

**A population-based longitudinal study  
of cognitive functioning  
in the menopausal transition  
(Studies of Women's Health Across the Nation - SWAN)**

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# Joint work with

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- The women and staff of the SWAN study in Chicago
  - Sponsored by: NIA, NINR, OWHR, NCCAM
- Meyer et al. A population-based longitudinal study of cognitive functioning in the menopausal transition. *Neurology* 2003;61:801-806.

# Overview

- Background
- Hypothesis
- Methods
- Results
- Comments
- Implications for further studies

# Background

- Reported forgetfulness during the menopausal transition

# Symptom items in cross-sectional interview

I am going to read you a list of common problems that affect us from time to time in our daily lives. Please answer yes or no for each problem. **Thinking back over the past two weeks, have you experienced:**

difficulty sleeping

night sweats

stiffness or soreness in joints, neck, or shoulders

headaches

hot flushes or flashes

**forgetfulness**

feeling tense or nervous

feeling blue or depressed

vaginal dryness

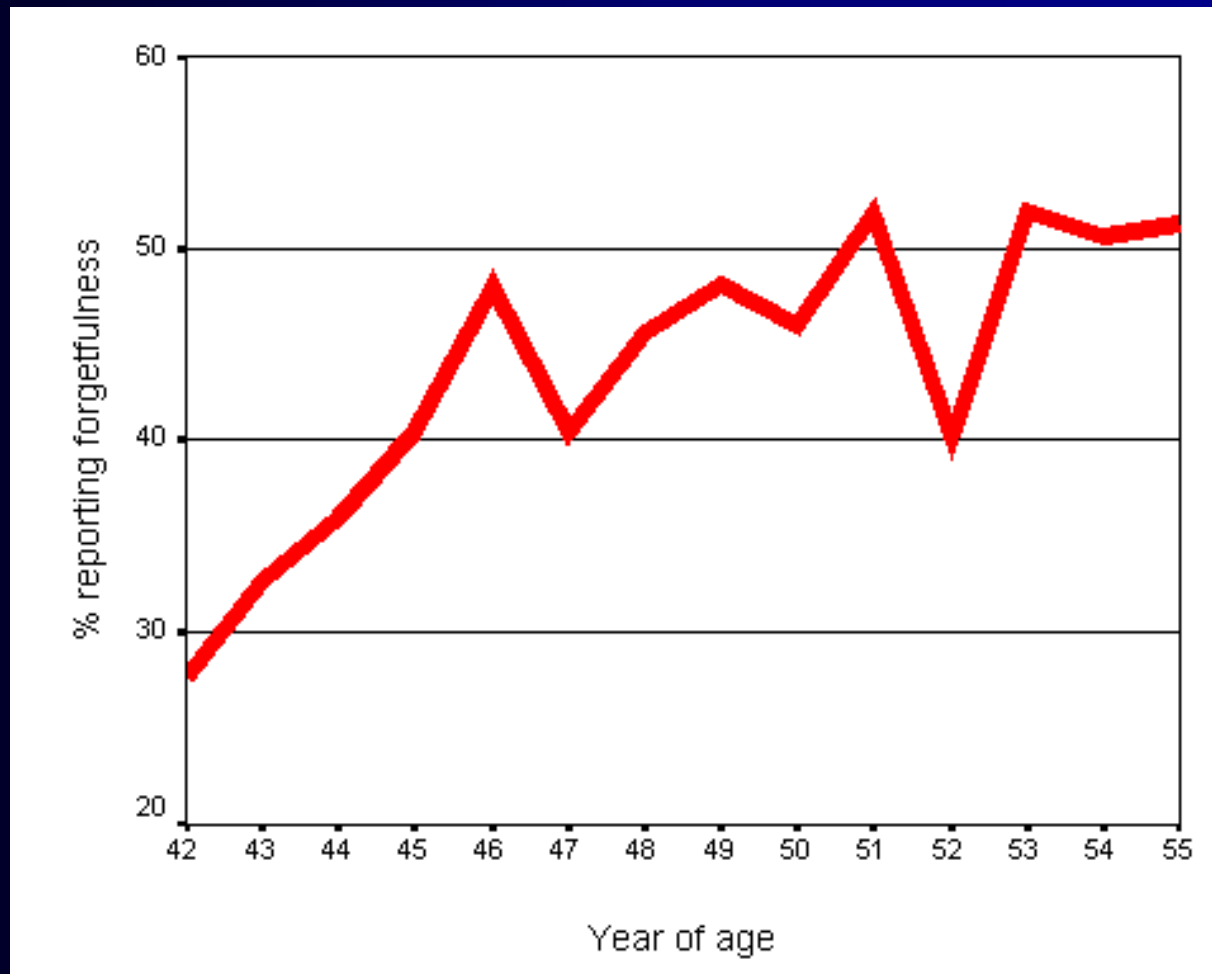
irritability or grouchiness heart pounding or racing

leaking urine

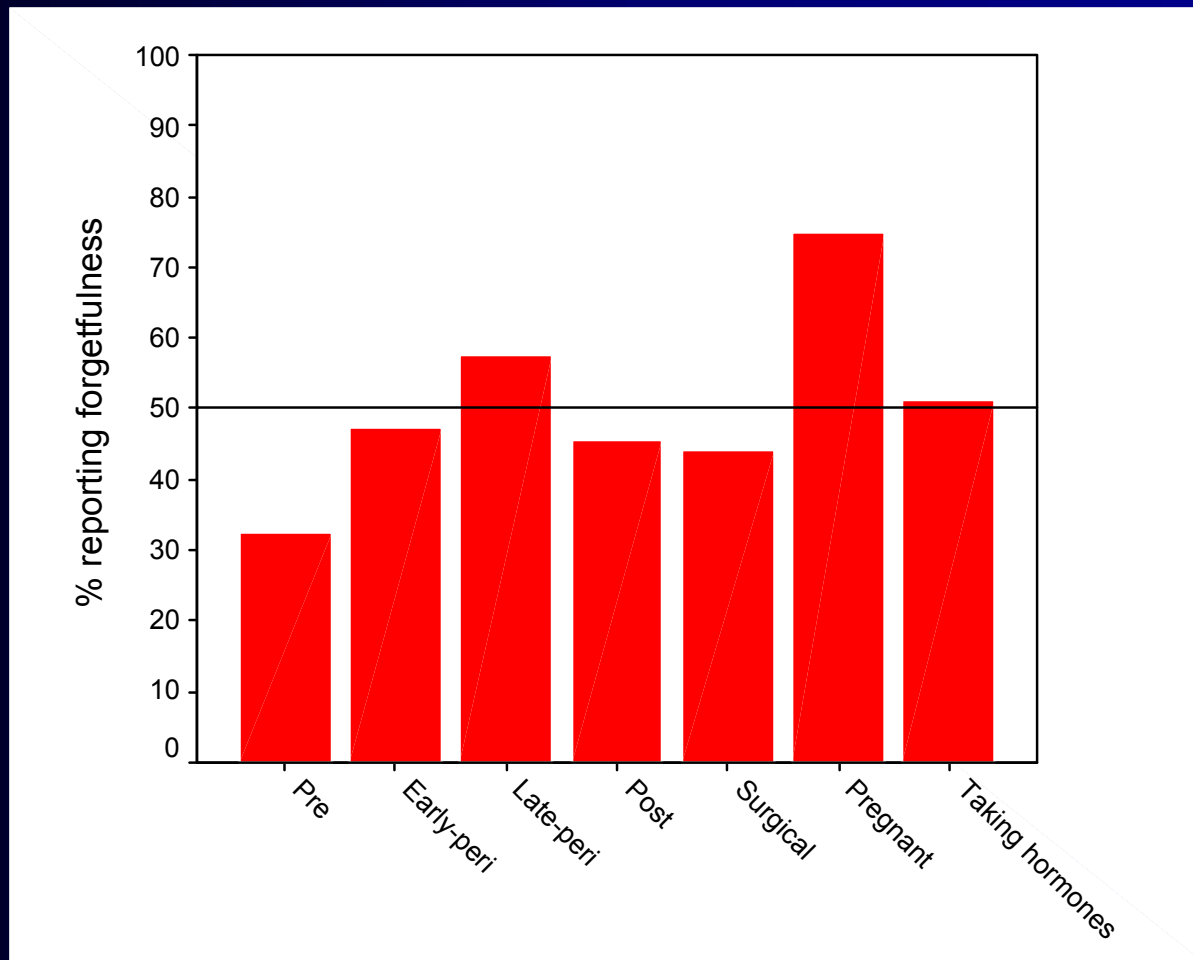
# Frequently reported symptoms

58%	Irritability or grouchiness
58%	Stiffness or soreness
56%	Tense or nervous
52%	Headaches
44%	<b>Forgetfulness</b>
44%	Blue or depressed
41%	Difficulty sleeping
31%	Hot flashes or flushes
27%	Night sweats
21%	Leaking urine
20%	Heart pounding or racing
15%	Vaginal dryness

# Percent reporting forgetfulness by year of age (n = 16,029)



# Percent reporting forgetfulness by menopausal status (n = 15,669)





# Background

- Reported forgetfulness during the menopausal transition
- Anxiety follows forgetfulness

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# Hypothesis

- We hypothesized that *progress through the menopausal transition* is associated with a decline in cognitive performance, after adjustment for ethnicity and baseline age, educational level, family income, and self-perceived health.
- Progress:
  - chronological aging
  - change in menopausal status

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# Methods

- Study design
- Sample
- Measures
- Statistical analysis

# The SWAN (Chicago) Study

1. Population-based
2. Longitudinal
3. Ethnic groups with overlapping demographics
4. Use of two standard cognitive measures
5. A large amount of additional information is being collected.

# Methods

- Study design
- Sample
- Measures
- Statistical analysis

# Sample

- Sample
  - Chicago women (868)*
  - Baseline exams began in January 1996*
  - Cognitive assessments began in October 1996*
  - Cognitive assessments are part of the annual follow-up exams*
- Censoring criteria
  - Focus: natural transition*
  - Pregnancy, Hysterectomy, Hormone use*



# Methods

- Study design
- Sample
- Measures
- Statistical analysis

# Measures

Cognitive measure

- Digit Span Backwards (*working memory*)

# Digit Span Backwards

Item	Response
• 1a. Ready? 5 - 1 .....	_____
• 1b. Here is another: 3 - 8 .....	_____
• 2a. Here is another: 4 - 9 - 3 .....	_____
• 2b. Here is another: 5 - 2 - 6 .....	_____

# Digits Backward in Framingham

Age	8-11	HS	>HS
55-59	3.9	4.2	5.3
60-64	3.8	4.3	4.7
65-69	3.8	4.6	4.5
70-74	3.9	4.1	4.8
75-79	4.0	4.4	4.4
80-84	3.8	4.6	4.4
85-89	3.3	4.3	3.8

*Farmer et al., Neuropsychological Test Performance in Framingham:  
A Descriptive Study, Psychological Reports, 1987: 60:1023-1040*

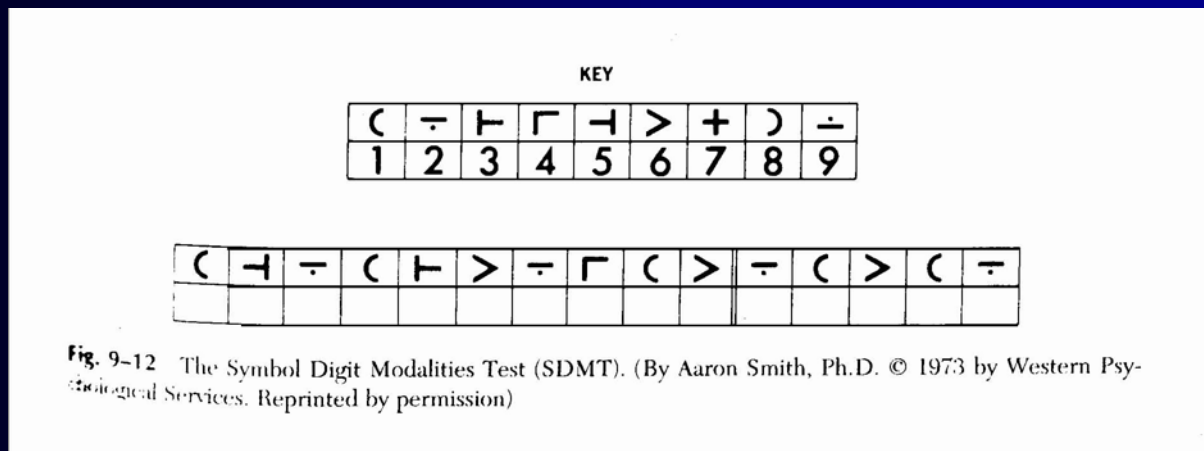
# Methods: Measures

## Cognitive measure

- Digit Span Backwards (*working memory*)
- Symbol Digit Modality Test (*perceptual speed*)

# Symbol Digit Modality

- **Perceptual speed - Test (Smith, 1982)** A participant is given a key showing a set of symbols and the number each represents. The participant is also given a sheet with a number of symbols in rows and asked to verbally identify the number that goes with each symbol, proceeding row by row. The interviewer records the subject's responses. 90 seconds are given to identify as many symbols as possible. The number of correct identifications is the score.



# Methods

- Study design
- Sample
- Measures
- Statistical analysis

# Methods: Statistical analysis

- Growth curves using random effects models  
Laird NM and Ware JH (1982). Random-effects models for longitudinal data. *Biometrics*, 38, 963-74.
- Unadjusted and adjusted models
- **First approach:**
  1. A common aging effect
  2. Change in level associated with change in menopausal status



# Methods: Statistical analysis

- Growth curves using random effects models  
Laird NM and Ware JH (1982). Random-effects models for longitudinal data. *Biometrics*, 38, 963-74.
- Unadjusted and adjusted models
- First approach:
  1. A common aging effect
  2. Change in level associated with change in menopausal status
- **Second approach:**
  1. Different aging effects depending upon menopausal status

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# Cohort characteristics

Variable	With DSB results	Neither DSB nor SDMT results	With SDMT results
	N = 771	N = 65	N = 801
Age	Mean (1Q,3Q) 46 (44, 48)	Mean (1Q,3Q) 47 (45, 49)	Mean (1Q,3Q) 46 (44, 48)
Ethnicity	n (%)	n (%)	n (%)
African-American	362 (47)	40 (62)	377 (47)
Caucasian	409 (53)	25 (38)	424 (53)

## Number of assessments by ethnicity

	Number of assessments					Mean
	1	2	3	4	5	
African-American	87	59	70	110	53	3.0
Caucasian	90	58	87	120	69	3.0

## Number of observed transitions

	Transition	
	Pre-Early	Late-Post
	183 (23%)	122 (15%)
	171 (21%)	

# Cognitive components at first assessment

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	Mean	SD
Working memory DSB	6.8	2.1
Perceptual speed SDMT	58.3	11.1

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Correlation of DSB and SDMT  
at first assessment (n = 767) : *0.33*

# Reminder: The Questions

- Does cognitive function decline...
  - with changes in menopausal status?
  - over time in mid-life women?

Q: Does cognitive function decline...with changes in menopausal status?

## Digit span backwards

Digit span backwards (range 2 - 12)	Estimate <sup>1</sup>	95% Confidence interval	p-value
Menopausal status (compared to premenopausal)			0.36
Early perimenopausal	0.18	(-0.06, 0.42)	
Late perimenopausal	0.03	(-0.40, 0.46)	
Post menopausal	0.26	(-0.15, 0.67)	
Time (items per year)	0.17	(0.10, 0.24)	<0.0001

<sup>1</sup>Adjusted for ethnicity, baseline education, income and self-reported health

Q: Does cognitive function decline...with changes in menopausal status?

## Symbol digit modality test

Symbol digit modality test (range 10 - 104)	Estimate <sup>1</sup>	95% Confidence interval	p-value
Menopausal status (compared to premenopausal)			0.24
Early perimenopausal	-0.12	(-1.14,0.90)	
Late perimenopausal	1.18	(-0.54, 2.90)	
Post menopausal	-0.50	(-2.19, 1.18)	
Time (items per year)	0.36	(0.08, 0.63)	0.002

<sup>1</sup>Adjusted for ethnicity, baseline education, income and self-reported health



Q: Does cognitive function decline...with changes in menopausal status?

## Answer: First approach

- Cognitive performance increases modestly over time in mid-life women.
- There is no indication that cognitive performance changes as a result of progression through the menopausal transition after adjustment for aging.

Q: Does cognitive function decline... at different rates according to menopausal status?

## Results: Second approach - DSB

Menopausal status	Estimate <sup>1</sup> (items per year)	95% Confidence interval	p-value
Premenopausal	0.17	(0.03, 0.30)	0.02
Early perimenopausal	0.19	(0.09, 0.28)	0.0001
Late perimenopausal	0.20	(-0.14, 0.54)	0.25
Post menopausal	0.03	(-0.26, 0.33)	0.82

<sup>1</sup>Adjusted for ethnicity, baseline education, income and self-reported health

Q: Does cognitive function decline... at different rates according to menopausal status?

## Results: Second approach-SDMT

Menopausal status	Estimate <sup>1</sup> (items per year)	95% Confidence interval	p-value
Premenopausal	0.52	( 0.05, 0.98)	0.03
Early perimenopausal	0.34	( 0.01, 0.67)	0.046
Late perimenopausal	1.51	( 0.35, 2.66)	0.01
Post menopausal	-1.13	(-2.11, -0.15)	0.02

<sup>1</sup>Adjusted for ethnicity, baseline education, income and self-reported health

Q: Does cognitive function decline... at different rates according to menopausal status?

## Answer: Second approach

- DSB (Working memory)  
Modest improvement pre- and early-peri.  
Late-peri estimate has same magnitude but is not significant.
- SDMT (Perceptual speed)  
Modest improvement pre-, early-peri and late-peri.  
Modest decrease post-menopausal.

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# Limitations: Menopausal status

- Menopausal status is treated as a categorical variable based on bleeding criteria, with categories:  
Pre, Early-peri, Late-peri, Post
- Most assessments are for subjects in Pre, Early-peri or Late-peri.
- The study is not about women on hormones or post-menopausal women.

# Limitations: Assessments

- We only measured women's performance using two measures of cognitive functioning.

Note: East Boston Memory Test included beginning with Follow-up 04.

- Women may be perceiving changes in cognition that are not reflected in performance differences.

Shaywitz SE, Shaywitz BA, Pugh KR, et al.

Effect of Estrogen on Brain Activation Patterns in Postmenopausal Women  
During Working Memory Tasks.

*JAMA*. April 7, 1999 1999;281(13):1197-1202.

- Objective: To investigate the effects of estrogen on brain activation patterns in post-menopausal women as they performed verbal and nonverbal working memory tasks.
- Intervention: Twenty-one day treatment with conjugated equine estrogens, 1.25 mg/d, randomly crossed over with identical placebo and a 14-day washout between treatments.
- Main outcome measures: Brain activation patterns measured using **functional magnetic resonance imaging** during tasks involving verbal and nonverbal working memory.
- Results: ... **Estrogen did not affect actual performance of the verbal and nonverbal memory tasks.**
- Conclusions: **Estrogen in a therapeutic dosage alters brain activation patterns in post-menopausal women in specific brain regions during the performance of the sorts of memory function that are called upon frequently during any given day. These results suggest that estrogen affects brain organization for memory in postmenopausal women.**



Mitchell ES, Woods NF.

Midlife Women's Attributions about Perceived Memory Changes:  
Observations from the Seattle Midlife Women's Health Study.  
*J Women Health Gen-B.* 2001;10(4):351-362.

- “The types of memory changes related to concentration problems, everyday personal behaviors, and forgetting personal events both current and in the future, such as not remembering the reason for entering a certain room, forgetting the location of an item, or forgetting an appointment or task, may reflect difficulty remembering a sequence of actions or perhaps difficulty suppressing competing stimuli and becoming distracted. Thus, the memory change may not reflect a cognitive problem but, instead, reflect role burden and stress from a life full of multitasking and competing demands.”

# Conclusions

1. There is no evidence of an average decline in working memory or perceptual speed over time in our sample of mid-life women (aged 42-58).
2. There is no evidence of a decline in working memory or perceptual speed associated with progress through the menopausal transition.

# SWAN Implications for further studies in humans

- If there is no global downward trend, are there
  - specific cognitive domains of decline?
  - specific subgroups that are declining?
  - hormonal markers or patterns that track with a decline?