Targeting Mild Behavioral Impairment to Delay or Prevent Dementia

A Precision Medicine Approach

Constantine G. Lyketsos, MD, MHS
Chair of Psychiatry, Johns Hopkins Bayview
Elizabeth Plank Althouse Professor, Johns Hopkins University
kostas@jhmi.edu

11th National Congress of Clinical Psychopharmacology by HACPP
Ioannina, Greece
20 April 2023

JOHNS HOPKINS MEDICINE

Learning objectives

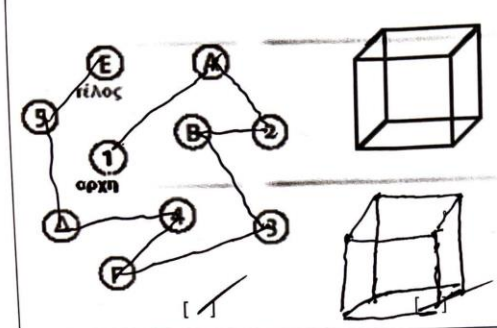
- Propose a novel approach to Precision Medicine
- Overview the MBI construct and its outcomes
- Lay the foundation for an effort to prevent AD dementia by targeting MCI+MBI

Illustrative patient
Mr. MCM

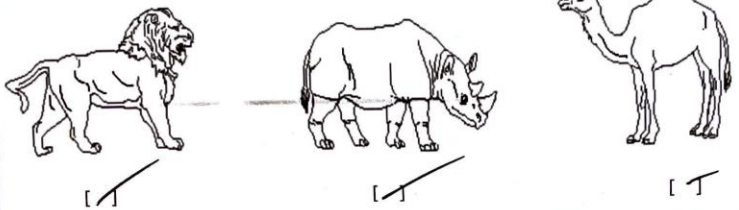
- 83 year old man
- College graduate, retired military
- Excellent health, no meds
- Behavioral changes for 3-4 years: MBI
  - Irritable, moody, seeking attention suspicious of wife, at times verbally aggressive
- Cognitive complaints for 1-2 years: MCI
  - Repeats, less disorganized, easily mixed up
- Treated with escitalopram for ~12mos

ΟΝΟΜΑ: ΜΜ

ΗΛΙΚΙΑ: 83 ΕΚΠΑΙΔΕΥΣΗ: U ΦΥΛΟ: Μ

ΟΠΤΙΚΟΧΩΡΙΚΕΣ/ΕΚΤΕΛΕΣΤΙΚΕΣ **Κύβος αντιγραφή**	ΣΧΕΔΙΟ ΡΟΛΟΓΙΟΥ (11και 10) (3 βαθμοί)	ΒΑΘΜΟΙ
 [ ] [ ]	 [ ] Κύκλος [X] Αριθμοί [ ] Δείκτες	4/5

ΚΑΤΟΝΟΜΑΣΙΑ 3/3



[ ] [ ] [ ]

ΜΝΗΜΗ Διαβάστε τη λίστα με τις λέξεις, το υποκείμενο πρέπει να τις επαναλάβει. Κάντε 2 δοκιμές και μια καθυστερημένη ανάκληση μετά από 5 λεπτά		ΠΡΟΣΩΠΟ	ΒΕΛΟΥΔΟ	ΕΚΚΛΗΣΙΑ	ΜΑΡΓΑΡΙΤΑ	ΚΟΚΚΙΝΟ	όχι βαθμοί
	ΔΟΚΙΜΗ 1	✓	✓	✓	✓	✓	
	ΔΟΚΙΜΗ 2	✓	✓	✓	✓	✓	

ΠΡΟΣΟΧΗ Διαβάστε τη λίστα των ψηφίων(1 ψηφίο/δευτ) Το υποκείμενο θα επαναλάβει με την ίδια σειρά τα εξής: [✓] 2 1 8 5 4 — 2/2

Το υποκείμενο θα επαναλάβει με την ανάποδη σειρά τα εξής: [✓] 7 4 2

Διαβάστε τον κατάλογο των γραμμάτων Το υποκείμενο θα χτυπά το χέρι στο τραπέζι κάθε φορά που ακούει το γράμμα Α Δε δίνονται βαθμοί εάν >2 λάθη 1/1

[ ] Φ Β Α Γ Μ Ν Α Α Ξ Κ Α Β Α Φ Α Κ Δ Ε Α Α Α Ξ Α Ν Ο Φ Α Α Β

Διαδοχική αφαίρεση ανά 7, ξεκινώντας από το 100 [✓] 93 [ ] 86 [✓] 79 [ ] 72 [ ] 65 — 2/3

4-5 σωστές αφαιρέσεις: 3 βαθ., 2-3 σωστές: 2 βαθ., 1 σωστή: 1 βαθ., 0 σωστές: 0 βαθ.

ΓΛΩΣΣΑ Επαναλάβετε: Το μόνο που ξέρω είναι ότι ο Γιάννης είναι αυτός που θα βοηθήσει σήμερα. 11 [ ] — 2/2

Η γάτα κρυβόταν πάντα κάτω από τον καναπέ όταν βρίσκονταν σκυλιά μέσα στο δωμάτιο [ ]

Ροή/ Πείτε όσες περισσότερες λέξεις μπορείτε, σε ένα λεπτό, που να αρχίζουν από Χ IIII 1 [ ] 6 (Ν ≥ 11 λέξεις) — 0/1

ΑΦΑΙΡΕΤΙΚΗ ΣΚΕΨΗ Ομοιότητα μεταξύ π.χ. μπανάνα- πορτοκάλι = φρούτο [✓] τρένο-ποδήλατο [X] ρολόι- χάρακας — 1/2

ΚΑΘΥΣΤΕΡΗΜΕΝΗ ΑΝΑΚΛΗΣΗ	ανάκληση λέξεων ΧΩΡΙΣ ΒΟΗΘΕΙΑ	ΠΡΟΣΩΠΟ [X]	ΒΕΛΟΥΔΟ [X]	ΕΚΚΛΗΣΙΑ [X]	ΜΑΡΓΑΡΙΤΑ [X]	ΚΟΚΚΙΝΟ [X]	βαθμοί μόνο για ανάκληση χωρίς βοήθεια	
Προαιρετικό	βοήθημα κατηγορίας	X	X	✓ 2	X	✓ 2		0/5
	βοήθημα πολλαπλής επιλογής	X	✓ 1		✓ 1			6/15

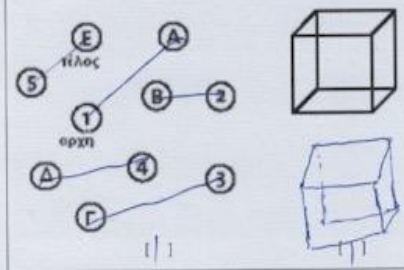
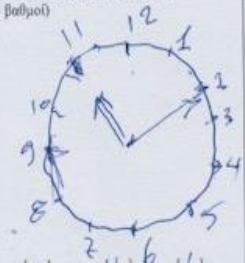
ΠΡΟΣΑΝΑΤΟΛΙΣΜΟΣ [✓] ημ/μηνία [✓] μήνας [✓] έτος [✓] ημέρα [✓] τόπος [✓] πόλη — 6/6

Φυσιολογική επίδοση ≥ 26

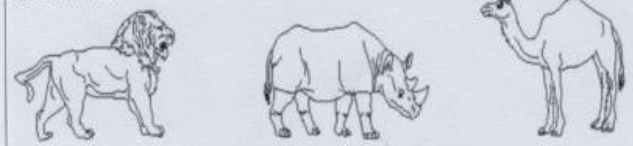
Προσθέστε έναν βαθμό αν ≤ 12 έτη εκπαίδευσης ΣΥΝΟΛΟ 22/30

ΟΝΟΜΑ: ΗΜΕΡΟΜΗΝΙΑ: 23/1/2022

ΗΛΙΚΙΑ: 84 ΕΚΠΑΙΔΕΥΣΗ: ΦΥΛΟ:

ΟΠΤΙΚΟΧΩΡΙΚΕΣ/ΕΚΤΕΛΕΣΤΙΚΕΣ **Κύβος αντιγραφή**	ΣΧΕΔΙΟ ΡΟΛΟΓΙΟΥ (11και 10) (3 βαθμοί)	ΒΑΘΜΟΙ
 [ ] [ ]	 [ ] Κύκλος [ ] Αριθμοί [ ] Δείκτες	5/5

ΚΑΤΟΝΟΜΑΣΙΑ 3/3



[ ] [ ] [ ]

ΜΝΗΜΗ Διαβάστε τη λίστα με τις λέξεις, το υποκείμενο πρέπει να τις επαναλάβει. Κάντε 2 δοκιμές και μια καθυστερημένη ανάκληση μετά από 5 λεπτά		ΠΡΟΣΩΠΟ	ΒΕΛΟΥΔΟ	ΕΚΚΛΗΣΙΑ	ΜΑΡΓΑΡΙΤΑ	ΚΟΚΚΙΝΟ	όχι βαθμοί
	ΔΟΚΙΜΗ 1	✓	✓	✓	✓	✓	
	ΔΟΚΙΜΗ 2						

ΠΡΟΣΟΧΗ Διαβάστε τη λίστα των ψηφίων(1 ψηφίο/δευτ) Το υποκείμενο θα επαναλάβει με την ίδια σειρά τα εξής: [ ] 2 1 8 5 4 — 1/2

Το υποκείμενο θα επαναλάβει με την ανάποδη σειρά τα εξής: [✓] 7 4 2

Διαβάστε τον κατάλογο των γραμμάτων Το υποκείμενο θα χτυπά το χέρι στο τραπέζι κάθε φορά που ακούει το γράμμα Α Δε δίνονται βαθμοί εάν >2 λάθη 1/1

[✓] Φ Β Α Γ Μ Ν Α Α Ξ Κ Α Β Α Φ Α Κ Δ Ε Α Α Α Ξ Α Ν Ο Φ Α Α Β

Διαδοχική αφαίρεση ανά 7, ξεκινώντας από το 100 [✓] 93 [✓] 86 [✓] 79 [✓] 72 [✓] 65 — 3/3

4-5 σωστές αφαιρέσεις: 3 βαθ., 2-3 σωστές: 2 βαθ., 1 σωστή: 1 βαθ., 0 σωστές: 0 βαθ.

ΓΛΩΣΣΑ Επαναλάβετε: Το μόνο που ξέρω είναι ότι ο Γιάννης είναι αυτός που θα βοηθήσει σήμερα. [ ] — 1/2

Η γάτα κρυβόταν πάντα κάτω από τον καναπέ όταν βρίσκονταν σκυλιά μέσα στο δωμάτιο

Ροή/ Πείτε όσες περισσότερες λέξεις μπορείτε, σε ένα λεπτό, που να αρχίζουν από Χ [✓] ____ (Ν ≥ 11 λέξεις) — 1/1

ΑΦΑΙΡΕΤΙΚΗ ΣΚΕΨΗ Ομοιότητα μεταξύ π.χ. μπανάνα- πορτοκάλι = φρούτο [✓] τρένο-ποδήλατο [✓] ρολόι- χάρακας — 2/2

ΚΑΘΥΣΤΕΡΗΜΕΝΗ ΑΝΑΚΛΗΣΗ	ανάκληση λέξεων ΧΩΡΙΣ ΒΟΗΘΕΙΑ	ΠΡΟΣΩΠΟ [ ]	ΒΕΛΟΥΔΟ [✓]	ΕΚΚΛΗΣΙΑ [✓]	ΜΑΡΓΑΡΙΤΑ [✓]	ΚΟΚΚΙΝΟ [ ]	βαθμοί μόνο για ανάκληση χωρίς βοήθεια	
Προαιρετικό	βοήθημα κατηγορίας					/		3/5
	βοήθημα πολλαπλής επιλογής	/						

ΠΡΟΣΑΝΑΤΟΛΙΣΜΟΣ [ ] ημ/μηνία [✓] μήνας [✓] έτος [✓] ημέρα [✓] τόπος [✓] πόλη — 5/6

Φυσιολογική επίδοση ≥ 26 +1 μονάδα

Προσθέστε έναν βαθμό αν ≤ 12 έτη εκπαίδευσης ΣΥΝΟΛΟ 25/30

Funding Sources: Thank you!

R01 AG052510

R01 AG031348

P30 AG066507

This work is supported by the Richman Family Precision Medicine Center of Excellence in Alzheimer's Disease including significant contributions from the *Richman Family Foundation*, the *Rick Sharp Alzheimer's Foundation*, the *Sharp Family Foundation* and others.

JOHNS HOPKINS MEDICINE

Acknowledgements

- Zahinoor Ismail, MD, FRCPC
- Paul Rosenberg, MD
- Anton Porsteinsson, MD

JOHNS HOPKINS MEDICINE

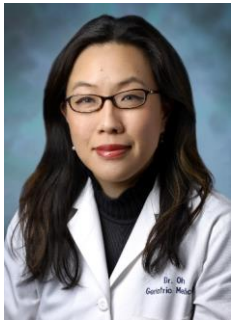
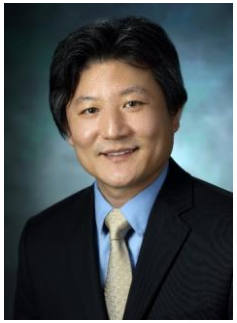
Richman PMCoE Brain Trust

- **Clinical research:** Lyketsos, Rosenberg, Oh, Kapogiannis, Yasar
- **Neuropsychology:** Vannorsdall
- **Large cohort management:** Samus, Lyketsos
- **Treatment development:** Lyketsos, Rosenberg, Yasar
- **Brain imaging:** Smith, Nowrangi, Oishi
- **Genetics & genomics:** Avramopoulos
- **Induced Pluripotent stem Cells (iPSC):** Machairaki
- **Extracellular vesicles** (EVs): Kapogiannis, Machairaki, Witwer
- **Analysis machine learning**: Moore, Leoutsakos, Zandi, API Team












JOHNS HOPKINS
MEDICINE

Precision Medicine in a nutshell

The right treatment for the right patient at the right time

JOHNS HOPKINS MEDICINE

CURRENT PARADIGM
The Amyloid Hypothesis

Ab 1-42 oligomers

↓

Tangles

↓

Neuronal Loss

↓

Circuit Loss

↓

Symptoms

Where are we in 2021?

After 40 years of research we have:

- Four approved symptomatic therapies
- None in the last 17 years
- NO clear disease modifying therapies

Failures of "anti-amyloid" therapies

when given to all comers with *clinical* AD symptoms

RESEARCH

Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis

Sarah F Ackley,[1] Scott C Zimmerman,[1] Willa D Brenowitz,[1,2] Eric J Tchetgen Tchetgen,[3] Audra L Gold,[1] Jennifer J Manly,[4] Elizabeth Rose Mayeda,[5] Teresa J Filshtein,[6] Melinda C Power,[7] Fanny M Elahi,[8] Adam M Brickman,[4] M Maria Glymour[1]

[1]Department of Epidemiology and Biostatistics, University of California, San Francisco, 550 16th Street, San Francisco, CA, USA
[2]Department of Psychiatry, University of California, San Francisco, CA, USA
[3]Department of Statistics, University of Pennsylvania, PA, USA
[4]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, G H Sergievsky Center, Department of Neurology, Columbia University, New York, NY, USA
[5]Department of Epidemiology, University of California, Los Angeles, CA, USA
[6]23&Me, Sunnyvale, CA, USA
[7]Department of Epidemiology, George Washington University, Milken Institute School of Public Health, Washington DC, USA
[8]UCSF Weill Institute for Neurosciences, University of California, San Francisco, CA, USA
Correspondence to: M M Glymour
maria.glymour@ucsf.edu
(or @MariaGlymour on Twitter;
ORCID 0000-0001-9644-3081)

Additional material is published online only. To view please visit the journal online.
Cite this as: BMJ 2021;372:n156
http://dx.doi.org/10.1136/bmj.n156
Accepted: 21 December 2020

ABSTRACT

OBJECTIVE
To evaluate trials of drugs that target amyloid to determine whether reductions in amyloid levels are likely to improve cognition.

DESIGN
Instrumental variable meta-analysis.

SETTING
14 randomized controlled trials of drugs for the prevention or treatment of Alzheimer's disease that targeted an amyloid mechanism, identified from ClinicalTrials.gov.

POPULATION
Adults enrolled in randomized controlled trials of amyloid targeting drugs. Inclusion criteria for trials vary, but typically include adults aged 50 years or older with a diagnosis of mild cognitive impairment or Alzheimer's disease, and amyloid positivity at baseline.

MAIN OUTCOME MEASURES
Analyses included trials for which information could be obtained on both change in brain amyloid levels measured with amyloid positron emission tomography and change in at least one cognitive test score reported for each randomization arm.

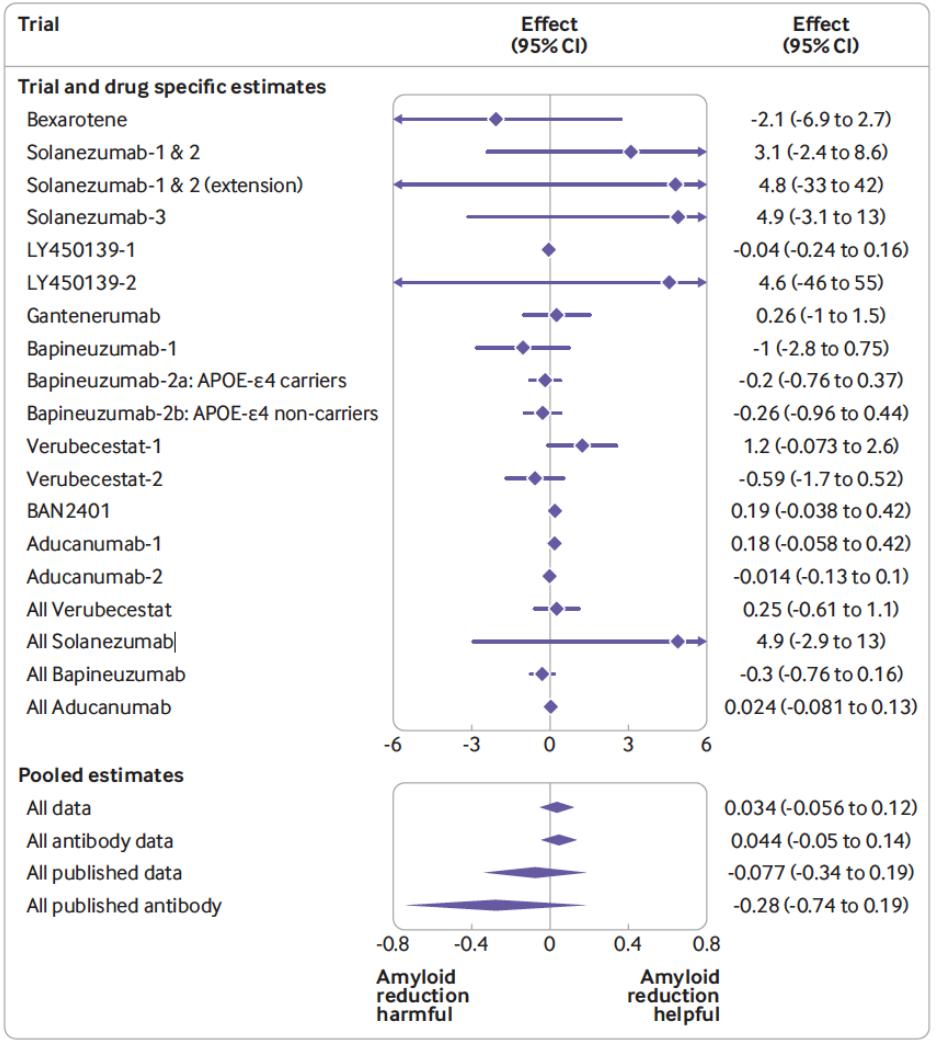
RESULTS
Pooled results from the 14 randomized controlled trials were more precise than estimates from any single trial. The pooled estimate for the effect of reducing amyloid levels by 0.1 standardized uptake value ratio units was an improvement in the mini-mental state examination score of 0.03 (95% confidence interval −0.06 to 0.1) points. This study provides a web application that allows for the re-estimation of the results when new data become available and illustrates the magnitude of the new evidence that would be necessary to achieve a pooled estimate supporting the benefit of reducing amyloid levels.

CONCLUSIONS
Pooled evidence from available trials reporting both reduction in amyloid levels and change in cognition suggests that amyloid reduction strategies do not substantially improve cognition.

Introduction

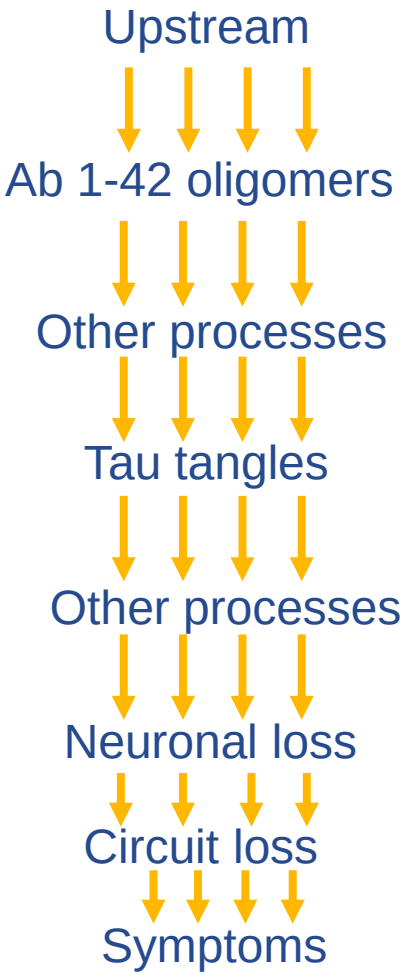
Amyloid plaques and oligomers are hypothesized to cause a cascade of pathological events resulting in cognitive decline in Alzheimer's disease.[1-3] Motivated by the amyloid cascade hypothesis, a primary aim of many new treatments for the prevention or management of Alzheimer's disease has been to reduce amyloid β levels in the brain.[4] Although the presence of amyloid plaques and oligomers in the brain is highly correlated with the progression of Alzheimer's disease,[5 6] the mechanisms by which amyloid might mediate neuronal pathology are currently not well understood.[7] To date, no anti-amyloid treatments have progressed sufficiently to receive approval from the Food and Drug Administration (the regulatory agency for pharmaceuticals in the United States).[8] Drugs have targeted various amyloid species—amyloid plaques, amyloid oligomers, and soluble oligomers—and have been performed in populations with mild to moderate Alzheimer's disease, as well as earlier stages of disease (prodromal Alzheimer's disease).[9] Most trials targeting amyloid failed to produce positive results in either early or late stages of the disease. The negative findings from these trials have prompted skepticism about amyloid's role in neuronal disease, and many have instead argued that amyloid could be a marker for other disease processes and therefore is not a viable drug target.[10 11]

No single trial has, however, provided conclusive



Shifting the paradigm

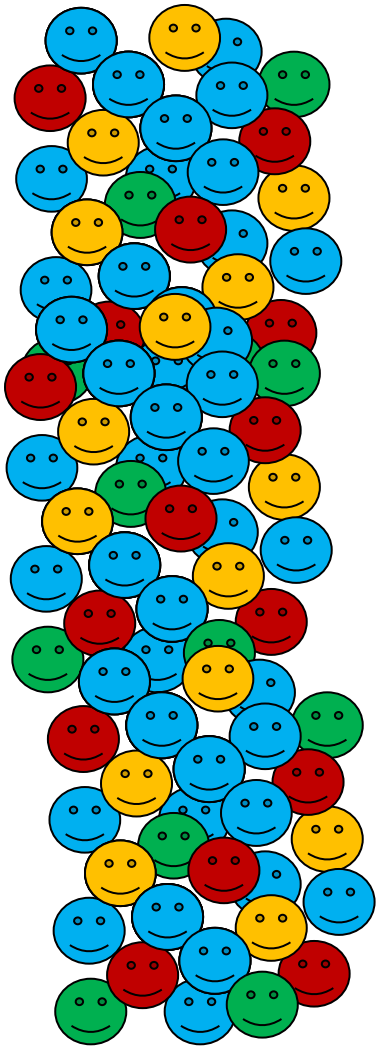
it's not one disease: different paths for different people



Upstream
-Genetics
-Reserve
-Trauma
-Stress

Other processes
-Inflammation
-Chronic stress
-Insulin resistance
-Brain hypoperfusion
-Aging linked NT loss

JOHNS HOPKINS
MEDICINE
Richman Family Precision Medicine
Center of Excellence in Alzheimer Disease



Genetic
Polygenic risk: overall
Polygenic risk: system

Stem Cells
Neuronal function
Effect of treatments

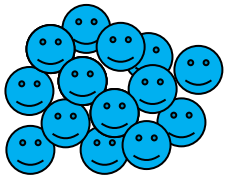
Imaging
Structure
Function

Physiology
Inflammation
Brain perfusion
Exosomes

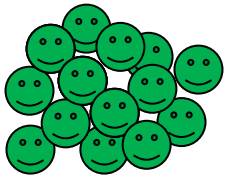
Clinical
Cognition
Behavior

Subgroup 1

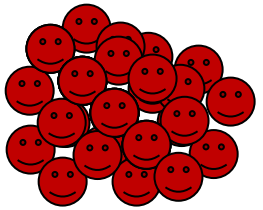
Subgroup 2

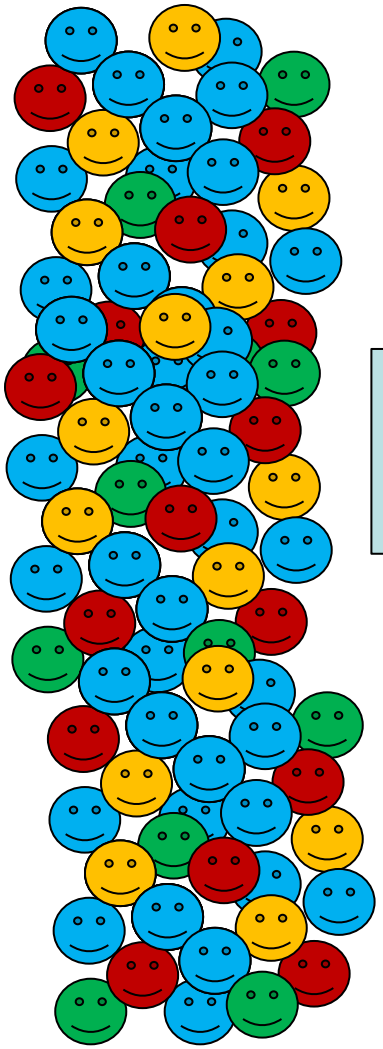


Subgroup 3



Subgroup 4





Genetic
Polygenic risk: overall
Polygenic risk: system

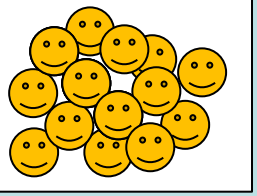
Stem Cells
Neuronal function
Effect of treatments

Imaging
Structure
Function

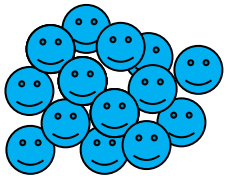
Physiology
Inflammation
Brain perfusion
Exosomes

Clinical
Cognition
Behavior

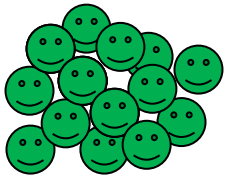
Vascular



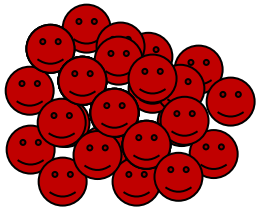
Subgroup 2



Subgroup 3



Subgroup 4



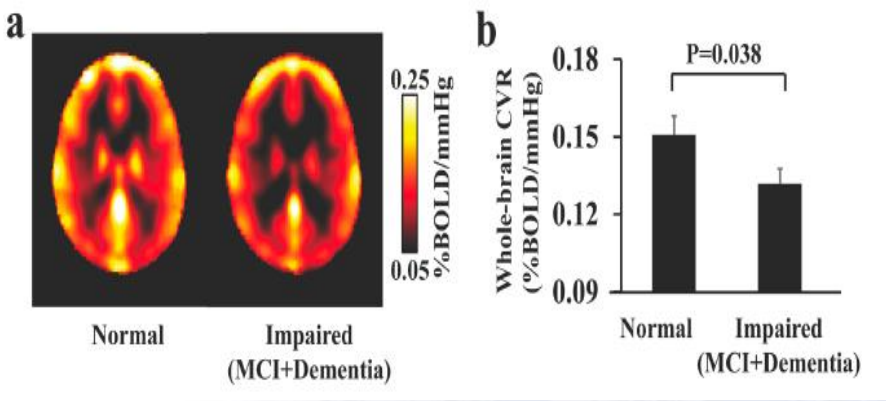
JOHNS HOPKINS MEDICINE
Richman Family Precision Medicine Center of Excellence in Alzheimer Disease

Vascular Subgroup project

Identify people where vascular factors play major role

Technique: brain vessel reactivity with inhaled CO_2

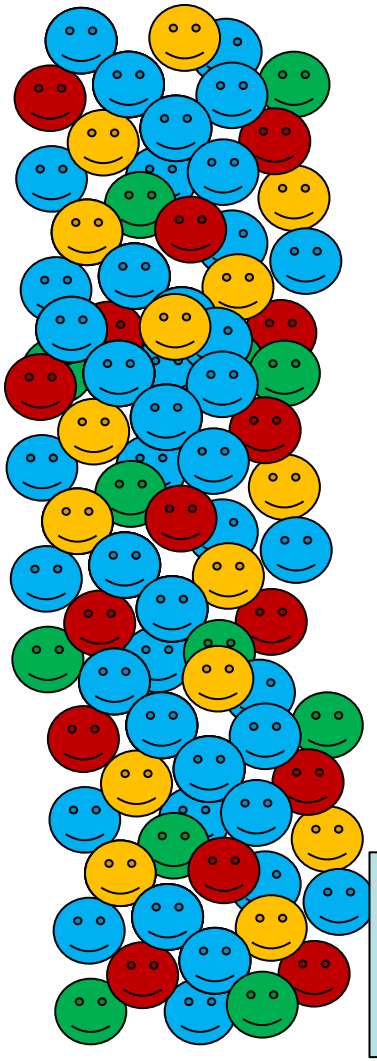
- Healthy perfusion
- Hypoperfusion



Improve CVR <u>in people with low CVR</u> using a widely available safe medication (atorvastatin)

PIs: Paul Rosenberg and Sevil Yasar

JOHNS HOPKINS MEDICINE



Genetic
Polygenic risk: overall
Polygenic risk: system

Stem Cells
Neuronal function
Effect of treatments

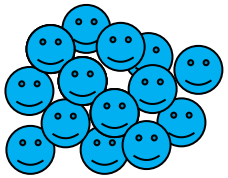
Imaging
Structure
Function

Physiology
Inflammation
Brain perfusion
Exosomes

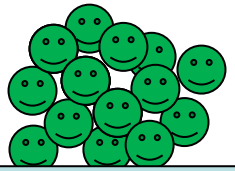
Clinical
Cognition
Behavior

Vascular

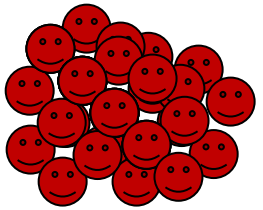
Inflammatory



Metabolic

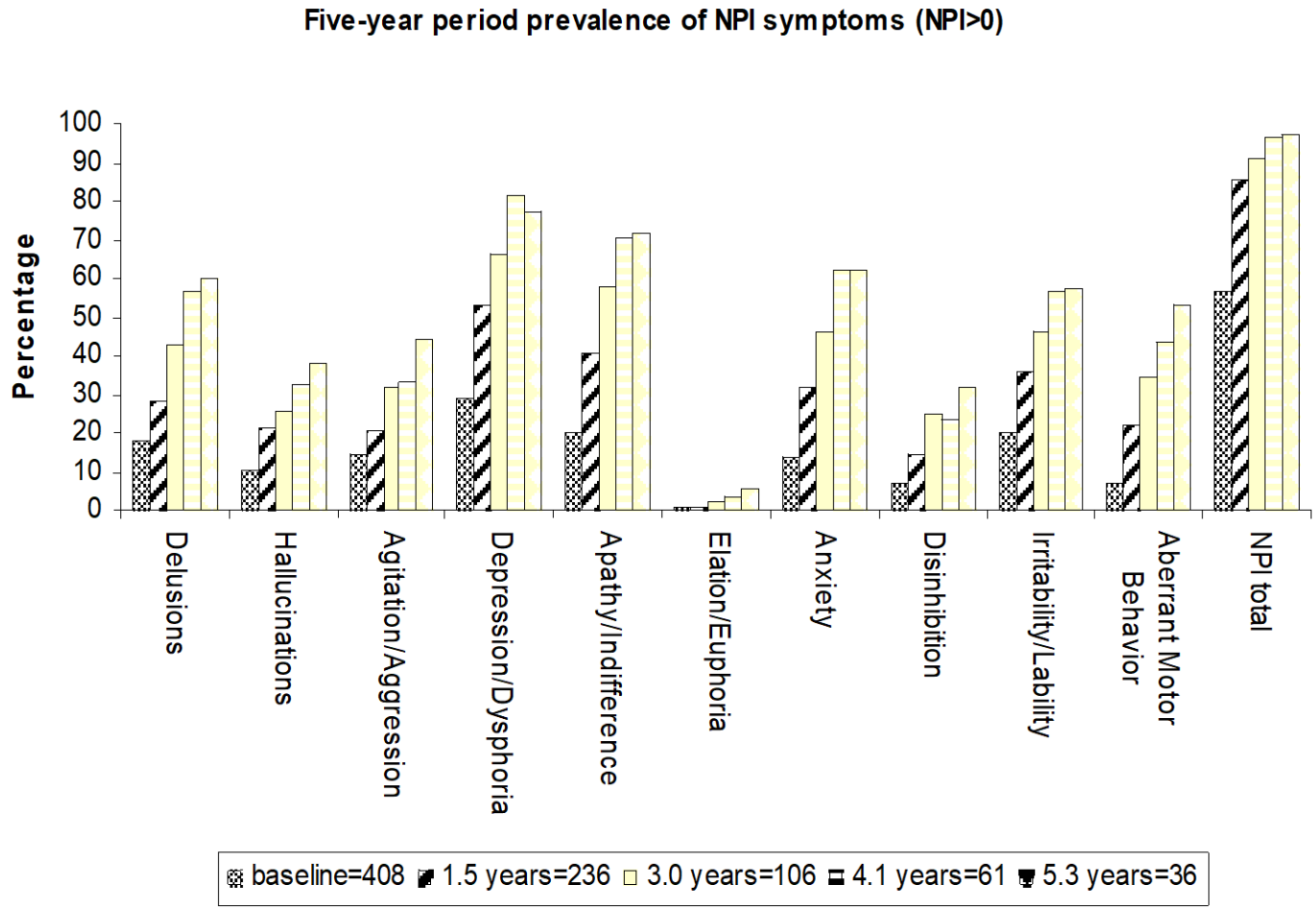


Early NPS/serotopenic



NPS are UNIVERSAL in Dementia

Cache County Dementia Progression Study

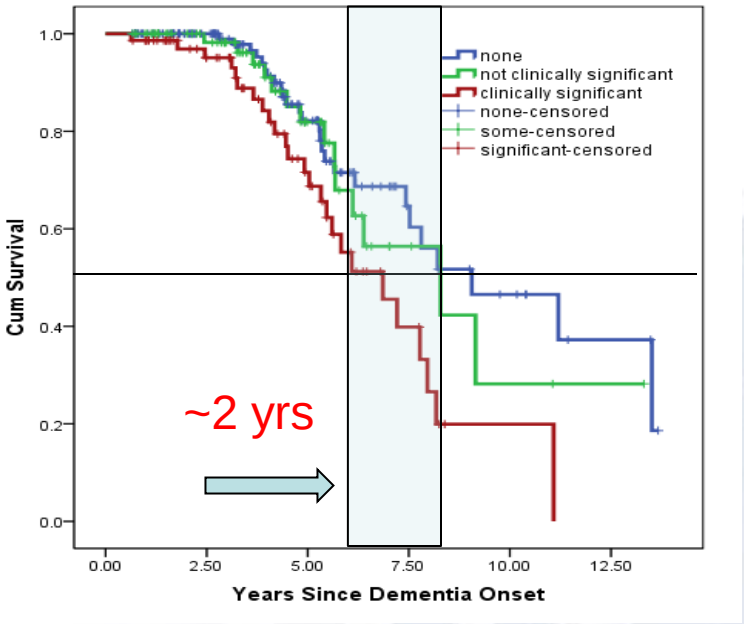


Steinberg 2008

JOHNS HOPKINS MEDICINE

NPS are “bad” for patients & caregivers

- Greater ADL impairment[1]
- Worse quality of life[2]
- Earlier institutionalization[3]
- Major source of burden[4]
- Higher costs[5]
- Faster to severe dementia[6]
- Accelerated mortality[6]



[1]Lyketsos et al, 1997; [2]Gonzales-Salvador et al, 1999; [3]Steele et al, 1990;

[4]Lyketsos et al, 1999; [5] Murman et al, 2002; [6] Peters et al, 2015

JOHNS HOPKINS MEDICINE

NPS in CIND/MCI

faster conversion to dementia

Neuropsychiatric Symptoms as Risk Factors for Progression From CIND to Dementia: The Cache County Study

M. E. Peters, M.D., P. B. Rosenberg, M.D., M. Steinberg, M.D., M. C. Norton, Ph.D., K. A. Welsh-Bohmer, Ph.D., K. M. Hayden, Ph.D., J. Breitner, M.D., M.P.H., J. T. Tschanz, Ph.D., C. G. Lyketsos, M.D., M.H.S., and the Cache County Investigato

Objectives: *To examine the association of neuropsychiatric symptom (NPS) severity with risk of transition to all-cause dementia, Alzheimer disease (AD), and vascular dementia (VaD).* **Design:** *Survival analysis of time to dementia, AD, or VaD onset.* **Setting:** *Population-based study.* **Participants:** *230 participants diagnosed with cognitive impairment, no dementia (CIND) from the Cache County Study of Memory Health and Aging were followed for a mean of 3.3 years.* **Measurements:** *The Neuropsychiatric Inventory (NPI) was used to quantify the presence, frequency, and severity of NPS. Chi-squared statistics, t-tests, and Cox proportional hazard ratios were used to assess associations.* **Results:** *The conversion rate from CIND to all-cause dementia was 12% per year, with risk factors including an APOE ε4 allele, lower Mini-Mental State Examination, lower 3MS, and higher CDR sum-of-boxes. The presence of at least one NPS was a risk factor for all-cause dementia, as was the presence of NPS with mild severity. Nighttime behaviors were a risk factor for all-cause dementia and of AD, whereas hallucinations were a risk factor for VaD.* **Conclusions:** *These data confirm that NPS are risk factors for conversion from CIND to dementia. Of special interest is that even NPS of mild severity are a risk for all-cause dementia or AD.* (Am J Geriatr Psychiatry 2012; 00:1–9)

Key Words: agitation, anxiety, Cache County, CIND, dementia, depression, MCI, NPS, NPI

The Association of Neuropsychiatric Symptoms in MCI with Incident Dementia and Alzheimer Disease

Paul B. Rosenberg, M.D., Michelle M. Mielke, Ph.D., Brian S. Appleby, M.D., Esther S. Oh, M.D., Yonas E. Geda, M.D., Constantine G. Lyketsos, M.D. M.H.S.

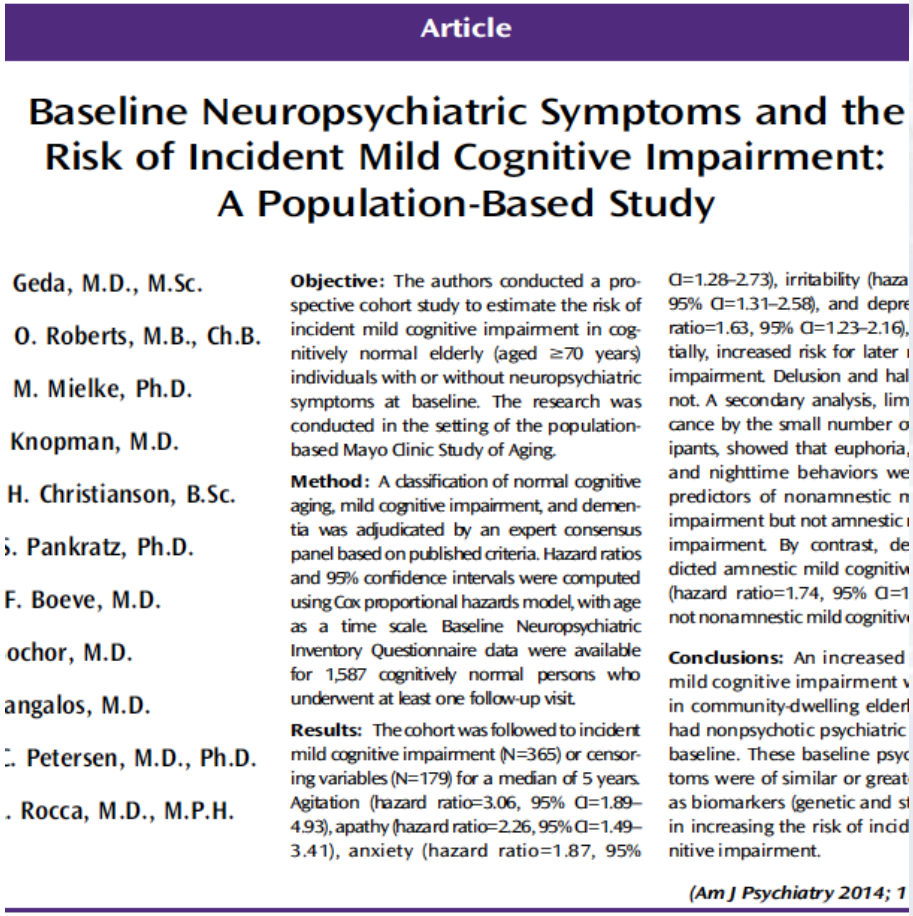
Objectives: *Individuals with mild cognitive impairment (MCI) are at high risk of developing dementia and/or Alzheimer disease (AD). Among persons with MCI, depression and anxiety have been associated with an increased risk of incident dementia. We examined whether neuropsychiatric symptoms in MCI increased the risk of incident dementia (all-cause) and incident AD.* **Design:** *Longitudinal cohort study followed annually (median: 1.58 years).* **Setting:** *National Alzheimer's Coordinating Center database combining clinical data from 29 Alzheimer's Disease Centers.* **Participants:** *A total of 1,821 participants with MCI.* **Measurements:** *1) Progression to dementia (all-cause) or AD, 2) Neuropsychiatric Inventory Questionnaire (NPI-Q), 3) Geriatric Depression Scale (GDS), 4) Clinical Dementia Rating Global Score and Sum of Boxes, and 5) Mini-Mental State Examination (MMSE). The association of covariates with risk of incident dementia or AD was evaluated with hazard ratios (HR) determined by Cox proportional-hazards models adjusted for age, ethnicity, Clinical Dementia Rating Global Score and Sum of Boxes, and MMSE.* **Results:** *A total of 527 participants (28.9%) progressed to dementia and 454 (24.9%) to AD. Baseline GDS > 0 was associated with an increased risk of incident dementia (HR: 1.47, 95% CI: 1.17–1.84) and AD (HR: 1.45, 95% CI: 1.14–1.83). Baseline NPI > 0 was associated with an increased risk of incident dementia (HR: 1.37, 95% CI: 1.12–1.66) and AD (HR: 1.35, 95% CI: 1.09–1.66).* **Conclusions:** *Neuropsychiatric symptoms in MCI are associated with significantly an increased risk of incident dementia and AD. Neuropsychiatric symptoms may be among the earliest symptoms of preclinical stages of AD and targeting them therapeutically might delay transition to dementia.* (Am J Geriatr Psychiatry 2013; 21:685–695)

Key Words: Alzheimer disease, dementia, depression, longitudinal study, mild cognitive impairment, neuropsychiatric symptoms

JOHNS HOPKINS MEDICINE

NPS cognitively unimpaired individuals

faster conversion to MCI



Article

Baseline Neuropsychiatric Symptoms and the Risk of Incident Mild Cognitive Impairment: A Population-Based Study

Geda, M.D., M.Sc.
O. Roberts, M.B., Ch.B.
M. Mielke, Ph.D.
Knopman, M.D.
H. Christianson, B.Sc.
. Pankratz, Ph.D.
F. Boeve, M.D.
ochor, M.D.
angalos, M.D.
. Petersen, M.D., Ph.D.
. Rocca, M.D., M.P.H.

Objective: The authors conducted a prospective cohort study to estimate the risk of incident mild cognitive impairment in cognitively normal elderly (aged ≥70 years) individuals with or without neuropsychiatric symptoms at baseline. The research was conducted in the setting of the population-based Mayo Clinic Study of Aging.

Method: A classification of normal cognitive aging, mild cognitive impairment, and dementia was adjudicated by an expert consensus panel based on published criteria. Hazard ratios and 95% confidence intervals were computed using Cox proportional hazards model, with age as a time scale. Baseline Neuropsychiatric Inventory Questionnaire data were available for 1,587 cognitively normal persons who underwent at least one follow-up visit.

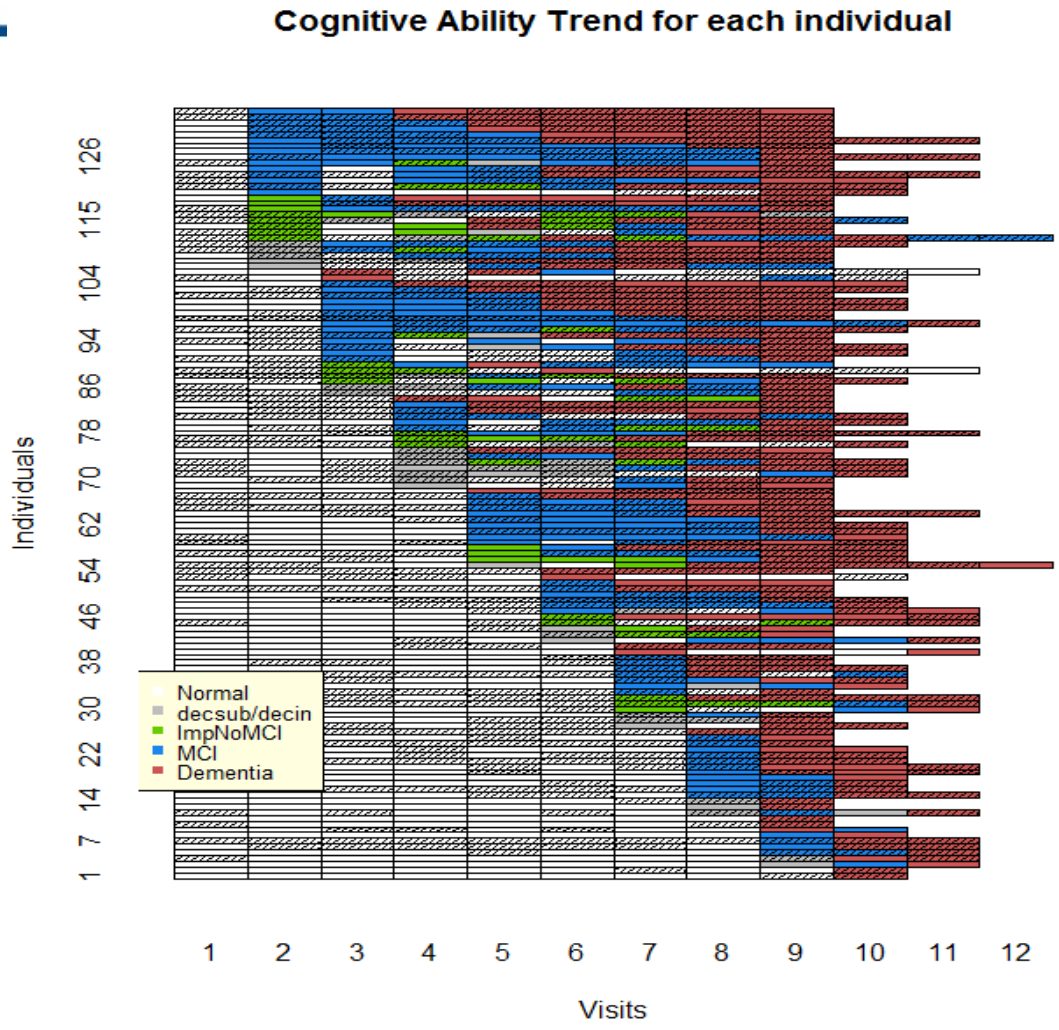
Results: The cohort was followed to incident mild cognitive impairment (N=365) or censoring variables (N=179) for a median of 5 years. Agitation (hazard ratio=3.06, 95% CI=1.89–4.93), apathy (hazard ratio=2.26, 95% CI=1.49–3.41), anxiety (hazard ratio=1.87, 95% CI=1.28–2.73), irritability (haza
95% CI=1.31–2.58), and depre
ratio=1.63, 95% CI=1.23–2.16),
tially, increased risk for later
impairment. Delusion and hal
not. A secondary analysis, lim
cance by the small number o
ipants, showed that euphoria,
and nighttime behaviors we
predictors of nonamnestic n
impairment but not amnestic
impairment. By contrast, de
dicted amnestic mild cognitiv
(hazard ratio=1.74, 95% CI=1
not nonamnestic mild cognitiv

Conclusions: An increased
mild cognitive impairment
in community-dwelling elder
had nonpsychotic psychiatric
baseline. These baseline psyc
toms were of similar or great
as biomarkers (genetic and s
in increasing the risk of incid
nitive impairment.

(Am J Psychiatry 2014; 1

JOHNS HOPKINS MEDICINE

In fact, over half of people who develop dementia develop NPS BEFORE cognitive symptoms



Sequencing of NPS Presence with Cognitive Diagnosis (overall N=1,980)

Normal→ MCI
NPS Before MCI: 55%

Normal→ Dementia
NPS Before MCI 55%

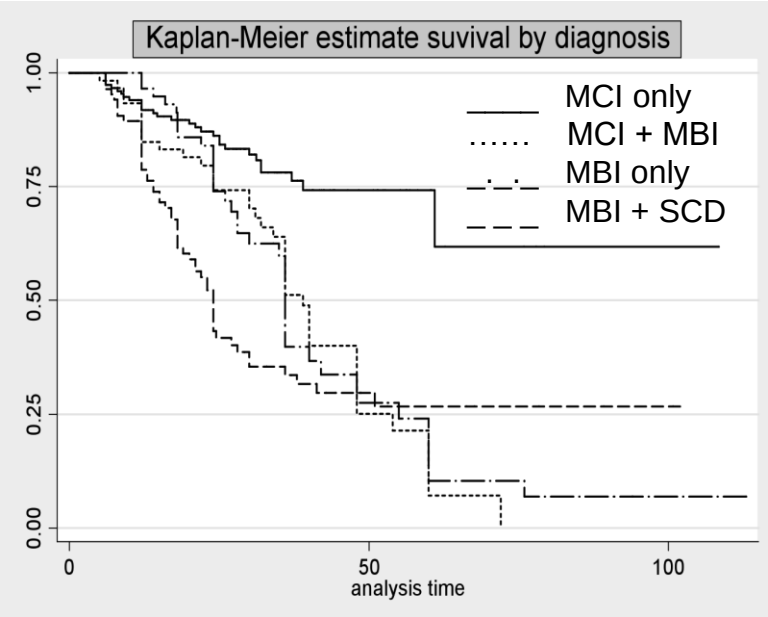
Normal→ Dementia (no MCI)
NPS Before Dementia 64%

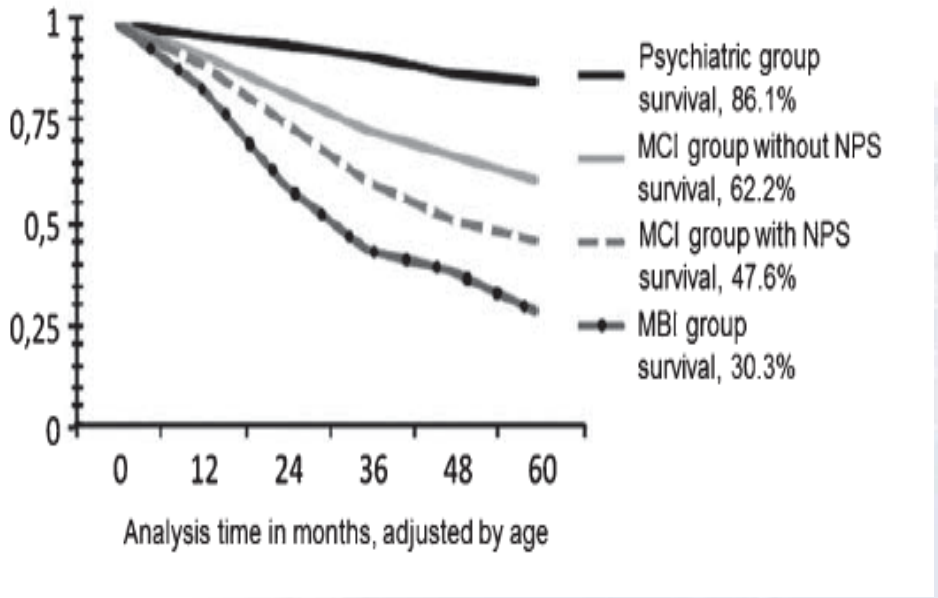
Wise 2019

JOHNS HOPKINS MEDICINE

Mild Behavioral Impairment (MBI)

faster conversion to dementia than MCI alone





Taragano 2009; Taragano 2018

JOHNS HOPKINS MEDICINE

ELSEVIER

Alzheimer's & Dementia ■ (2015) 1-8

Alzheimer's & Dementia

ISTAART research diagnostic criteria for MBI

1. Changes in behavior or personality observed by patient, informant, or clinician, starting later in life (age ≥50 years) and persisting at least intermittently for ≥6 months. These represent clear change from the person's usual behavior or personality as evidenced by at least one of the following:
   a. Decreased motivation (e.g., apathy, aspontaneity, indifference)
   b. Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability)
   c. Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind)
   d. Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits)
   e. Abnormal perception or thought content (e.g., delusions, hallucinations)
2. Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas:
   a. Interpersonal relationships
   b. Other aspects of social functioning
   c. Ability to perform in the workplace

   The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance.
3. Although comorbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication.
4. The patient does not meet criteria for a dementia syndrome (e.g., Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). MCI can be concurrently diagnosed with MBI.

Abbreviations: ISTAART, International Society to Advance Alzheimer's Research and Treatment; MBI, mild behavioral impairment; MCI, mild cognitive impairment.

MBI: accelerated onset of dementia

ISTAART criteria

- 739 with MCI to dementia (NACC cohort)
  - MBI v. no MBI: OR 2.13
- 820 with MCI to dementia (French clinic)
  - MBI v. no MBI: OR 2.76
- 2,853 with MCI to dementia (Japanese cohort)
  - MBI v. other psych: OR 8.07

- 2,769 CU with SCD to CDR>0 (Canadian cohort)
  - MBI v. no MBI: OR 8.15

McGirr 2022; Chen 2021; Matsuoka 2019; Ismail 2021

JOHNS HOPKINS MEDICINE

Might we prevent AD dementia by targeting MBI?

How do we target MBI?

Pathophysiology of MBI

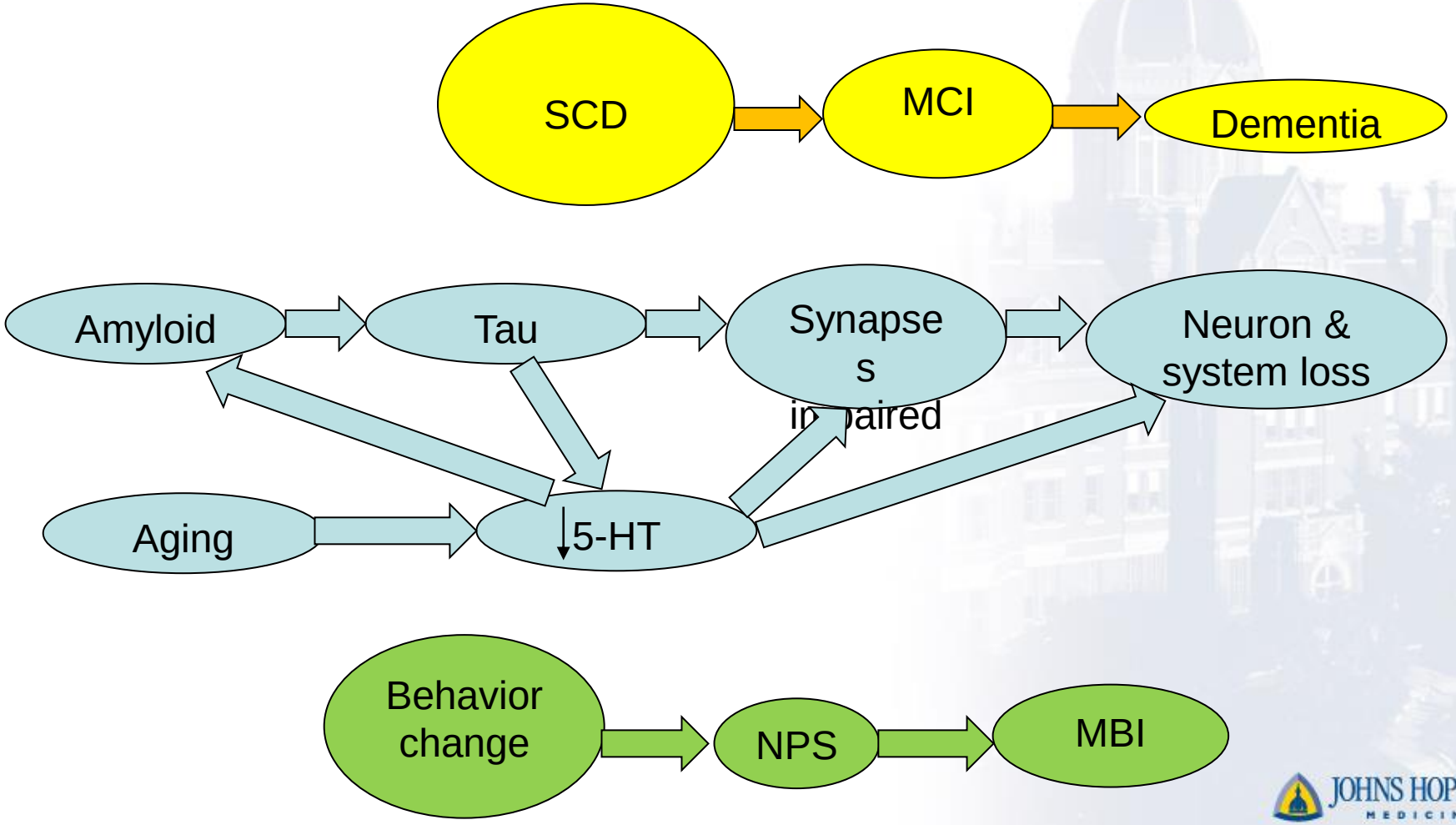
complex interplay of aging, ATN, SER loss

- NPS/MBI linked to
  - Monoamine, esp. *SER* system loss
  - *ATN* pathology

- Aging leads to monoamine, *SER* system loss
- *ATN* pathology accelerates *SER* system loss
- SER system loss accelerates amyloid pathology

Pathophysiology of MBI

complex interplay of aging, ATN, SER loss

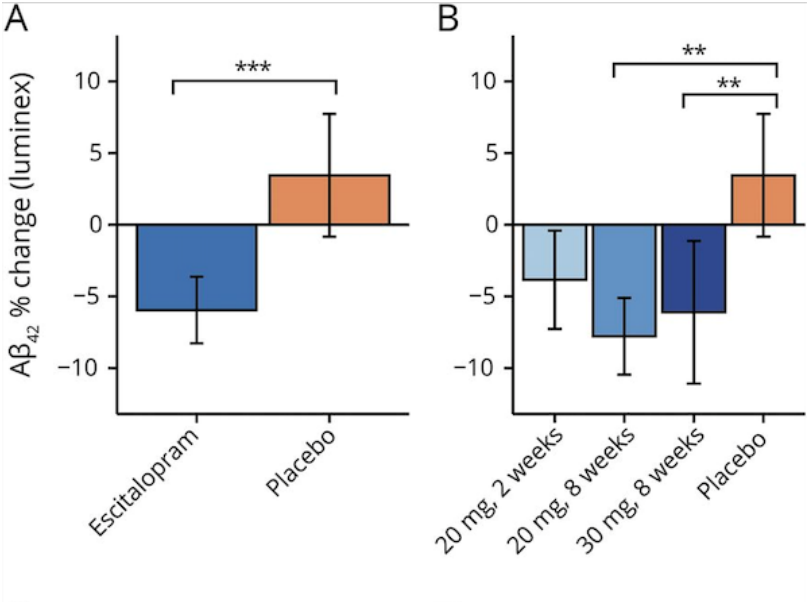


JOHNS HOPKINS MEDICINE

Is there a treatment that targets both *ATN* and *SER* pathology and that can reduce MBI symptoms?

JOHNS HOPKINS MEDICINE

Escitalopram: SSRI



Research

Original Investigation

Effect of Citalopram on Agitation in Alzheimer Disease
The CitAD Randomized Clinical Trial

Anton P. Porsteinsson, MD; Lea T. Drye, PhD; Bruce G. Pollock, MD, PhD; D. P. Devanand, MD; Constantine Frangakis, PhD; Zahinoor Ismail, MD; Christopher Marano, MD; Curtis L. Meinert, PhD; Jacobo E. Mintzer, MD, MBA; Cynthia A. Munro, PhD; Gregory Pelton, MD; Peter V. Rabins, MD; Paul B. Rosenberg, MD; Lon S. Schneider, MD; David M. Shade, JD; Daniel Weintraub, MD; Jerome Yesavage, MD; Constantine G. Lyketsos, MD, MHS; for the CitAD Research Group

CONCLUSIONS AND RELEVANCE Among patients with probable Alzheimer disease and agitation who were receiving psychosocial intervention, the addition of citalopram compared with placebo significantly reduced agitation and caregiver distress; however, cognitive and cardiac adverse effects of citalopram may limit its practical application at the dosage of 30 mg per day.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00898807

JAMA. 2014;311(7):682-691. doi:10.1001/jama.2014.93

Sheline 2020; Sheline 2014; Cirrito 2020; Posteinsson 2014

JOHNS HOPKINS MEDICINE

Might escitalopram prevent dementia?

YES in people with MBI

Published in final edited form as:

Int J Geriatr Psychiatry. 2018 January ; 33(1): 200–211. doi:10.1002/gps.4709.

Decreasing hazards of Alzheimer's disease with the use of antidepressants: mitigating the risk of depression and apolipoprotein E

served between treatment groups.

Method: Data sets from 755 currently nondepressed participants from the longitudinal Alzheimer's Disease Neuroimaging Initiative were evaluated by Kaplan-Meier analysis and analyses of variance and covariance with ApoE4 status and age as covariates.

Conclusions: Long-term SSRI treatment may delay progression from MCI to Alzheimer's dementia.

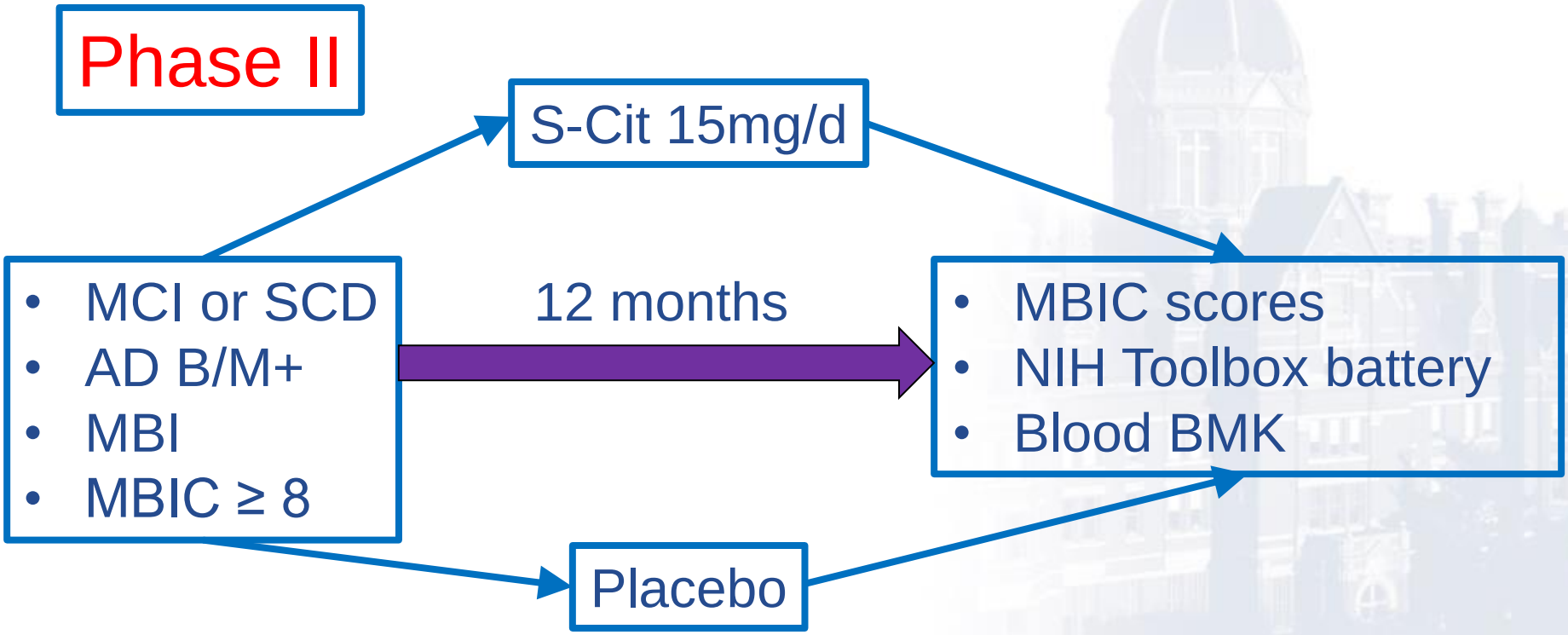
AJP in Advance (doi: 10.1176/appi.ajp.2017.17040404)

JOHNS HOPKINS MEDICINE

Design issues

- Primary aim: improve MBI
- SCD or MCI
- Blood AD biomarkers present
- Moderate+ MBI
- Escitalopram dose: 15mg/day
- Duration: 12 months
- Effects on cognition and biomarkers

Proof of concept trial design



JOHNS HOPKINS MEDICINE

Time to find out if we can prevent AD dementia by targeting MBI!

JOHNS HOPKINS MEDICINE

JOHNS HOPKINS
MEDICINE

JOHNS HOPKINS
BAYVIEW MEDICAL CENTER

JOHNS HOPKINS
MEDICINE
Richman Family Precision Medicine
Center of Excellence in Alzheimer Disease

Thank you!
Ευχαριστώ!

Questions & Discussion

JOHNS HOPKINS
MEDICINE

Serotonin system loss in AD

early but not universal

- Pathology
  - Loss of dorsal raphe cells early in AD
  - Loss of cortical serotonin projections early
  - Loss of SERT by PET imaging

- Loss of serotonin impairs memory function
- Serotonin regulates Abeta & tau levels
- In AD models loss of 5-HT precedes Abeta

Lyness 2003; Smith 2021; Rub 2000; Vakalopoulos 2017; Metaxas 2019

JOHNS HOPKINS MEDICINE

Pathophysiology of MBI
links to *ATN*

- Lower CSF Abeta, higher tau/Aβ42, t-tau/Aβ42
- Decreasing CSF Aβ42, Aβ42/40
- Increasing p-tau, t-tau, p-tau/Aβ42, t-tau/Aβ42
- Higher amyloid-PET SUVR
- Higher tau-PET SUVR
- Entorhinal & hippocampal atrophy

Chen 2021; Ismail 2021; Matsukova 2021; Lussier 2020; Johansson 2021

Pathophysiology of MBI
links to serotonin system loss

- Pathologically NPS linked to
  - Loss of cortical serotonin innervation
  - Serotonin-cholinergic imbalance
  - Lower cell counts in *Dorsal Raphe*
- *Absent* serotonin pathology → absent NPS
- In AD models loss of 5-HT precedes NPS

Palmer 1996; Chen 1996; Lai 2003; Garcia Alloza 2005; Zweig 1988; Forstl 1994; Liu 2008

JOHNS HOPKINS MEDICINE