related conditions (*e.g.*, stroke) that could contribute to neurodegeneration.[35] In a report from the Mayo Clinic Study of Aging it was shown that neurodegeneration markers such as CSF T-tau and neurofilament light protein increased the risk for progression from cognitively normal to MCI in the general population, independent of amyloid pathology status,[36] a finding that may reflect that participant with underlying neurodegeneration signs may have higher risk for conversion even

to non-AD dementia and is in line with our findings. We could not show a relationship between total-tau pathology (A+T-N+, A-T-N+, Table 3) and differences in cognitive performance, despite seeing subtle differences in the A-T-N+ subgroup and supra span memory test. This may be due to the small sample size.

Although participants with and without preclinical AD performed similar on a number of cognitive tests, we unexpectedly found that the A+T+N+ group performed better than the A-T-N- group in word fluency. However, as the A+T+N+ group consists of only 6 people, it is difficult to draw any conclusions based on this finding.

As expected, participants with CDR 0.5 performed worse on all cognitive tests compared to participants with CDR 0.[37-39]

Participants with CDR 0.5 in the amyloid positive ATN groups performed worse than participants with CDR 0.5 and no CSF pathology (A-T-N-) in visuospatial and category fluency tests. Participants with CDR 0.5 and amyloid positivity are on the AD-pathway, while the A-T-N- CDR0.5 group could be more heterogeneous, and may include people with various types of brain damage or dementias unrelated to AD. That our study showed that amyloid positive participants with CDR 0.5 perform worse and probably are nearer a conversion to dementia is in line with a study from the Mayo Clinic Study of Aging where amyloid positive participants with MCI had a higher risk for AD dementia than amyloid-negative participants with MCI.[6]

In our comparisons of people with CDR 0.5, although it was shown that those with amyloid pathology had lower scores on the category fluency test (word fluency) than those without such pathology, the two groups scored similar on the letter fluency test (FAS). People with AD perform worse in category fluency than in letter fluency tests[40-42] and the impairment in

category fluency can be seen as early as in the MCI stage,[43-46] although the performance of MCI patients might be low in both category and letter fluency.[47]

The participants with CDR0.5 and amyloid (A+T-N-) also had worse scores on the visuospatial test than A-T-N-, but there were only 5 people in this group so the result should be interpreted with caution. Impairments in visuospatial abilities can be present in AD and may appear early in the disease progression.[48-50] It is not clear to which extent visuospatial impairment is present in normal aging and MCI, and studies in AD have been less focused on visuospatial than memory-related deficits.[48]

Strength and limitations

The strengths of this study include the comprehensively examined population based sample, which was systematically selected based on birth year. In contrast to many other studies that use convenience samples or volunteers, this sample is likely to be representative of the general population of 70-year olds in Sweden. Many of the participants agreed to lumbar puncture, yielding a relatively large CSF sample. However, due to contraindications, participants taking anticoagulant treatment were excluded from LP, which may have led to a selection bias with an overrepresentation of healthier participants. Another limitation is that many ATN groups were small, this may give rise to spurious significances. Hence, it is possible that in these smaller subsamples there might have been subtle cognitive differences between the groups that were not detected, (due to either low power in small groups or that the cognitive tests were not challenging enough) while some differences that we did detect may be false positives, especially since correction for multiple testing was not used. Lastly, this study examined 70-year old Swedish citizens, and therefore the results cannot be generalizable to younger populations.

In conclusion, this study showed that cognitively normal participants with preclinical AD performed similarly to those without preclinical AD in most cognitive domains. Our study shows, that preclinical AD biomarkers are altered before cognitive decline.

Tables

Table 1. The study participants of the Gothenburg Birth Cohort Studies with CDR 0 or CDR 0.5 and CSF data on preclinical Alzheimer's disease.

Characteristics	**CDR 0 (n=259)**	**CDR 0.5 (n=57)**	**p**
Age, mean (SD) y	70.55 (0.25)	70.56 (0.23)	0.726
MMSE score, mean (SD)	29.25 (0.94)	27.61 (1.49)	**<0.001**
Education, mean (SD), y	13.04 (3.83)	11.30 (3.64)	**0.002**
Women, n (%)	129 (49.8)	23 (40.4)	0.241
Stroke, n (%)	9 (3.5)	7 (12.3)	**0.013**
Any depression n (%)	21 (8.1)	8 (14.3)	0.198
APOE ε4-positive n (%)	87 (34.1)	27 (48.2)	0.065

Table 2. Cognitive test performance in participants with CDR0 and CDR0.5

	CDR0	Mean score	CDR0.5	Mean score	p
MMSE (SD)	N=258	29.25 (0.94)	N=57	27.61 (1.49)	<0.001
Memory					
Immediate recall (SD)	N=258	8.21 (1.64)	N=55	6.55 (1.66)	<0.001
Delayed recall (SD)	N=258	7.70 (1.72)	N=55	5.89 (1.92)	<0.001
Word memory (SD)	N=254	5.59 (1.79)	N =54	3.69 (1.50)	<0.001
Supra Span (BUSII)(SD)	N=245	7.66 (1.50)	N=50	7.00 (1.64)	0.006
Thurstone's picture memory test (SD)	N=238	22.77 (3.87)	N=51	20.10 (4.19)	<0.001
Language					
Word fluency (SD)	N=258	25.05 (6.46)	N=55	21.64 (6.03)	<0.001
FAS (SD)	N=246	41.93 (13.75)	N=47	32.15 (10.61)	<0.001
Executive function					
SRB2 (SD)	N=253	20.53 (4.08)	N=53	18.43 (3.51)	0.001
Backward digit span(SD)	N=253	4.57 (1.12)	N=55	3.82 (1.00)	<0.001
Visuospatial					
SRB3 (SD)	N=249	21.90 (6.77)	N=53	16.87 (7.58)	<0.001
Mental speed					
Psif (SD)	N=254	29.72 (7.66)	N=54	22.44 (6.88)	<0.001

Table3. Cognitive test performance and CSF biomarker status in 70 year-olds from the Gothenburg Birth Cohort Studies with CDR0

	Amyloid pathology N= 60	Amyloid pathology mean score	No amyloid pathology mean score	P[1]	T-tau pathology N=87	T-tau pathology mean score	No T-tau pathology mean score	P[2]	P-tau pathology N=18	P-tau pathology mean score	No P-tau pathology mean score	P[3]
MMSE	60	29.20	29.27	0.629	86	29.16	29.30	0.286	18	28.94	29.28	0.154
Memory												
Immediate recall	60	8.13	8.23	0.698	86	24.29	25.43	0.114	18	8.33	8.20	0.732
Delayed recall	60	7.53	7.75	0.401	86	7.43	7.83	0.078	18	7.94	7.68	0.530
Word memory	59	5.37	5.66	0.281	84	5.54	5.62	0.715	17	5.53	5.60	0.878
Supra span (BUSII)	55	7.71	7.64	0.771	81	7.43	7.77	0.099	17	7.94	7.64	0.420
Thurstone's picture memory test	56	21.86	23.05	0.098	82	22.60	22.86	0.622	18	22.89	22.76	0.892
Language												
Word fluency	60	25.45	24.93	0.586	86	24.29	25.43	0.183	18	27.89	24.84	0.053
FAS	57	42.30	41.81	0.817	81	41.20	42.28	0.561	16	41.75	41.94	0.958
Executive function												
SRB2	59	20.54	20.52	0.972	85	20.47	20.55	0.879	18	20.83	20.50	0.741
Backward digit span	58	4.62	4.56	0.715	83	4.55	4.58	0.852	17	4.71	4.56	0.616
Visuospatial												
SRB3	57	22.56	21.70	0.402	83	21.10	22.30	0.187	17	22.59	21.85	0.665
Mental speed												
Psif	58	29.12	29.90	0.496	85	29.46	29.86	0.696	18	29.94	29.71	0.900

P[1]= difference in mean score for amyloid pathology compared to non-amyloid pathology with T-test
P[2]= difference in mean score for T-tau pathology compared to non-T-tau pathology with T-test
P[3]= difference in mean score for P-tau pathology compared to non-P-tau pathology with T-test

Table 4. Cognitive test performance and CSF biomarker status in 70 year-olds from the Gothenburg Birth Cohort Studies with CDR0.5

	Amyloid pathology N= 13	**Amyloid pathology mean score**	**No amyloid pathology mean score**	**P[1]**	**T-tau pathology N=18**	**T-tau pathology mean score**	**No T-tau pathology mean score**	**P[2]**	**P-tau pathology N=2**	**P-tau pathology mean score**	**No P-tau pathology mean score**	**P[3]**
MMSE	13	27.08	27.77	0.142	18	27.33	27.74	0.341	2	26.00	27.67	0.122
Memory												
Immediate recall	12	6.67	6.51	0.778	17	6.06	6.76	0.149	2	7.50	6.51	0.414
Delayed recall	12	6.67	5.67	0.114	17	5.65	6.00	0.534	2	7.00	5.85	0.411
Word memory	12	3.58	3.71	0.793	17	3.35	3.84	0.275	2	**3.00**	**3.71**	**0.001**
Supra span (BUSII)	10	6.90	7.03	0.832	14	7.43	6.83	0.150	1	7.00	7.00	-
Thurstone's picture memory test	10	20.20	20.07	0.933	16	20.94	19.71	0.339	1	20.00	20.10	-
Language												
Word fluency	13	**17.38**	**22.95**	**0.003**	18	20.44	22.22	0.311	2	17.00	21.81	0.272
FAS	7	27.14	33.03	0.179	15	30.60	32.88	0.499	1	24.00	32.33	-
Executive function												
SRB2	12	18.42	18.44	0.985	16	19.56	17.95	0.126	1	24.00	18.33	-
Backward digit span	12	3.42	3.93	0.117	17	3.53	3.95	0.155	1	4.00	3.81	-
Visuospatial												
SRB3	11	15.45	17.24	0.493	16	18.38	16.22	0.346	1	22.00	16.77	-
Mental speed												
Psif	12	20.58	22.98	0.293	17	23.35	22.03	0.516	1	25.00	22.40	-

P[1]= difference in mean score for amyloid pathology compared to non-amyloid pathology with T-test
P[2]= difference in mean score for T-tau pathology compared to non-T-tau pathology with T-test
P[3]= difference in mean score for P-tau pathology compared to non-P-tau pathology with T-test

Table 5. Cognitive test performance in 70 year olds from the Gothenburg Birth Cohort Studies with CDR0 according to the ATN classification system for preclinical Alzheimer's disease

	Normal CSF (A-T-N-) N= 138	**A-T-N- Mean Score**	**A+T-N- N=34**	**A+T-N- Mean score**	**P[1]**	**A+T-N+ N=20**	**A+T-N+ Mean score**	**P[2]**	**A+T+N+ N=6**	**A+T+N+ Mean score**	**P[3]**	**A-T-N+ N=49**	**A-T-N+ Mean score**	**P[4]**	**A-T+N+ N=12**	**A-T+N+ Mean score**	**P[5]**
MMSE	138	**29.28**	34	29.35	0.677	20	29.15	0.542	6	**28.50**	**0.043***	48	29.25	0.841	12	29.17	0.672
Memory																	
Immediate recall	138	**8.38**	34	8.06	0.299	20	8.10	0.487	6	8.67	0.682	48	**7.79**	**0.033**	12	8.17	0.669
Delayed recall	138	**7.91**	34	7.53	0.256	20	7.20	0.096	6	8.67	0.285	48	**7.33**	**0.042**	12	7.58	0.539
Word memory	137	5.73	33	5.18	0.131	20	5.50	0.601	6	6.00	0.730	47	5.55	0.563	11	5.27	0.429
Supra span (BUSII)	132	**7.82**	32	7.56	0.384	18	7.89	0.841	5	8.00	0.778	46	**7.07**	**0.003**	12	7.92	0.817
Thurstone's picture memory test	124	23.06	32	22.09	0.193	18	21.89	0.428	6	20.50	0.369	46	22.76	0.621	12	24.08	0.341
Language																	
Word fluency	137	**25.33**	34	25.85	0.678	20	23.30	0.215	6	**30.33**	**0.003**	48	23.35	0.070	12	26.67	0.506
FAS	132	42.27	33	42.33	0.982	19	42.84	0.863	5	40.00	0.712	46	40.33	0.419	11	42.55	0.949
Executive function																	
SRB2	134	20.56	34	20.53	0.970	19	20.68	0.907	6	20.17	0.824	48	20.25	0.659	12	21.17	0.638
Backward digit span	136	4.63	34	4.41	0.333	19	4.95	0.273	5	4.80	0.743	47	4.34	0.146	12	4.67	0.907
Visuospatial																	
SRB3	133	22.11	33	23.09	0.436	19	21.74	0.827	5	22.20	0.975	47	20.30	0.110	12	22.75	0.754
Mental speed																	
Psif	136	29.90	33	29.67	0.870	19	27.95	0.309	6	29.83	0.982	48	29.88	0.982	12	30.00	0.965

P[1]= difference in mean score for A+T-N- compared to normal CSF with T-test
P[2]= difference in mean score for A+T-N+ compared to normal CSF with T-test
P[3]= difference in mean score for A+T+N+ compared to normal CSF with T-test
P[4]= difference in mean score for A-T-N+ compared to normal CSF with T-test
P[5]= difference in mean score for A-T+N+ compared to normal CSF with T-test
*Previously published in Neurology (Kern et al).

Table 6. Cognitive test performance in 70 year olds from the Gothenburg Birth Cohort Studies with CDR0.5 according to the ATN classification system for preclinical Alzheimer's disease

	A-T-N- (N=34)	Mean score	A+T-N- (N=5)	Mean score	P[1]	A+T-N+ (N=6)	Mean score	P[2]	A-T-N+ (N=10)	Mean score	P[3]	A+T+N+ (N=2)	Mean score	P[4]
MMSE	34	27.85	5	27.00	0.277	6	27.50	0.607	10	27.50	0.522	2	26.00	0.119
Memory														
Immediate recall	33	6.61	5	7.80	0.122	5	5.20	0.085	10	6.20	0.461	2	7.50	0.443
Delayed recall	33	5.76	5	7.60	0.052	5	5.60	0.862	10	5.40	0.605	2	7.00	0.389
Word memory	33	**3.70**	4	5.00	0.127	6	2.83	0.219	9	3.78	0.893	2	**3.00**	**0.020**
Supra span (BUSII)	32	6.91	4	6.25	0.503	5	7.40	0.547	8	7.50	0.384	1	7.00	-
Thurstone's picture memory test	31	19.81	4	19.00	0.730	5	21.20	0.166	10	20.90	0.507	1	20.00	-
Language														
Word fluency	32	**22.84**	5	18.20	0.078	6	**16.83**	**0.011**	10	23.30	0.823	2	17.00	0.110
FAS	30	33.57	2	22.50	0.177	4	30.25	0.557	10	31.40	0.594	1	24.00	-
Executive function														
SRB2	32	18.06	5	17.20	0.621	6	18.50	0.795	9	19.78	0.204	1	24.00	-
Backward Digit span	33	4.06	5	3.20	0.100	6	3.50	0.204	10	3.50	0.125	1	4.00	-
Visuospatial														
SRB3	32	**17.06**	5	**10.80**	**0.007**	5	18.80	0.656	10	17.80	0.794	1	22.00	-
Mental speed														
Psif	32	22.25	5	20.60	0.581	6	19.83	0.365	10	25.30	0.388	1	25.00	-

P[1]= difference in mean score for A+T-N- compared to normal CSF with T-test
P[2]= difference in mean score for A+T-N+ compared to normal CSF with T-test
P[3]= difference in mean score for A-T-N+ compared to normal CSF with T-test
P[4]= difference in mean score for A+T+N+ compared to normal CSF with T-test

Supplementary materials

Supplementary materials Table 1. The characteristics of the 259 participants with CDR0, stratified by pathology.

	No pathology N= 138	**Amyloid pathology N= 60**	**P[1]**	**Total tau pathology N=87**	**P[2]**	**Phospho tau pathology N=18**	**P[3]**
Age mean (SD) y	70.54 (0.24)	70.56 (0.23)	0.598	70.54 (0.29)	0.947	70.53 (0.26)	0.896
MMSE score mean (SD)	29.28(0.90)	29.20 (0.89)	0.555	29.16 (1.07)	0.371	28.94 (1.05)	0.145
Education mean (SD) y	13.04 (4.09)	13.00 (3.42)	0.943	12.85 (3.58)	0.719	11.67 (3.23)	0.173
Women n (%)	75 (54.3)	26 (43.3)	0.167	35 (40.2)	**0.041**	9 (50.0)	0.804
Stroke n (%)	5 (3.6)	3 (5.1)	0.698	2 (2.3)	0.710	1 (5.6)	0.527
Any depression n (%)	14 (10.1)	2 (3.3)	0.156	5 (5.7)	0.327	1 (5.6)	1.000
***APOE*ε4**	31 (23.0)	35 (59.3)	**0.000**	37 (43.0)	**0.003**	**12 (66.7)**	**0.000**

P[1] = difference in means between participants without pathology and amyloid pathology
P[2] = difference in means between no pathology and T-tau pathology
P[3] = difference in means between no pathology and P-tau pathology

Supplementary materials Table 2. The characteristics of the 57 participants with CDR=0.5, stratified by pathology.

	No pathology N= 34	**Amyloid pathology N= 13**	**P[1]**	**Total tau pathology N=18**	**P[2]**	**Phospho tau pathology N=2**	**P[3]**
Age mean (SD) y	70.56 (0.21)	70.60 (0.19)	0.565	70.57 (0.25)	0.917	70.56 (0.13)	0.995
MMSE score mean (SD)	27.85 (1.59)	27.08 (1.38)	0.130	27.33 (1.18)	0.231	26.00(1.41)	0.119
Education mean (SD) y	11.74 (3.72)	10.08 (3.14)	0.162	11.17 (3.69)	0.602	8.00 (1.41)	0.171
Women n (%)	15 (44.1)	4 (30.8)	0.515	7 (38.9)	0.775	1 (50.0)	1.000
Stroke n (%)	3(8.8)	0(0.0)	0.550	4 (22.2)	0.218	0 (0.0)	1.000
Any depression n (%)	4 (12.1)	2 (15.4)	1.000	4 (22.2)	0.430	1 (50.0)	0.269
***APOE*ε4**	10 (30.3)	11 (84.6)	**0.001**	12 (66.7)	**0.018**	2 (100.0)	0.111

P[1] = difference in means between participants without pathology and amyloid pathology
P[2] = difference in means between no pathology and T-tau pathology
P[3] = difference in means between no pathology and P-tau pathology

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