APOE e4, Subjective Memory Symptoms and Cognitive Decline

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Disclosures

- Research (Site or National PI): Roche, Navidea, Genentech, Avid, vTv Therapeutics, Neuronix, Functional Neuromodulation, Takeda, Roche, Merck,
- Consultant/Advisor: Forum, Biogen, Piramal, Lilly/Avid, FujiRebio, vTv Therapeutics

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Subjective memory complaint predictive value

- A Brazilian study examined 248 subjects. They were asked whether they had memory complaints and underwent a cognitive impairment screening.
- A total of 147 patients presented with subjective memory complaints, and 43 were further classified as demented or "cognitively impaired not demented". Subjective memory complaints presented a sensitivity of 100% and a negative predictive value of 100%. This suggests that subjective memory complaints are an indicator for cognitive impairment screening.

Subjective memory complaints in the elderly: a sign of cognitive impairment? Jacinto AF, Brucki SM, Porto CS, Arruda Martins Md, Nitrini R, - Clinics (Sao Paulo) - March 1, 2014; 69 (3); 194-7

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APOE e4, Subjective Memory Symptoms and Cognitive Decline

- ***SMC and amyloid positivity***
- SMC and contribution of Apo E to risk
- SMC and decline on memory measures
- SMC and prediction of progression

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SMC and Aβ on PET

- A community volunteer sample of 92 healthy older adults, underwent subjective cognitive self-report measures included the Memory Functioning Questionnaire (MFQ), Cognitive Failures Questionnaire, and the Subjective Cognitive Complaint Scale.
- Brain amyloid-β deposition was assessed with (PiB)-PET imaging.
- The MFQ, was associated with global PiB retention (standardized beta = -0.230, p = 0.046, adjusting for age, sex and depressive symptoms).
- Evidence for association between subjective cognition and brain amyloid-β deposition in healthy older adults is demonstrable but measure-specific to the subjective instruments that focus on memory (Snitz 2015)

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SMC and Aβ PET (AIBL)

- The AIBL group recruited 120 subjects which were healthy controls or MCI. 67 (HC = 47,MCI = 20) had Aβ scans available for analysis.
- HCAβ+ acknowledged a progressive memory decline compared to HCAβ-, while Healthy Aβ+ individuals acknowledged progressive memory change, suggesting they are aware of memory changes not yet detectable via neuropsychological measures.
- Qualitative analysis of SMCs can inform the earliest clinical manifestations of Alzheimer's disease. (Buckley, 2015)

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Subjective cognitive concerns, amyloid-β, and neurodegeneration in clinically normal elderly.

- 257 participants underwent PIB PET, FDG-PET , and structural MRI, as well as a battery of neuropsychological measures including several questionnaires regarding SCC.
- Individuals were classified into 4 biomarker groups: biomarker negative (Aβ-/ND-), amyloidosis alone (Aβ+/ND-), amyloidosis plus ND (Aβ+/ND+), and ND alone (Aβ-/ND+).
- There was greater SCC in individuals with Aβ or ND positivity compared to biomarker-negative individuals. In addition, greater SCC predicted Aβ positivity when controlling for ND status.
- Those who were positive on Aβ or ND had the highest report of SCC compared to biomarker-negative individuals. Taken together, results suggest that both Aβ and ND are associated with SCC independent of objective memory performance.
- Amariglio 2015

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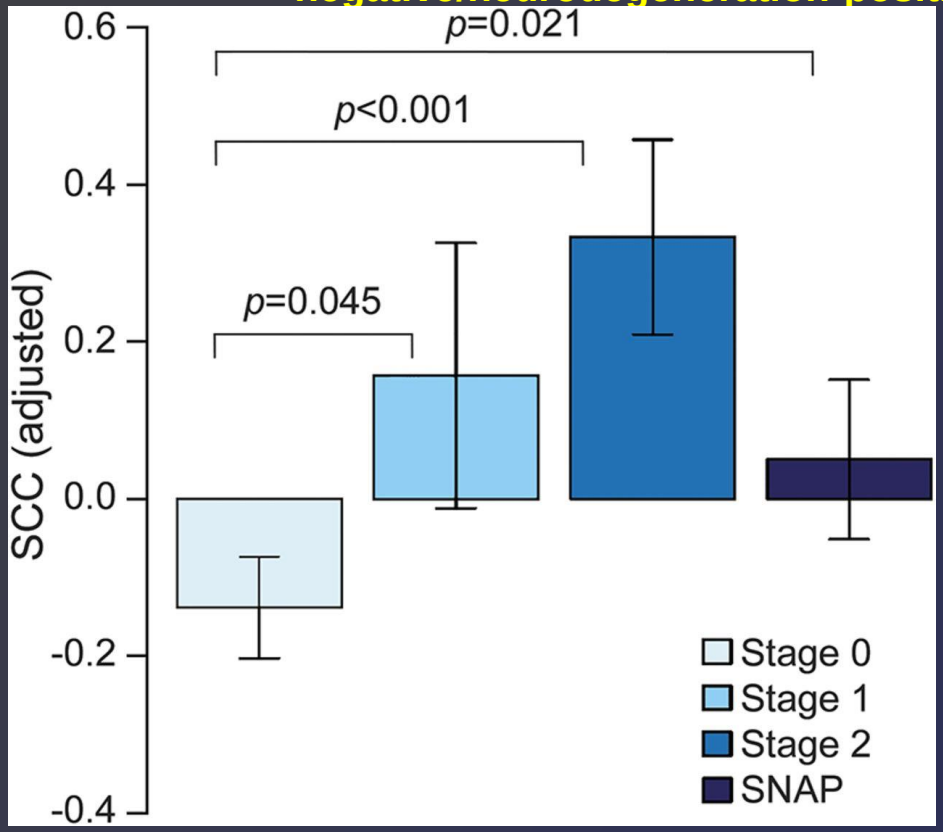
Figure Comparison of subjective cognitive concerns across biomarker stages defined by amyloid-β and neurodegeneration Stage 0: amyloid-β-negative/neurodegeneration-negative; stage 1: amyloid-β-positive/neurodegeneration-negative; stage 2: amyloid-β-positive/neurodegeneration-positive; suspected non-Alzheimer pathology (SNAP): amyloid-β-negative/neurodegeneration-positive.



Rebecca E. Amariglio et al. Neurology 2015;85:56-62

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Amyloid-β related memory decline is not associated with subjective or informant rated cognitive impairment in healthy adults.

- Healthy older adults (n = 289) enrolled in AIBL study were studied at baseline and underwent PIB-PET. At baseline and 18 months assessments, subjective memory impairment was assessed using the Memory Complaint Questionnaire and the Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly. Cognition was measured using the Cogstate Brief Battery.
- At baseline, there were no differences between low and high Aβ groups in subjective or informant-rated cognitive impairment, or cognitive function. Longitudinal analyses showed moderate decline in learning and working memory over the 18 months in the high Aβ group. However there was no change over time in subjective or informant-rated cognitive impairment, depressive and anxiety symptoms, or cognition in either Aβ group.
- Although healthy older adults with high Aβ levels show decline in learning and working memory over 18 months, subjective or informant ratings of cognitive impairment do not change over the same period suggesting subjective cognitive impairment may have limited utility for the very early identification of AD.
- (Hollands 2015)

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Subjective memory concerns and ApoE4

- Cognitively normal, SMC, and eMCI participants from ADNI were divided by APOE ε4 carrier status. Diagnostic and APOE effects were evaluated with emphasis on SMC. Additional analyses in SMC evaluated the effect of the interaction between APOE and [^{18}F]FBP amyloid positivity on CSF biomarkers.
- SMC ε4+ showed greater amyloid deposition than SMC ε4-, but no hypometabolism or medial temporal lobe (MTL) atrophy. SMC ε4+ showed lower amyloid beta 1-42 and higher tau/p-tau than ε4-, which was most abnormal in APOE ε4+ and cerebral amyloid positive SMC.
- SMC APOE ε4+ show abnormal changes in amyloid and tau biomarkers, but no hypometabolism or MTL neurodegeneration, reflecting the at-risk nature of the SMC group and the importance of APOE in mediating this risk.
- (Risacher 2015)

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Subjective Memory Complaints in APOEε4 Carriers are Associated with High Amyloid-β Burden.

- To assess whether APOEε4 genotype, age, SMC, and episodic memory are risk factors for high amyloid-β (Aβ) burden in normal controls (NC), 307 NC (72.7 ± 6.8 years, 53% female, 55% SMC) underwent amyloid PET and APOE genotyping. Logistic regression analyses were performed to determine the association of APOEε4 genotype, age, SMC, and episodic memory with Aβ pathology.
- Stratified analyses showed that odds of SMC for high Aβ burden were increased in specifically APOEε4 carriers (OR=4.58, 95% CI=1.83-11.49) and younger participants (OR=3.73, 95% CI=1.39-10.01).
- Aging, APOEε4 genotype, and SMC were associated with high Aβ burden. SMC were especially indicative of high Aβ burden in younger participants and in APOEε4 carriers.
- (Zwan 2015)

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Trajectory of memory decline AIBL

- The AIBL group followed 333 cognitively healthy older at baseline and 18-, 36-, and 54-month follow-up.
- Latent growth mixture modeling revealed 3 predominant trajectories of memory change: a below average, subtly declining memory trajectory (30.9%); a below average, rapidly declining memory trajectory (3.6%); and an above average, stable memory trajectory (65.5%).
- Compared with the subtly declining memory trajectory group, APOE ε4 carriage (RRR = 8.4), and subjective memory complaints (RRR = 1.2) were associated with a rapidly declining memory trajectory.
- (Pietzrak 2015)

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Subjective cognitive concerns, episodic memory, and the APOE ε4 allele

- MCI participants were drawn from ADNI and dichotomized SMC(-) n = 191, 77 ± 7 years or SMC (+) n = 206, 73 ± 8 years.
- Cognitive outcomes included episodic memory, executive functioning, information processing speed, and language.
- Imaging outcomes included regional lobar volumes (frontal, parietal, temporal, cingulate) and specific medial temporal lobe structures (hippocampal volume, entorhinal cortex thickness, parahippocampal gyrus thickness).
- Linear regressions, adjusting for age, gender, race, education, MMSE score, mood, and apolipoprotein E4 status, found that SMC(+) related to immediate ($\beta = -1.07$, $p < 0.001$) and delayed episodic memory performances assessed on a serial list learning task ($\beta = -1.06$, $p = 0.001$) but no other cognitive measures or neuroimaging markers.
- SMC was unrelated to structural neuroimaging markers of atrophy and measures of information processing speed, executive functioning, or language. SMC related to objective verbal episodic learning performance.
- Giffiord 2015

Subjective cognitive concerns, episodic memory, and the APOE ε4 allele.

- The relationship of self-reported SMC, among APOE ε4 carriers and non-carriers from the Nurses' Health Study was assessed.
- In both groups, increasing subjective cognitive concern score predicted worse baseline memory and faster rates of subsequent memory decline, after adjustment for age, education and depression. The relation with baseline memory appeared statistically stronger in APOE ε4 carriers (P-interaction = 0.03).
- APOE ε4 carriers with self-assessed cognitive concerns appear to have worse memory, and possibly accelerated memory decline.

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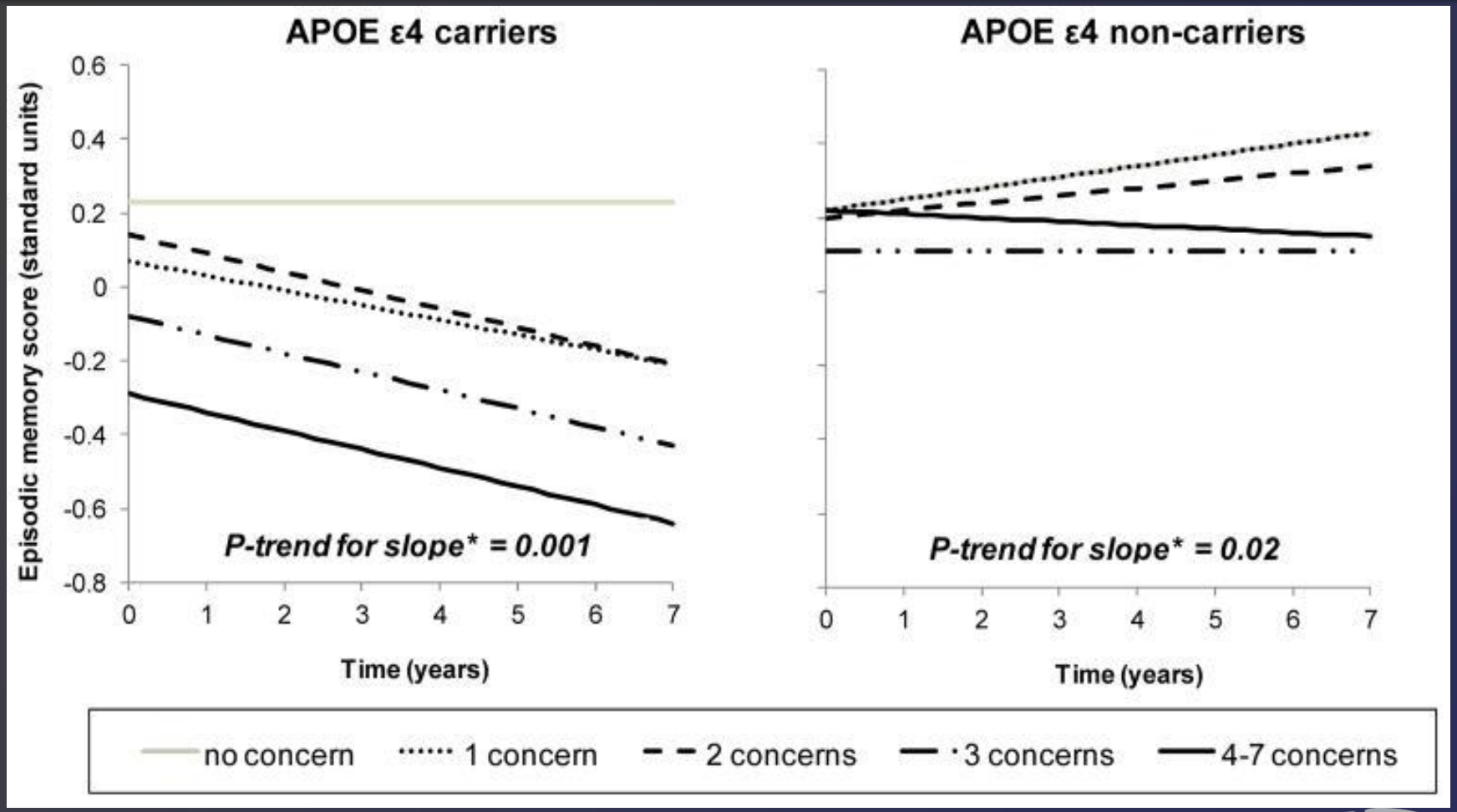

For memory decline, mean differences in slopes of episodic memory (95% CI) for 4 to 7 versus no concern = -0.05 (-0.10, 0.01) standard units in APOE ε4 carriers, and -0.04 (-0.08, -0.01) standard units in non-carriers.

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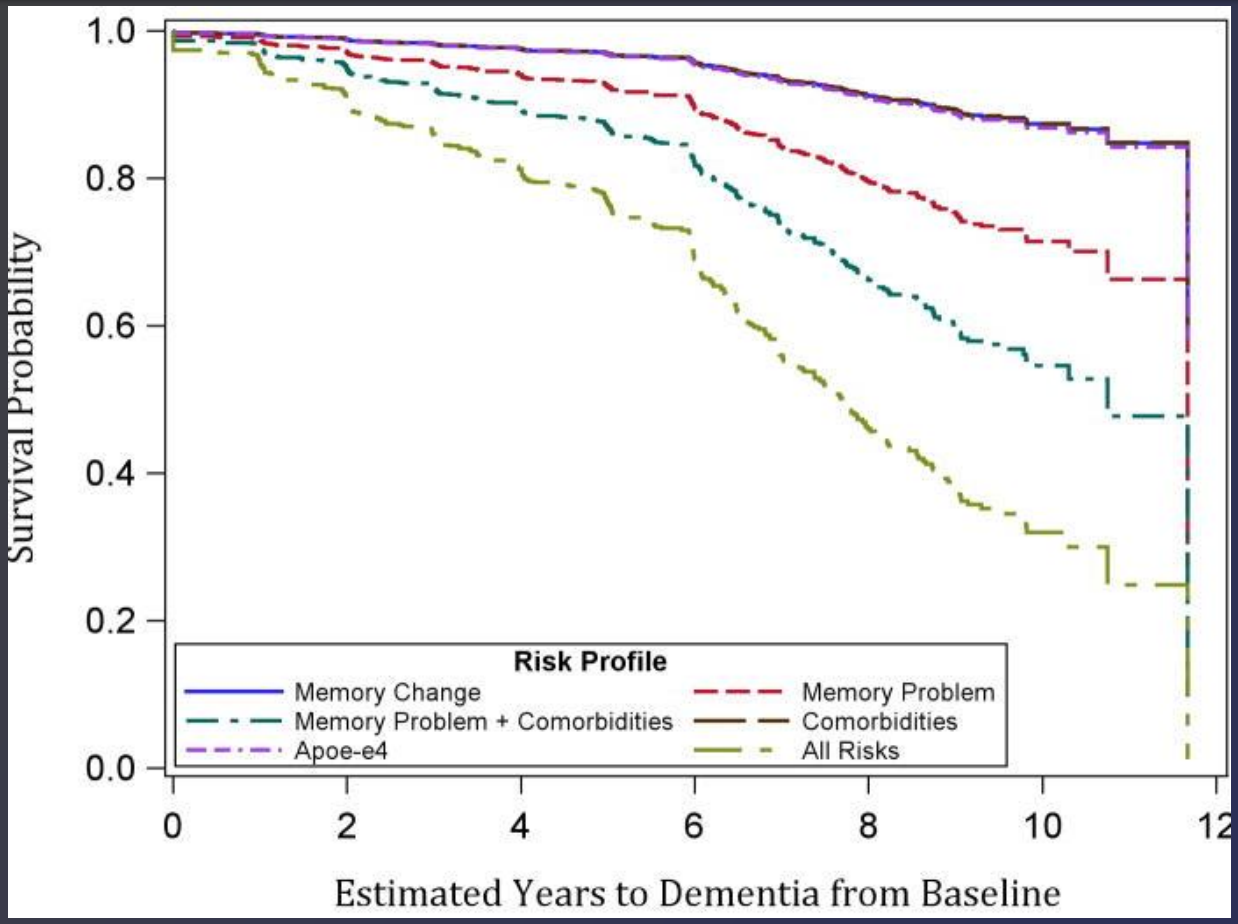
PREADVISE

- PREADVISE enrolled a total of 7,547 nondemented men over the age of 60;
- Participants were interviewed at baseline for SMC. The Memory Impairment Screen (MIS) was administered to each participant at the annual memory screening. Participants who failed the MIS also received a more detailed neurocognitive assessment: an expanded Consortium to Establish a Registry in Alzheimer's Disease (CERADe) neuropsychological battery was used during the RCT, and the modified Telephone Interview for Cognitive Status (TICS-m) was used during the observational study. Participants who failed the second screen were asked to have a memory work-up with a local physician and to share their medical records with PREADVISE.
- After controlling for important risk factors for dementia, Cox proportional hazards regression revealed that men who reported SMC at baseline had an 80% increase in the hazard of incident dementia compared to men who reported no SMC. Men who reported SMC at baseline had almost a 6-fold increase in the hazard of incident dementia compared to men who reported no memory complaint.
- Memory complaints in nondemented older men predicted future dementia. (abner J Prev Alzheimers Dis. 2015 Mar;2(1):11-16. 2015)



Estimated years to dementia diagnosis based on Cox regression results for hypothetical participants with different risk profiles. All hypothetical participants are white, age 70 at baseline, and have 12 years of education. 'Comorbidities' indicates presence of hypertension, diabetes, sleep apnea, and history of head injury.

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SMC and risk of progression

- To investigate whether people with SMC but no objective deficits are at increased risk of developing MCI or dementia
- A meta-analysis of 28 studies, there were 29,723 unique individuals (14,714 with SMC and 15,009 without SMC) (mean 71.6 years) followed on average for 4.8 years through to dementia. The annual conversion rate (ACR) of SMC to dementia was 2.33% (95% CI = 1.93%-2.78%) a relative risk (RR) of 2.07 (95% CI = 1.76-2.44) compared with those without SMC (n = 15,009). From 11 studies the ACR of developing MCI was 6.67% (95% CI = 4.70-8.95%). In long-term studies over 4 years, 14.1% (9.67-19.1%) of people with SMC developed dementia and 26.6% (95% CI = 5.3-39.7) went on to develop MCI..
- Older people with SMC but no objective impairments are twice as likely to develop dementia as individuals without SMC. Approximately 2.3% and 6.6% of older people with SMC will progress to dementia and MCI per year.

- Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B, - Acta Psychiatr Scand - December 1, 2014; 130 (6); 439-51

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Subjective memory complaints, education, and risk of Alzheimer's disease.

- Using the Rotterdam Study, SMC and level of education were assessed in the baseline interview (1990 to 1993). During a mean follow-up of 9.0 years 568 incident Alzheimer's disease patients were identified. The association between SMC and risk of dementia by means of Cox proportional hazard models was estimated.
- The risk of Alzheimer's disease associated with subjective memory complaints was higher in highly educated persons (age- and sex-adjusted hazard ratio, 2.33; 95% confidence interval [CI], 1.00-5.49) than in persons with a low education (age- and sex-adjusted hazard ratio, 1.53; 95% CI, 1.15-2.05) (P value for interaction, .02). In highly educated persons without objective cognitive impairment (MMSE score, 29 or 30) the risk of AD was highest (age- and sex-adjusted hazard ratio, 2.98; 95% CI, 1.76-5.02).
- Especially in persons with a high level of education who still perform well on formal cognitive tests, SMC might be an important first sign of imminent AD.

- **van Oijen** M, de Jong FJ, Hofman A, Koudstaal PJ, Breteler MM. Subjective memory complaints, education, and risk of Alzheimer's disease. Alzheimers Dement. **2007** Apr;3(2):92-

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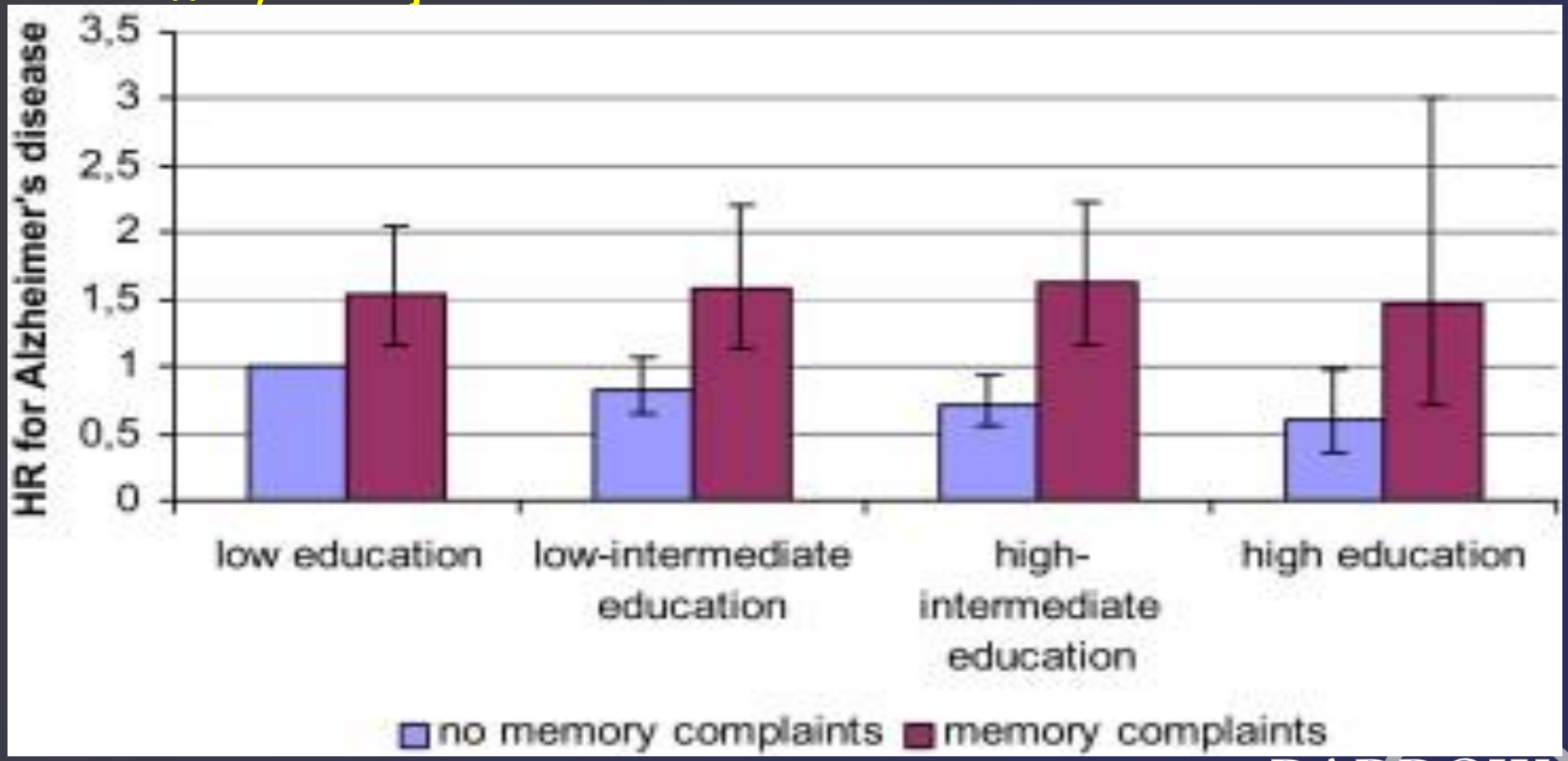
Fig. 1 Association between subjective memory complaints and risk of Alzheimer's disease, stratified on level of education, with persons with low education and no subjective memory complaints as the reference category (R) (HR and 95% CI). Van ojien 2007



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Memory complaints and risk of cognitive impairment after nearly 2 decades among older women

- To investigate the association between subjective memory complaints (SMCs) and long-term risk of cognitive impairment 1,107 NC subjects were followed for 2 decades. SMCs were assessed shortly after baseline and repeatedly over time with the yes/no question, "Do you feel you have more problems with memory than most?"
- Cognitive status 18 years later (normal or impaired with mild cognitive impairment or dementia) was determined by an expert panel. Using logistic regression, the association between SMCs over time and risk of cognitive impairment, adjusting for demographics, baseline cognition, and characteristics that differed between those with and without SMCs was investigated.
- At baseline, 8.0% of participants (n = 89) endorsed SMCs. Baseline SMCs were associated with increased risk of cognitive impairment 18 years later (adjusted odds ratio [OR] = 1.7, 95% confidence interval 1.1-2.8. The association between SMCs and cognitive impairment was greatest at the last SMC assessment time point (18 years before diagnosis: adjusted OR = 1.7 [1.1-2.9]; 14 years before diagnosis: adjusted OR = 1.6 [0.9-2.7]; 10 years before diagnosis: adjusted OR = 1.9 [1.1-3.1]; 4 years before diagnosis: adjusted OR = 3.0 [1.8-5.0]).
- SMCs are associated with cognitive impairment nearly 2 decades later among older women.

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Neurology Volume 85(21):1852-1858; November 24, 2015

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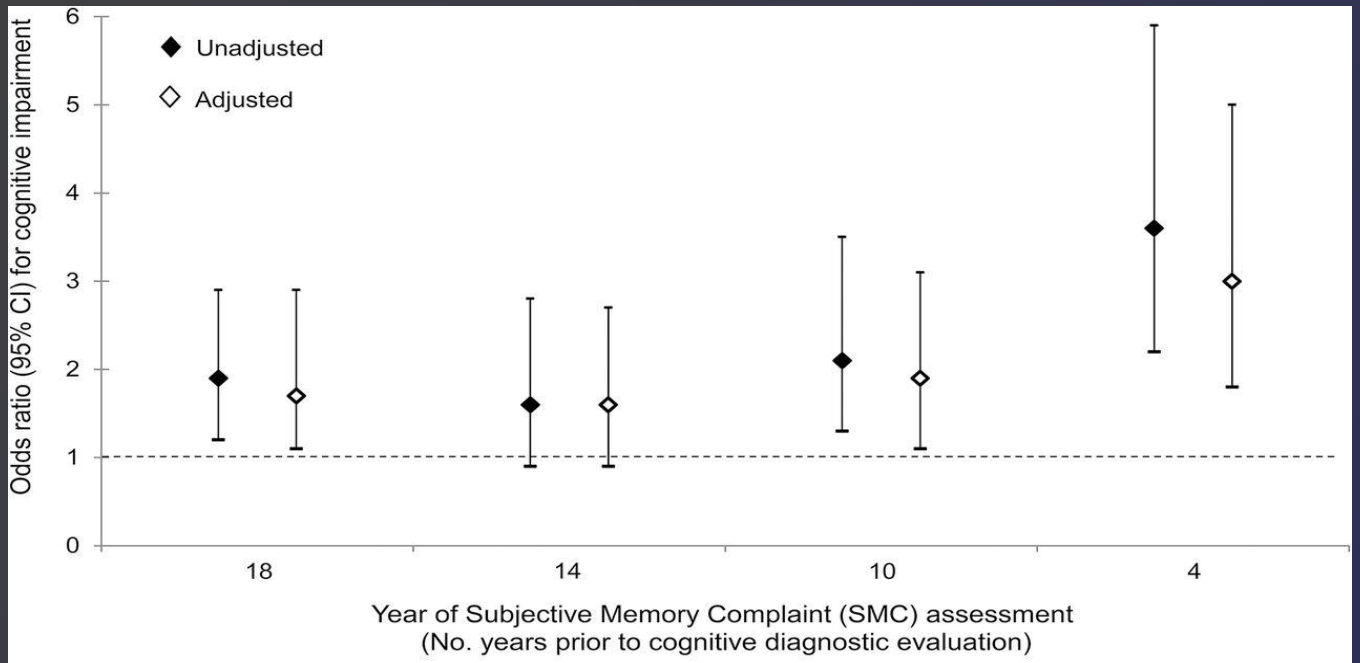
Figure SMCs at varying time points before the diagnostic evaluation and risk of cognitive impairment



Additional details by timepoint of SMC assessment:

	18 years before	14 years before	10 years before	4 years before
N	1025	990	977	943
% of participants with SMC	8.2%	5.6%	7.3%	8.3%
% with cognitive impairment at diagnostic evaluation	No SMC: 37.2% SMC: 52.4%	No SMC: 37.7% SMC: 49.1%	No SMC: 36.2% SMC: 54.9%	No SMC: 34.1% SMC: 65.4%

Allison R. Kaup et al. Neurology 2015;85:1852-1858

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Other studies do not find SMC as an increased risk for dementia

- The purpose of this longitudinal study was to examine the prognostic value of SMC in 156 cognitively intact community-dwelling older adults with a mean age of 83 years.
- Participants were assessed for subjective memory complaints, cognitive performance, functional status, and mood at annual evaluations with a mean follow-up of 4.5 years.
- Subjective memory complaint at entry (n=24) was not associated with impaired memory performance and did not predict memory decline or progression to incipient dementia. Memory complaints were inconsistent across examinations for 62% of participants who reported memory problems.
- (Howieson 2015)

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The source of cognitive complaints predicts diagnostic conversion differentially among non-demented older adults.

- This study was to compare whether different sources of SMC (i.e., subjective and informant) to predict diagnostic conversion in non-demented older adults.
- Participants from NACC had a baseline diagnosis of NC; n = 4414; mean age, 73 ± 8 years; or MCI; n = 1843; mean age, 74 ± 8 years. Multinomial logistic regression related baseline cognitive complaint (no complaint, self only, informant only, or both self and informant) to diagnostic outcome (reversion, stable, or conversion).
- Among NC participants, self complaint only (odds ratio [OR], 2.1; 99% confidence interval (CI),1.5-2.9; P < .001), informant complaint only (OR, 2.2; 99% CI, 1.2-3.9; P < .001), and both self and informant complaint (OR, 4.2; 99% CI, 2.9-6.0; P < .001) were associated with diagnostic conversion compared with no complaint.
- Cognitive complaints are related to conversion among nondemented older adults. Complaint from both (i.e. mutual complaint) sources was most predictive of diagnostic outcome, followed by informant complaint,.

- Gifford 2014Alzheimers Dement. 2014 May;10(3):319-2

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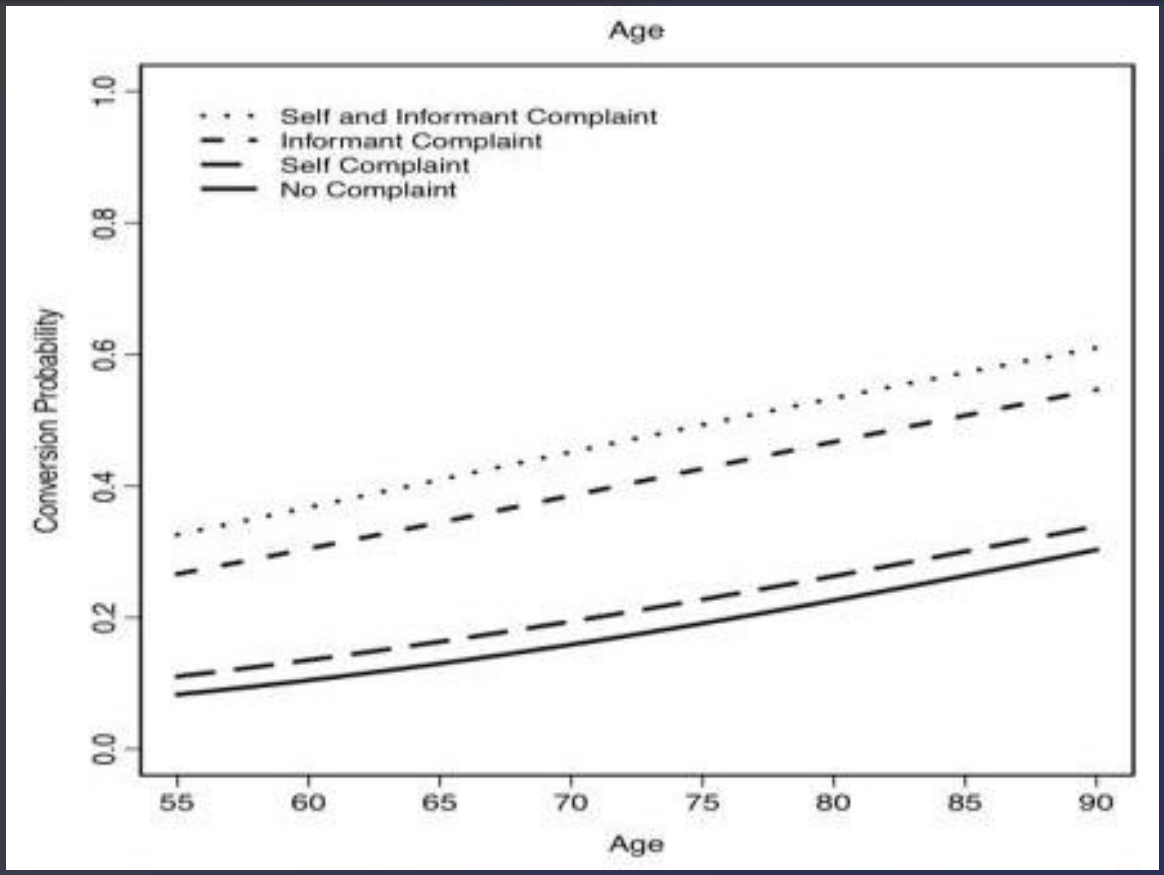

Figure 2b reflects the likelihood of conversion in individuals with MCI as compared to remaining diagnostically stable

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SMC and AD neuropathology

- **531 subjects** cognitively intact were asked annually if they perceived changes in memory since their last visit. The association between SMCs and Alzheimer-type neuropathology was assessed from autopsies (n = 243).
- SMCs were reported by more than half (55.7%) of the cohort, and were associated with increased risk of impairment (unadjusted odds ratio = 2.8, $p < 0.0001$). Multistate modeling showed that SMC reporters with an *APOE* ε4 allele had double the odds of impairment (adjusted odds ratio = 2.2, $p = 0.036$). Among participants (n = 176) who died without a diagnosed clinical impairment, SMCs were associated with elevated neuritic amyloid plaques in the neocortex and medial temporal lobe.
- SMC reporters are at a higher risk of future cognitive impairment and have higher levels of Alzheimer-type brain pathology.
- (Kryscio et al 2014)

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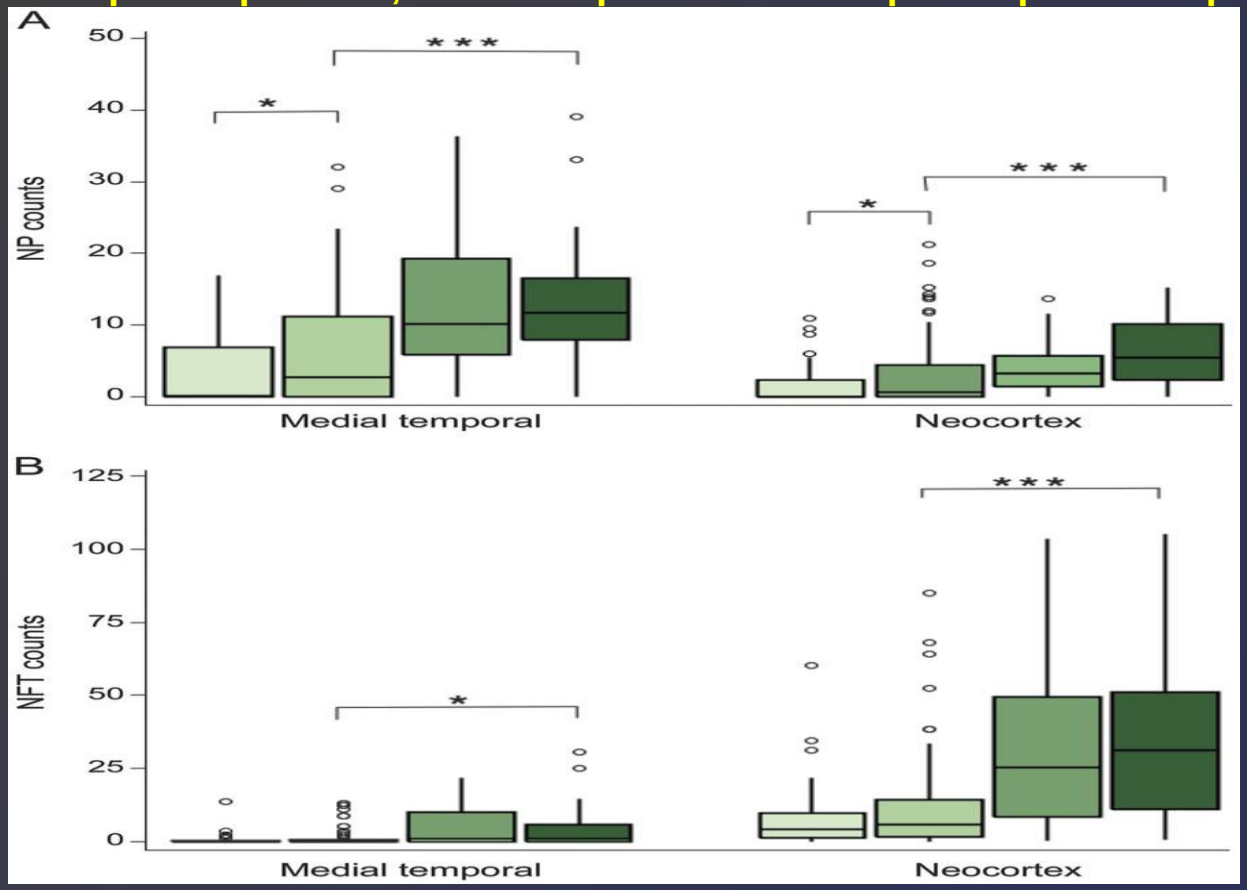
Figure 2 Boxplots of neuritic plaque counts and neurofibrillary tangle counts in 2 brain regions. The boxplots provide neuritic plaque (NP) (A) and neurofibrillary tangle (NFT) (B) counts for each of 4 groups (in order and shaded light to dark): subjective memory complaint (SMC) negative and impaired negative; SMC positive and impaired negative; SMC negative and impaired positive; and SMC positive and impaired positive. *p < 0.05, ***p < 0.001.



Richard J. Kryscio et al. Neurology 2014;83:1359-1365

Conclusions

- SMC is associated with increased risk of progression
- SMC is associated with higher amyloid burden on PET
- ApoE4 carrier status influences the effect of SMC on burden and progression
- SMC associated with neuropathology of AD

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