

# Self-reported Memory Complaints: Implications from a Longitudinal Cohort with Autopsies

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# Self-reported memory complaints

## Implications from a longitudinal cohort with autopsies



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### ABSTRACT

**Objective:** We assessed salience of subjective memory complaints (SMCs) by older individuals as a predictor of subsequent cognitive impairment while accounting for risk factors and eventual neuropathologies.

**Methods:** Subjects (n = 531) enrolled while cognitively intact at the University of Kentucky were asked annually if they perceived changes in memory since their last visit. A multistate model estimated when transition to impairment occurred while adjusting for intervening death. Risk factors affecting the timing and probability of an impairment were identified. The association between SMCs and Alzheimer-type neuropathology was assessed from autopsies (n = 243).

**Results:** 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,  $p < 0.0001$ ). Mild cognitive impairment (dementia) occurred 9.2 (12.1) years after SMC. Multistate modeling showed that SMC reporters with an APOE  $\epsilon 4$  allele had double the odds of impairment (adjusted odds ratio = 2.2,  $p = 0.036$ ). SMC smokers took less time to transition to mild cognitive impairment, while SMC hormone-replaced women took longer to transition directly to dementia. 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.

**Conclusion:** SMC reporters are at a higher risk of future cognitive impairment and have higher levels of Alzheimer-type brain pathology even when impairment does not occur. As potential harbingers of future cognitive decline, physicians should query and monitor SMCs from their older patients. *Neurology*® 2014;83:1359-1365

# Motivation

- \* The meaning of SMCs among older adults without a diagnosis of cognitive impairment (MCI or dementia) is not clear
  - \* Risk of transition is higher overall, but many never progress beyond the complaint
- \* The relationship between SMCs and neuropathology has not been well studied
  - \* A number of studies have evaluated the relationship between SMCs and neuroimaging & CSF biomarkers

# Outline

- \* Background
- \* Methods
  - \* Subjective memory complaints
  - \* Semi-Markov models
- \* Results
- \* Conclusions & future directions

# Background

- \* Subjective memory complaints (SMCs) are self-identified deficits in memory
  - \*  $\pm$  objective deficits,  $\pm$  clinical diagnosis
- \* SMCs are common among adults age 60+
  - \* Nurses Health Study – 56.4%
  - \* PREADVISE – 22%

# Participants

- \* Enrolled in UK ADC longitudinal 'control' cohort (BRAiNS) prior to 2005
- \* Age 60+ at baseline & cognitively intact
- \* At least two study assessments
- \* APOE genotype known

# Assessments

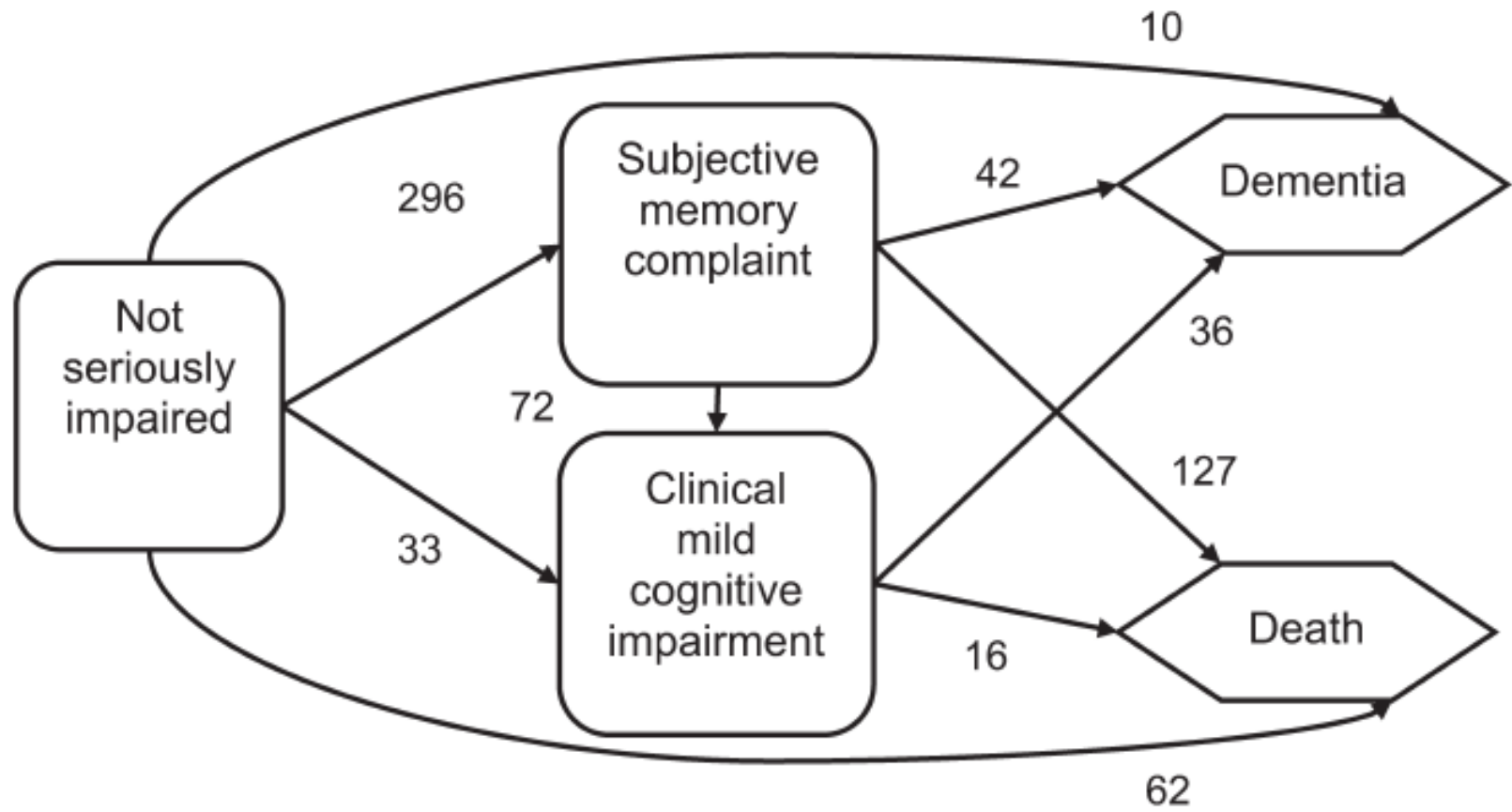
- \* Baseline interview
  - \* Demographics
  - \* Past medical history & current medications
- \* Annual cognitive assessments
  - \* “Have you noticed any changes in your memory?”
  - \* Measures of memory, language, executive, and visuospatial function

# Statistical Analysis

- \* Results from annual assessments were used to classify participants into 4 mutually exclusive cognitive states at each study visit
  - \* Not seriously impaired (intact cognition)
  - \* Subjective memory complaint
  - \* Clinical diagnosis of MCI
  - \* Clinical diagnosis of dementia
- \* A 5<sup>th</sup> state was created for participants who died without becoming demented



**Figure 1** Flow diagram and frequency of transitions among states



# Semi-Markov Model

- \* Semi-Markov models can be used to describe how participants move through the states over time
- \* Each transition involves two quantities
  - \* The probability of making the transition
  - \* The time required for the transition to occur

# Semi-Markov Assumptions

- \* Movement through the states is uni-directional
- \* Probability of making a future transition depends on the time spent in the current state
  - \* e.g., the more time you spend in the MCI state, the less likely you are to transition to dementia at the next assessment
- \* Exact timing is assumed for transitions to SMC and death, all other transitions are interval censored

# Semi-Markov Implementation

- \* A polytomous logistic regression model determines the probability of making a transition
- \* Time spent in each state follows a Weibull distribution

See Kryscio et al. Adjusting for mortality when identifying risk factors for transitions to mild cognitive impairment and dementia. *JAD* 2013;35:823-32.

# Results

- \* Participants were assessed  $10.3 \pm 4.1$  times
- \* SMCs were reported by 55.7% of the cohort
- \* SMCs increased odds of a later diagnosis of either MCI/dementia: OR = 2.8,  $p < 0.0001$

**Table 1** Baseline characteristics of the cohort  
(n = 531)

Baseline characteristic	Summary
Age, y	73.2 ± 7.4
Years of education	16.0 ± 2.4
Low education (<13 y)	11.7
Female	63.1
APOE ε4 carrier	30.3
Family history of dementia	40.3
Ever smoker	52.7
Former smoker	43.5
Baseline smoker	9.2
Type II diabetes	8.3
Body mass index >25 kg/m <sup>2</sup>	42.7
High blood pressure	36.5
Hormone replacement therapy (% all subjects)	18.6

Results presented are mean ± SD or percent.

# Risk Factors for Transition

**Table 2** ORs for transition to a state vs dying for significant baseline risk factors

From	To	Baseline risk factor	OR (95% CI)
NSI	MCI	Current smoker	0.21 (0.05-0.98)
		Female	0.29 (0.15-0.57)
		High blood pressure	8.4 (2.2-32.2)
NSI	SMC	Diabetes	0.35 (0.17-0.72)
		Current smoker	0.25 (0.12-0.52)
MCI	Dementia	High blood pressure	0.28 (0.09-0.86)
		Family history of dementia	3.3 (1.9-10.0)
SMC	MCI	APOE $\epsilon$ 4 carrier	2.2 (1.2-4.1)
SMC	Dementia	APOE $\epsilon$ 4 carrier	2.2 (1.1-4.6)
		High blood pressure	3.0 (1.2-7.5)
		Female	2.6 (1.1-5.8)

Abbreviations: CI = confidence interval; MCI = mild cognitive impairment; NSI = no serious impairment; OR = odds ratio; SMC = subjective memory complaint.

# Key Results for Holding Times

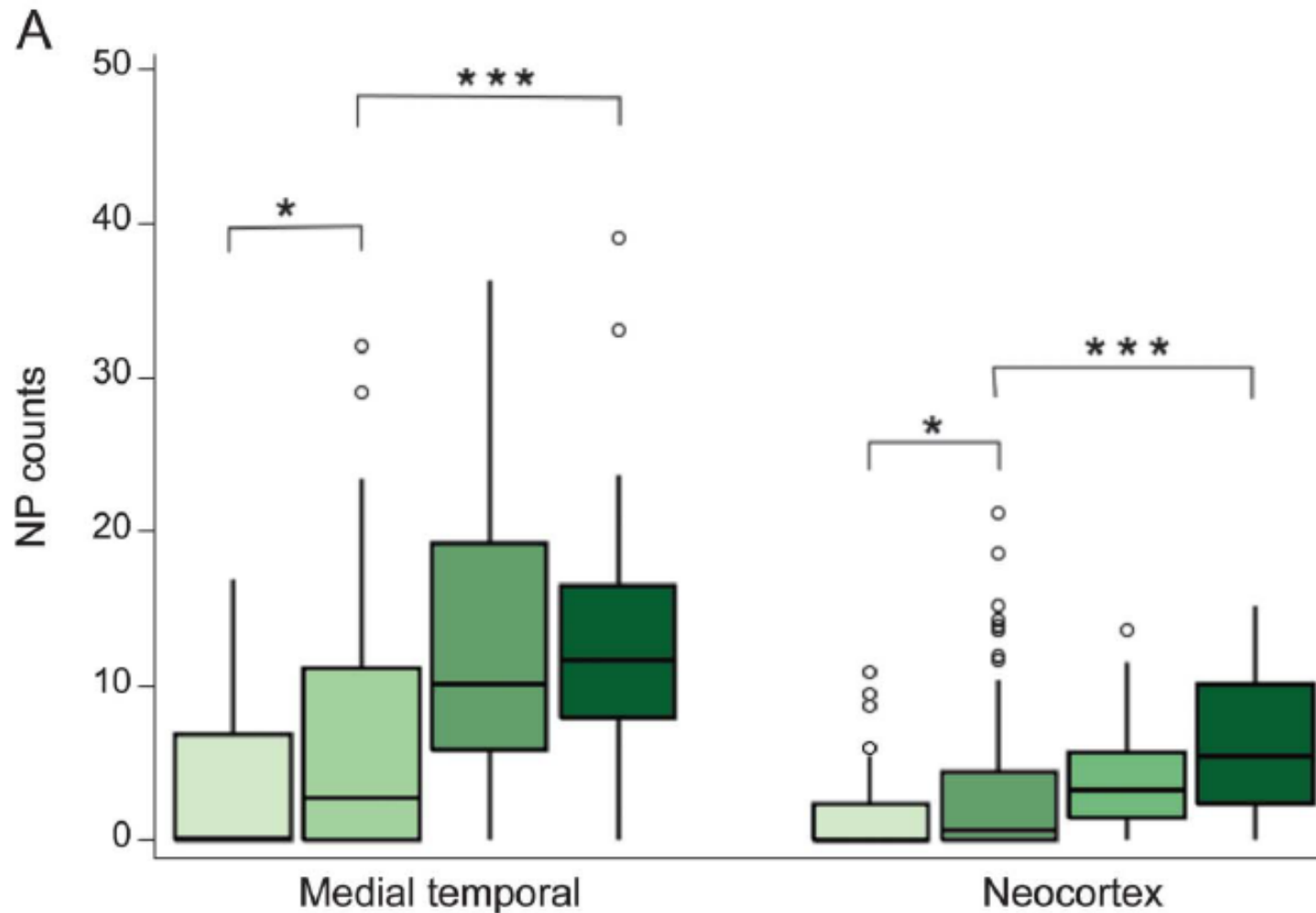
- \* In this cohort,
  - \* MCI was diagnosed ~9.2 years after the first SMC
    - \* MCI → Dementia (~2.9 years)
    - \* MCI → Death w/o dementia (~6.0 years)
- \* Holding times were affected by risk factors
  - \* For former smokers, time to MCI from SMC was reduced to ~6.4 years



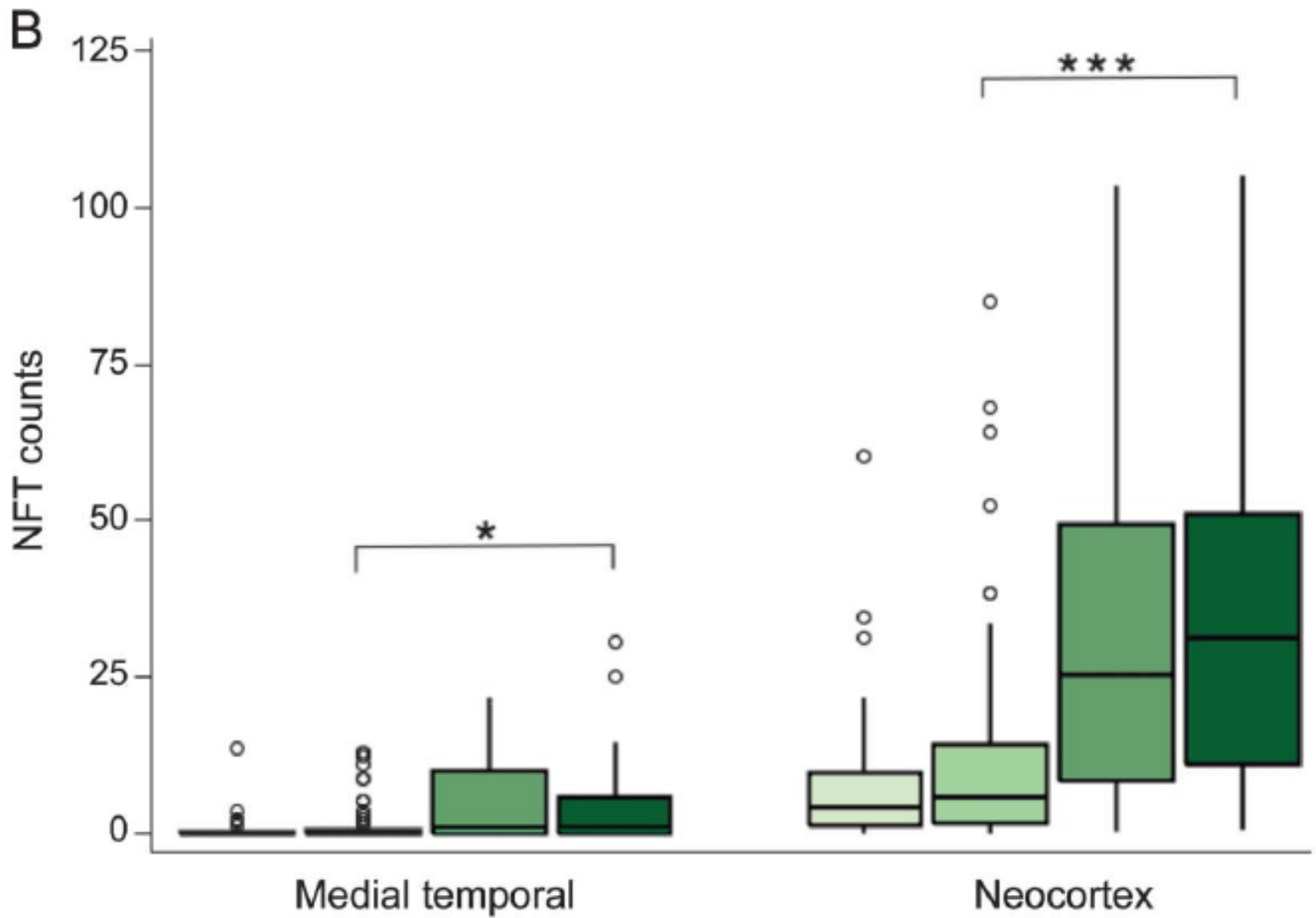
# SMCs and neuropathology

- \* We wanted to know what the AD-type neuropathology of these participants looked like based on their history of SMC and diagnosed cognitive impairment (MCI or dementia)
- \* Four groups:
  - \* SMC no, diagnosed impairment no (n=56)
  - \* SMC yes, diagnosed impairment no (n=120)
  - \* SMC no, diagnosed impairment yes (n=17)
  - \* SMC yes, diagnosed impairment yes (n=50)

**Figure 2** Boxplots of neuritic plaque counts and neurofibrillary tangle counts in 2 brain regions



From lightest to darkest: SMC -/Dx -, SMC +/Dx-, SMC-/Dx+, SMC+/Dx+



From lightest to darkest: SMC -/Dx -, SMC +/Dx-, SMC-/Dx+, SMC+/Dx+

# Summary & Conclusions

- \* SMCs are common among older adults, and many complaints do not progress to clinical impairment
- \* SMCs that do progress to clinical impairment may take many years to do so
- \* Both risk and timing of transitions were affected by risk factors
- \* Importantly, persons with SMCs that did not progress still showed elevated AD-type pathology relative to those who did not complain

# Future Directions

- \* SMCs and cognitive trajectories
- \* SMCs and neuropathology
  - \* Collaborative R01 (SMART study)

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