Plenary: Mind over Metabolism - Choosing Brain Health

David Perlmutter, MD, FACN, ABIHM

Mind over Metabolism - Choosing Brain Health

David Perlmutter, MD, ABIHM, FACN

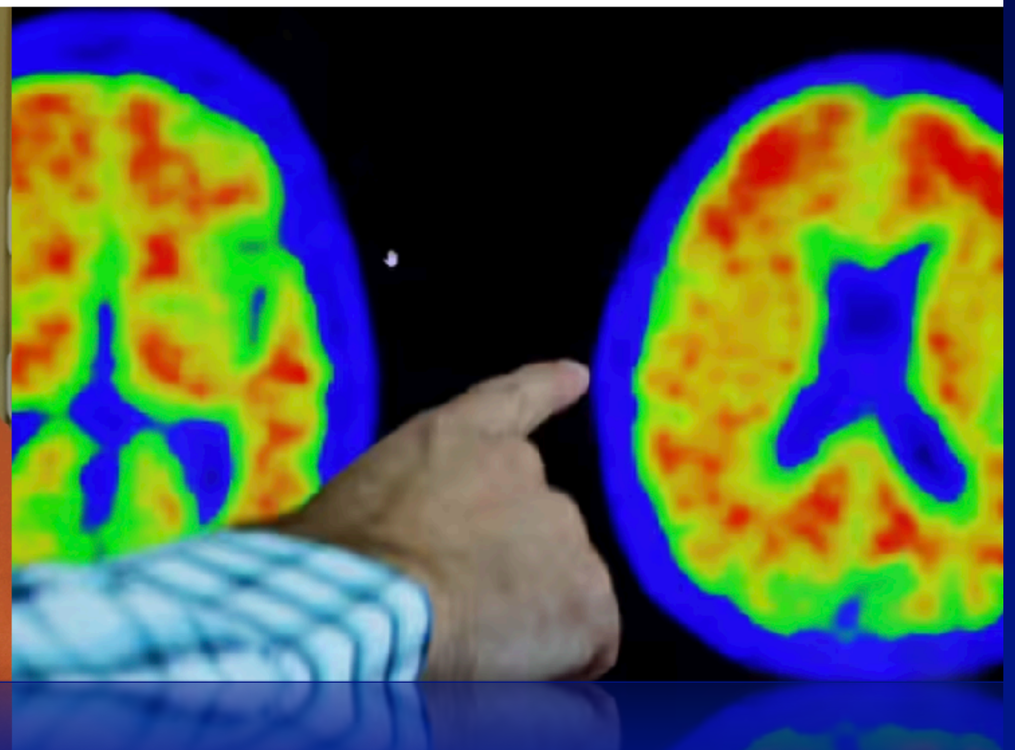
DrPerlmutter.com

The Washington Post
Democracy Dies in Darkness

July 6, 2023

FDA gives full approval to first drug to clearly, but modestly, slow Alzheimer's

Leqembi, administered intravenously every other week, will get a "boxed warning" because it can cause brain bleeding and swelling



January 8, 2020

BIOTECH

STAT+

Medicare to cover more brain scans for Alzheimer's patients

July 17, 2023

A newly approved Alzheimer's drug made by Eisai and Biogen, called Leqembi, aims to clear out amyloid plaques in patients' brains.

ILLUSTRATION: ALEX HOGAN/STAT; PHOTO: EISAI VIA AP

The Harvard Gazette

HEALTH & MEDICINE

Start of new era for Alzheimer's treatment

NIH via AP

Expert discusses recent lecanemab trial, why it appears to offer hope for those with deadly disease

JAMA January 8, 2020

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AMERICAN ACADEMY OF NEUROLOGY

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis

March 27, 2023 RESEARCH ARTICLE

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis

Francesca Alves, Pawel Kallinowski, Scott Ayton

First published March 27, 2023, DOI: https://doi.org/10.1212/WNL.0000000000207156

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis

JAMA January 8, 2020

Objectives: To evaluate brain volume changes caused by different sub-classes of anti- amyloid beta (Aβ) drugs trialled in patients with Alzheimer’s disease.

Alves, F., et al., *Neurology.* April, 2023

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis

JAMA January 8, 2020

Anti–β-Amyloid Drugs

- Secretase inhibitors
- Anti-amyloid monoclonal antibodies

aducanamab - Aduhelm™
lecanemab - Leqembi™

Alves, F., et al., *Neurology.* April, 2023

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis

JAMA January 8, 2020

- Systematic review of patients enrolled in randomized trials of anti-Aβ drugs (n=8062 to 10279)
- Detailed evaluation of volumetric MRI data involving hippocampus, lateral ventricals and whole brain

Alves, F., et al., *Neurology.* April, 2023

- Secretase inhibitors → hippocampal and whole brain atrophy

- Anti-amyloid monoclonal antibodies → ventricular enlargement

aducanamab - Aduhelm™
lecanemab - Leqembi™

Alves, F., et al., *Neurology.* April, 2023

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis

JAMA January 8, 2020

- Mild Cognitively Impaired participants treated with anti-Aβ drugs were projected to have a material regression toward brain volumes typical of Alzheimer's dementia ~8 months earlier than if they were untreated These findings reveal the potential for anti-Aβ therapies to compromise long-term brain health by accelerating brain atrophy.

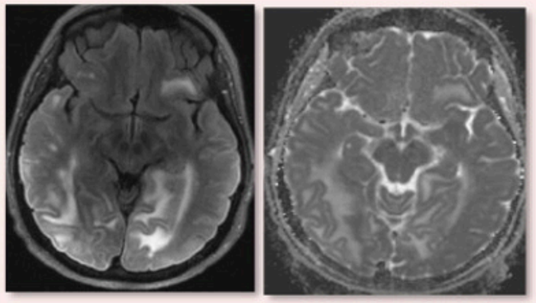
Alves, F., et al., *Neurology.* April, 2023

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis

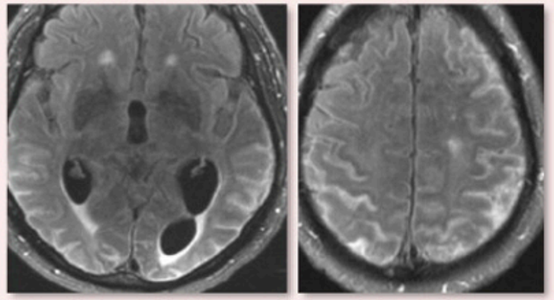
JAMA January 8, 2020

Amyloid-related Imaging Abnormalities in Alzheimer Disease Treated with Anti-amyloid-β Therapy

Amyloid-related imaging abnormalities (ARIA)

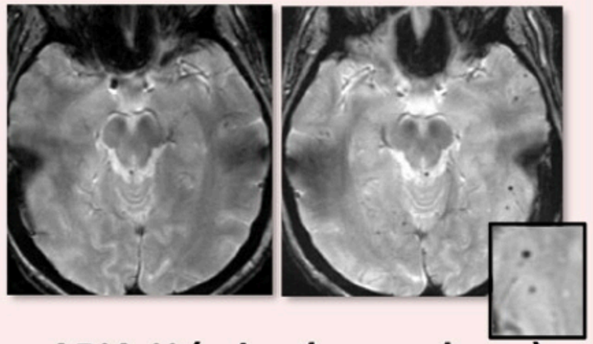


ARIA-E (edema)



ARIA-E (effusion)

ARIA-E is characterized by parenchymal edema and/or sulcal effusion. This is the most common side effect of monoclonal antibodies.



ARIA-H (microhemorrhage)

ARIA-H is characterized by parenchymal microhemorrhages and/or superficial siderosis.

Increased vascular permeability forms the basis of both ARIA-E and ARIA-H. Therefore, both entities can occur **concurrently**.

Agarwal A et al. Published online: August 31, 2023
https://doi.org/10.1148/rg.230009

RadioGraphics

Alves, F., et al., *Neurology.* April, 2023

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis

JAMA January 8, 2020

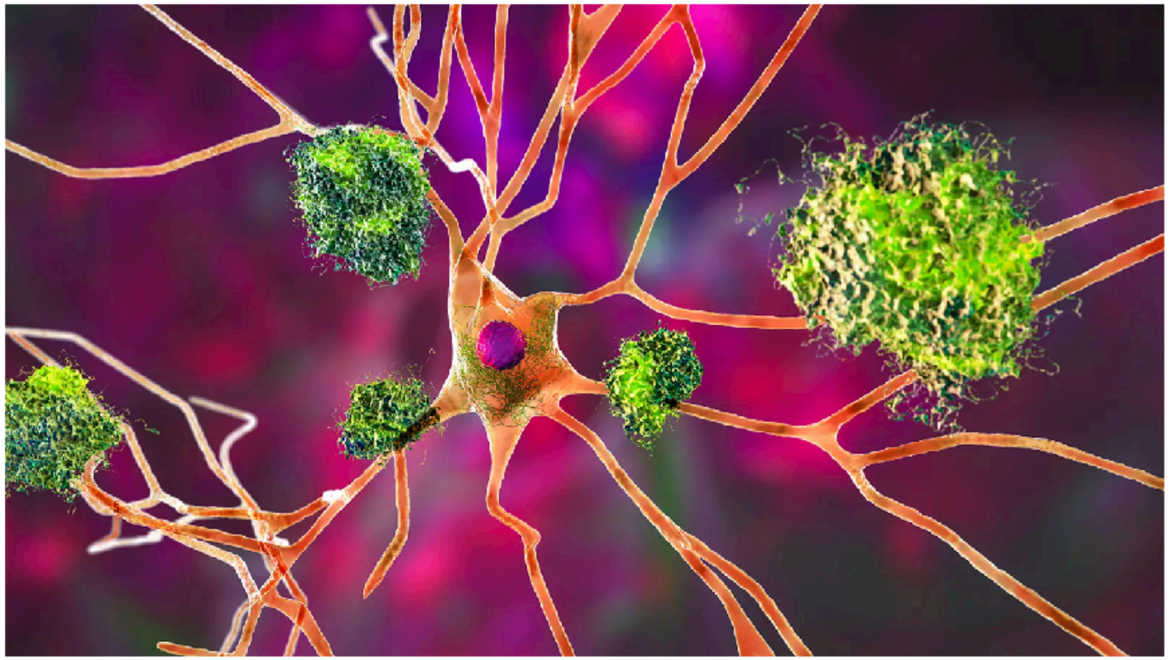
- Pharmaceutical companies that have conduced trials of anti-Aβ drugs should interrogate prior data on brain volume (e.g. stratifications by ARIA, analysis of additional brain structures), report the findings, and release the data for researchers to investigate.

Alves, F., et al., *Neurology.* April, 2023

Brains Shrink With Anti-Amyloid Alzheimer's Drugs

— Treatments accelerate brain atrophy, but reasons why remain a mystery

by Judy George, Deputy Managing Editor, MedPage Today March 31, 2023



Medical News From Around the Web

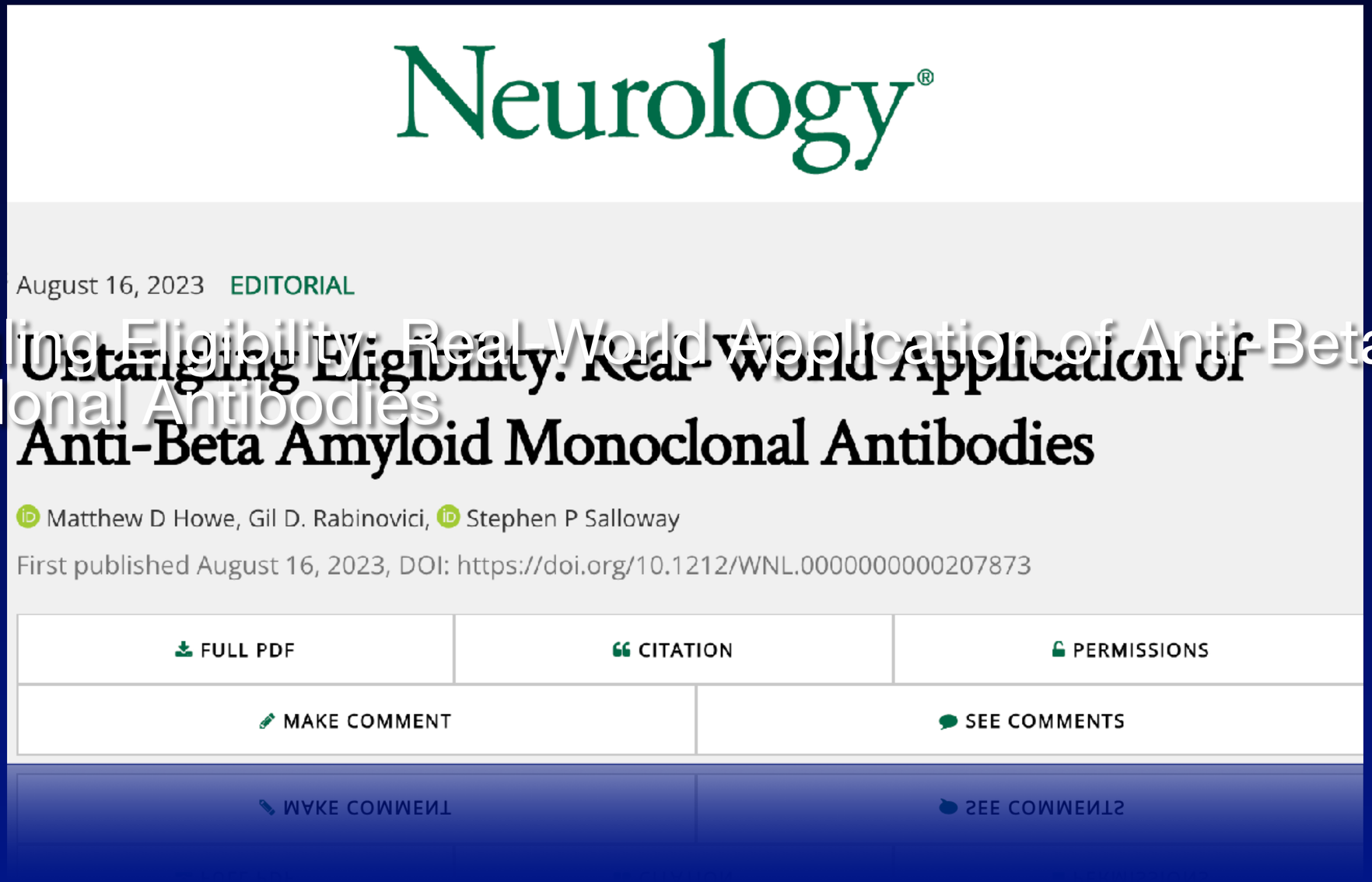
THE NEW ENGLAND JOURNAL OF MEDICINE

Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants.

JOURNAL OF CLINICAL ONCOLOGY

Treatment Exposure and Discontinuation in the PALbociclib CoLlaborative Adjuvant Study of Palbociclib With Adjuvant Endocrine Therapy for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Early Breast Cancer (PALLAS/AFT-05/ABCSG-42/BIG-14-03).

Untangling Eligibility: Real-World Application of Anti-Beta Amyloid Monoclonal Antibodies



Untangling Eligibility: Real-World Application of Anti-Beta Amyloid Monoclonal Antibodies

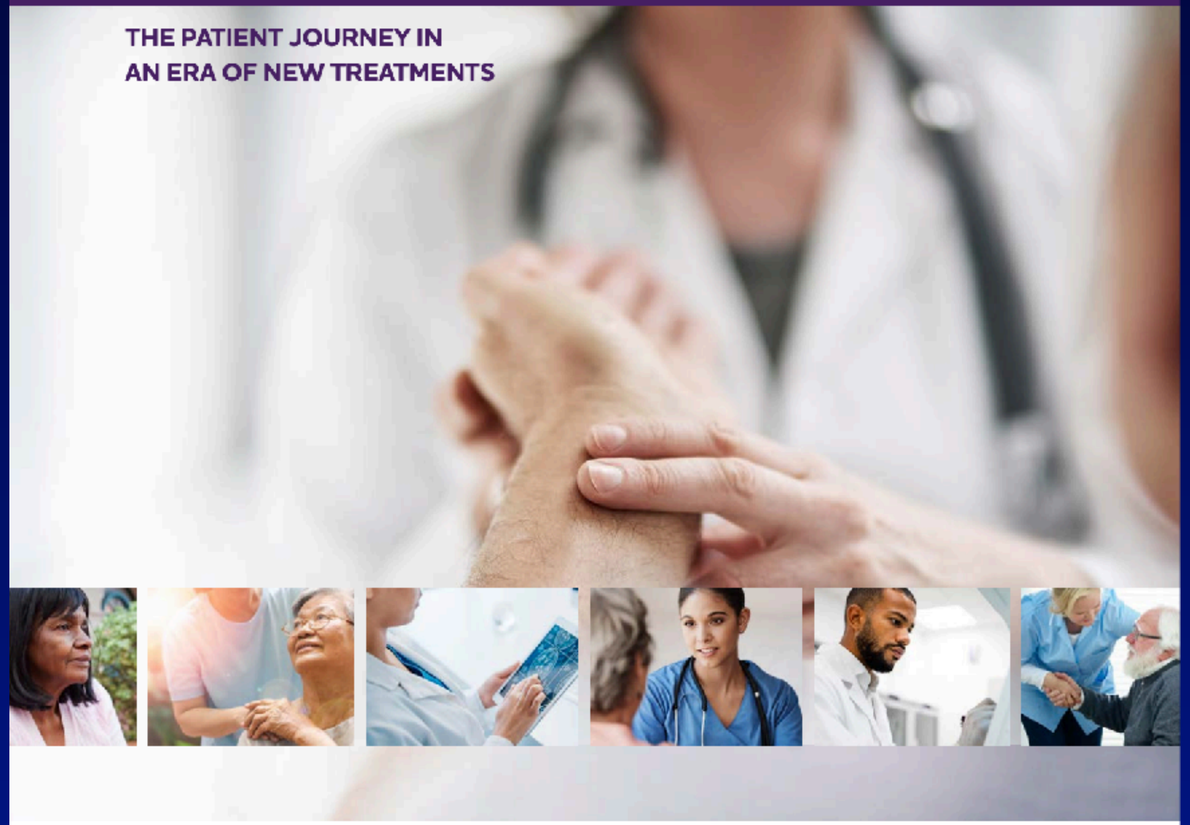
Fewer than 10% of early Alzheimer's patients in real-world cohort would qualify for anti-amyloid beta monoclonal antibodies.

Howe, M., et al., *Neurology.* August 16, 2023

2023 ALZHEIMER'S DISEASE FACTS AND FIGURES

SPECIAL REPORT

THE PATIENT JOURNEY IN AN ERA OF NEW TREATMENTS



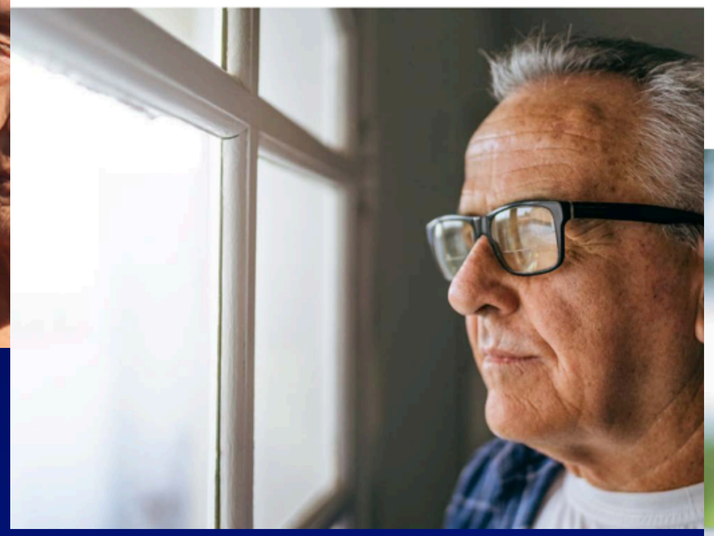
ALZHEIMER'S ASSOCIATION®

PREVALENCE

AN ESTIMATED 6.7 MILLION AMERICANS ARE LIVING WITH ALZHEIMER'S DEMENTIA.

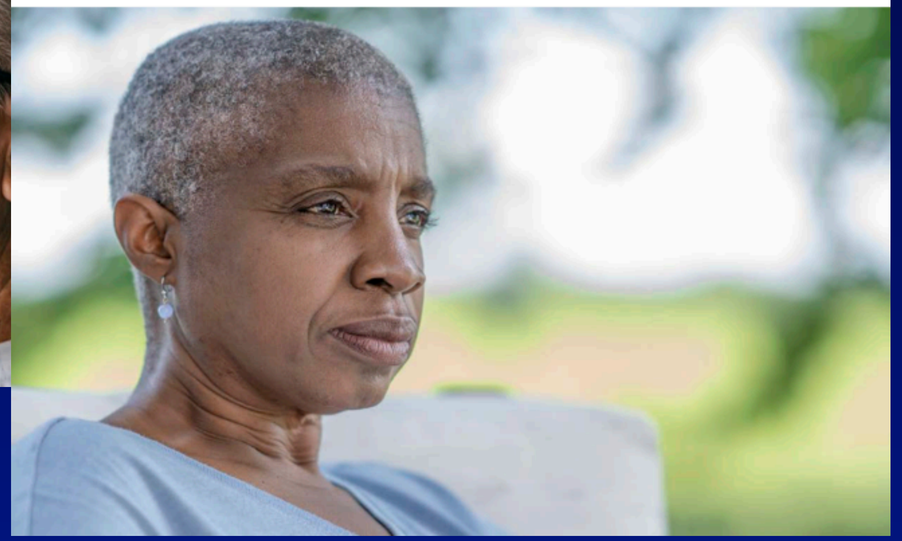
MORTALITY AND MORBIDITY

AMONG PEOPLE AGE 70, 61% OF THOSE WITH ALZHEIMER'S DEMENTIA ARE EXPECTED TO DIE BEFORE AGE 80 COMPARED WITH 30% OF PEOPLE WITHOUT ALZHEIMER'S DEMENTIA.

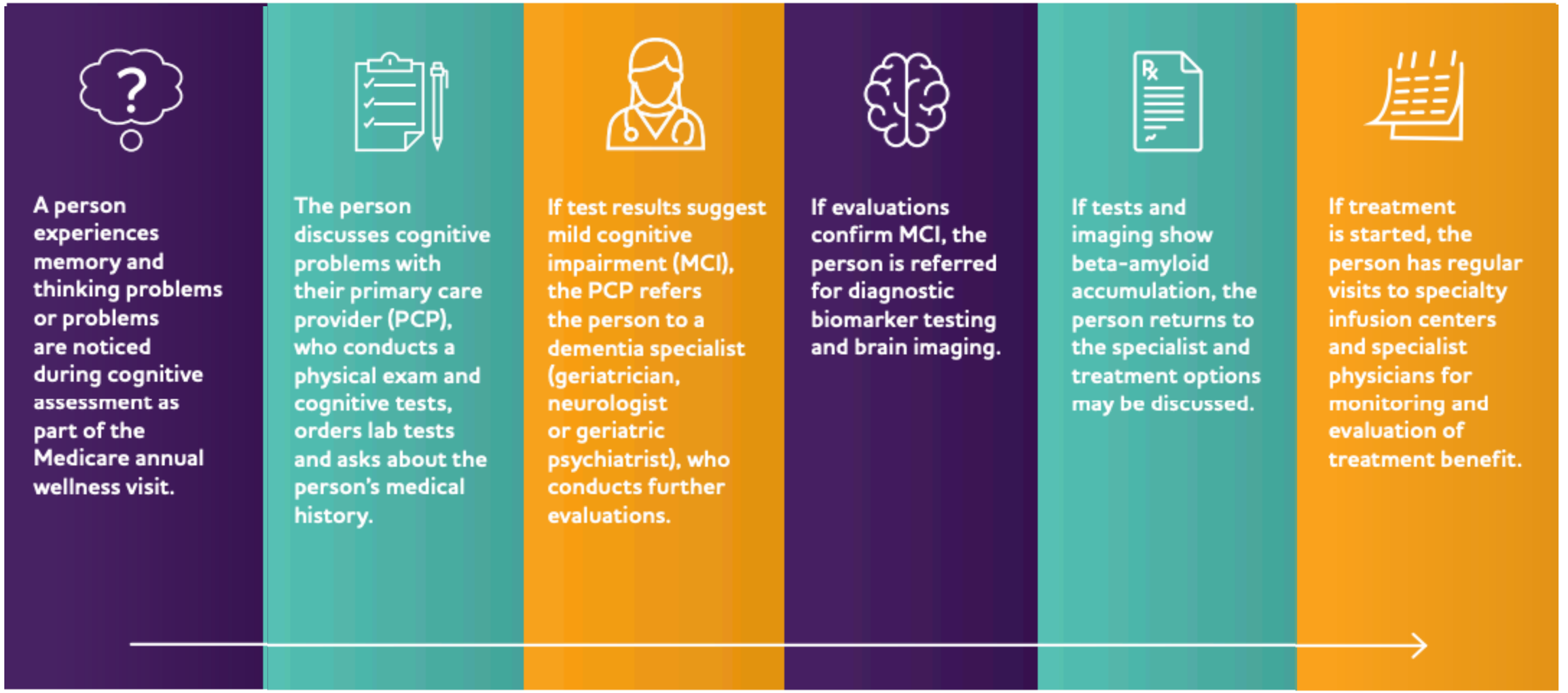


OVERVIEW

ALZHEIMER'S BEGINS 20 YEARS OR MORE BEFORE MEMORY LOSS AND OTHER SYMPTOMS DEVELOP.



Patient Journey from Awareness of Cognitive Issues to Care from a Physician Specialist and Treatment[655, 809]



A person experiences memory and thinking problems or problems are noticed during cognitive assessment as part of the Medicare annual wellness visit.

Cognitive concerns

If treatment is started, the person has regular visits to specialty infusion centers and specialist physicians for monitoring and evaluation of treatment benefit.

Treatment and ongoing specialist care

OVERVIEW

ALZHEIMER'S BEGINS 20 YEARS OR MORE BEFORE MEMORY LOSS AND OTHER SYMPTOMS DEVELOP.

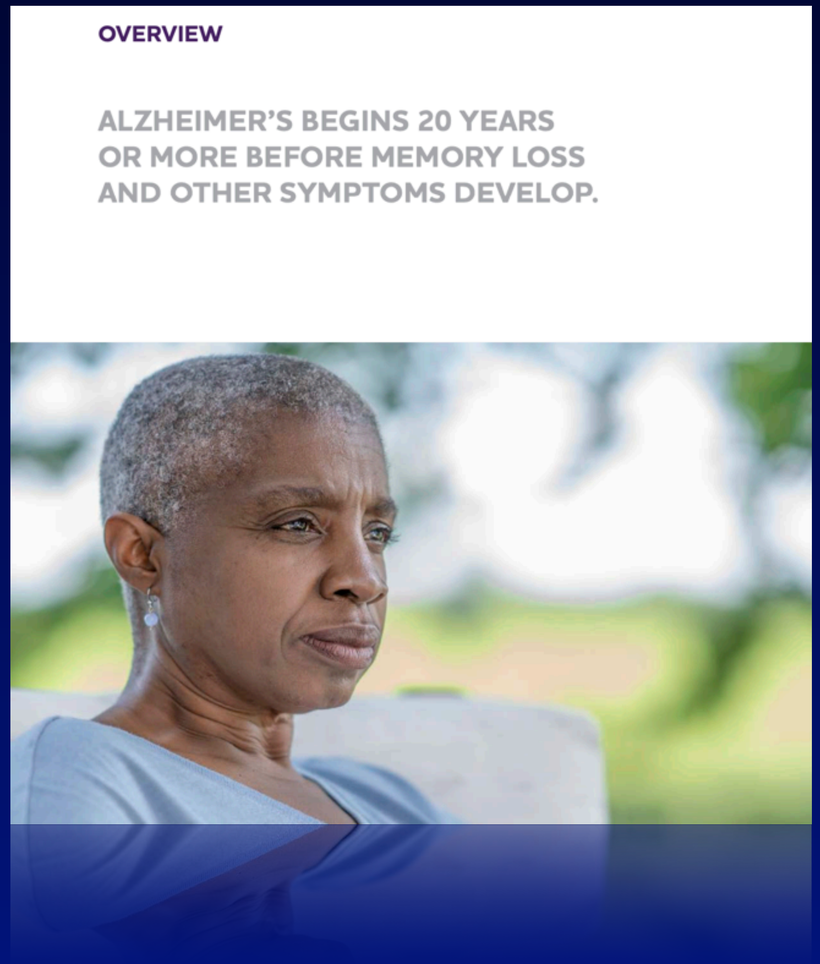
Insulin Resistance and Alzheimer's Disease: Bioenergetic Linkages

Neth, B., et al., *Frontiers in Aging Neuroscience.* October, 2017

Insulin Resistance and Alzheimer's Disease: Bioenergetic Linkages

- Brain glucose hypometabolism occurs potentially decades before clinical manifestations of Alzheimer's.

- Individuals with insulin resistance or type 2 diabetes have increased risk for development of Alzheimer's disease.



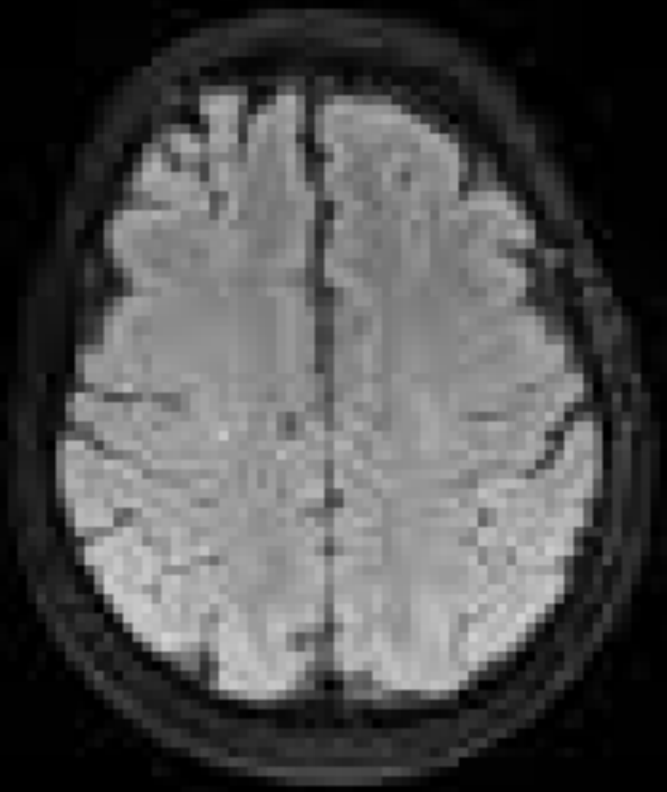
Neth, B., et al., *Frontiers in Aging Neuroscience.* October, 2017

Insulin Resistance and Alzheimer's Disease: Bioenergetic Linkages

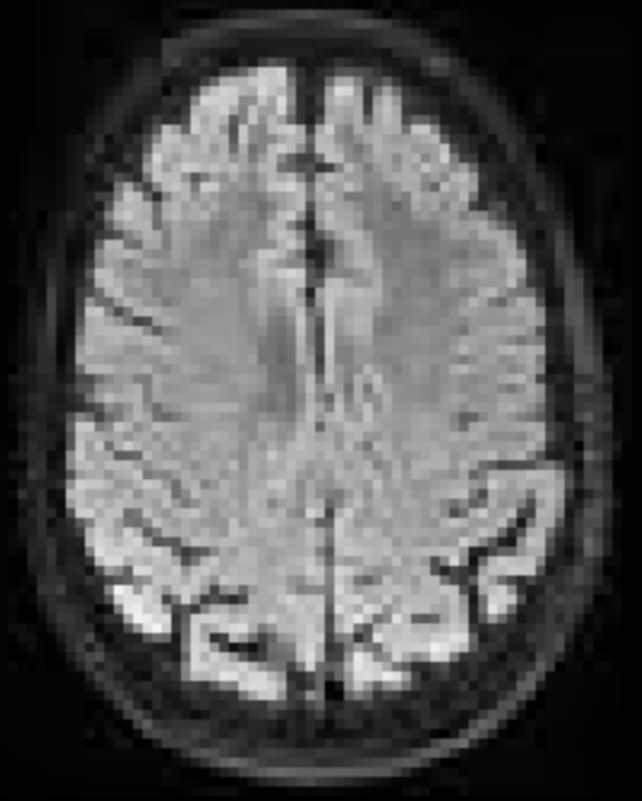
"Moreover, we may be able to characterize "brain metabolic fingerprints" that may be used to offer patients and research participants more personalized therapeutic options if they were to develop a condition impacting brain metabolism."

Neth, B., et al., *Frontiers in Aging Neuroscience.* October, 2017

MRI

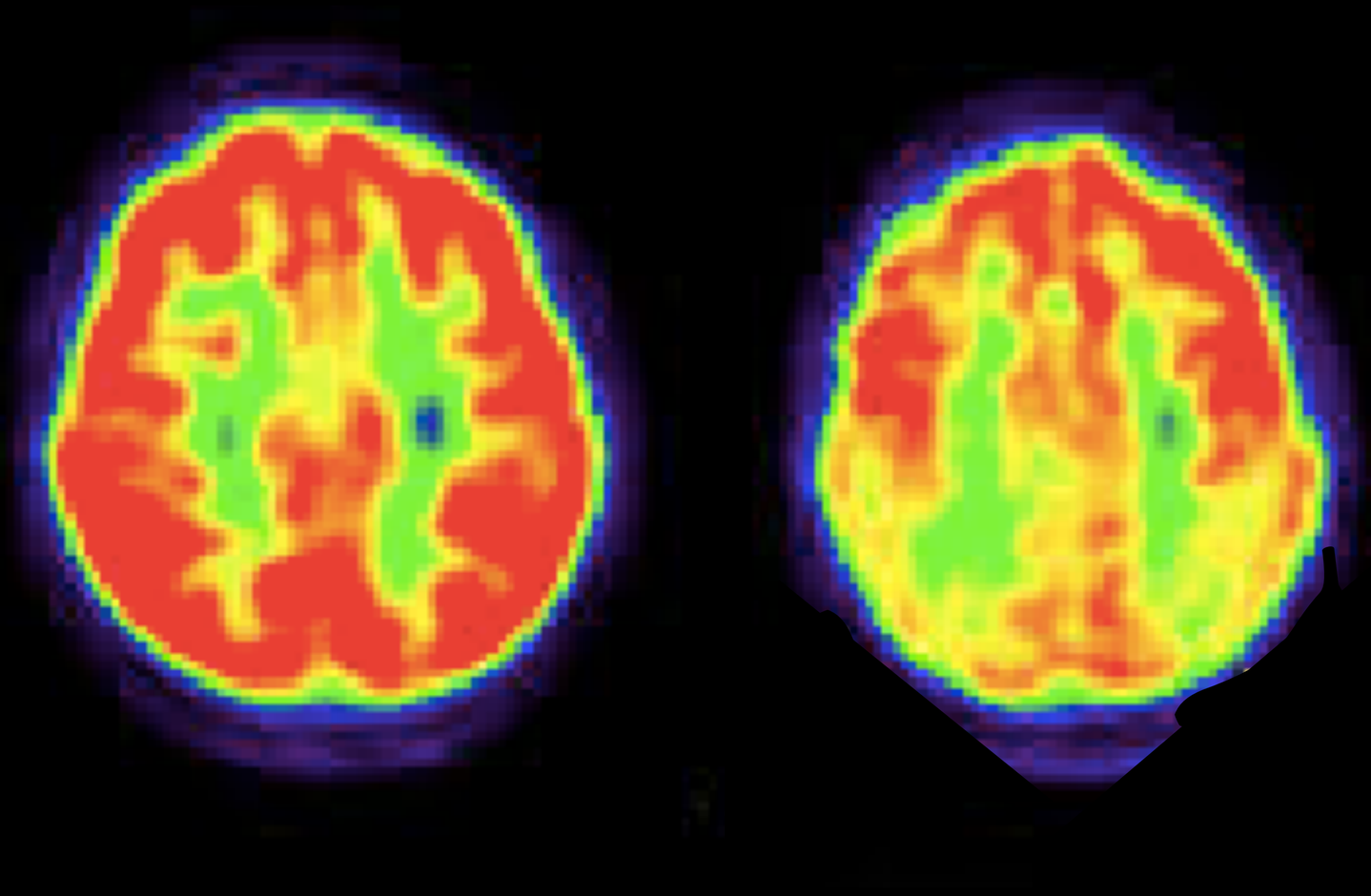


Control



Alzheimer’s Disease

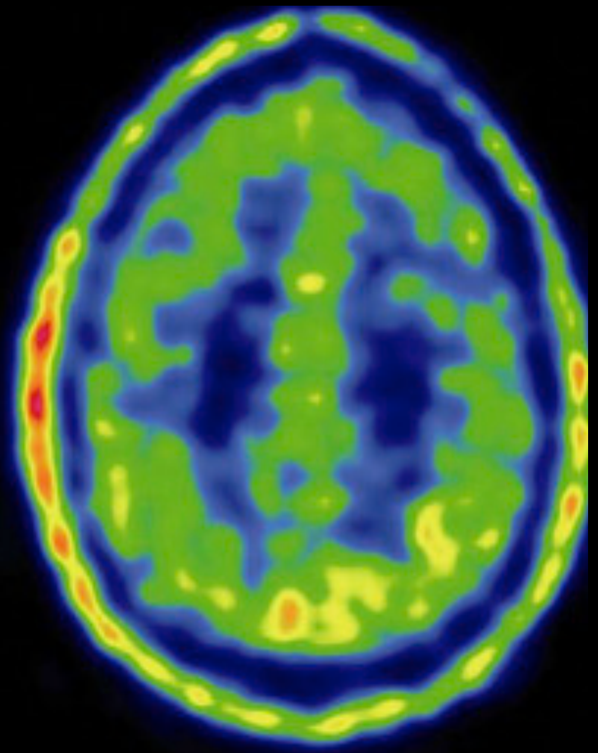
FDG - PET



Control

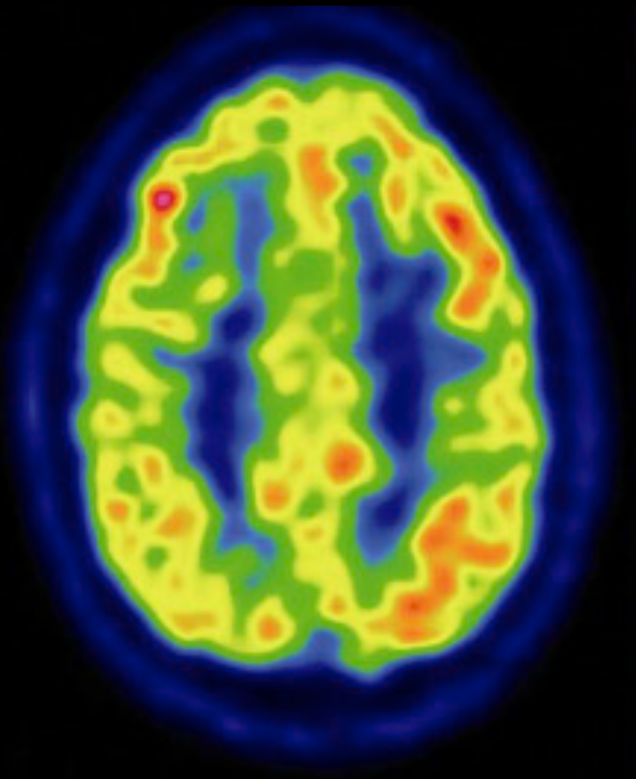
Alzheimer’s Disease

^{11} C-Acetoacetate



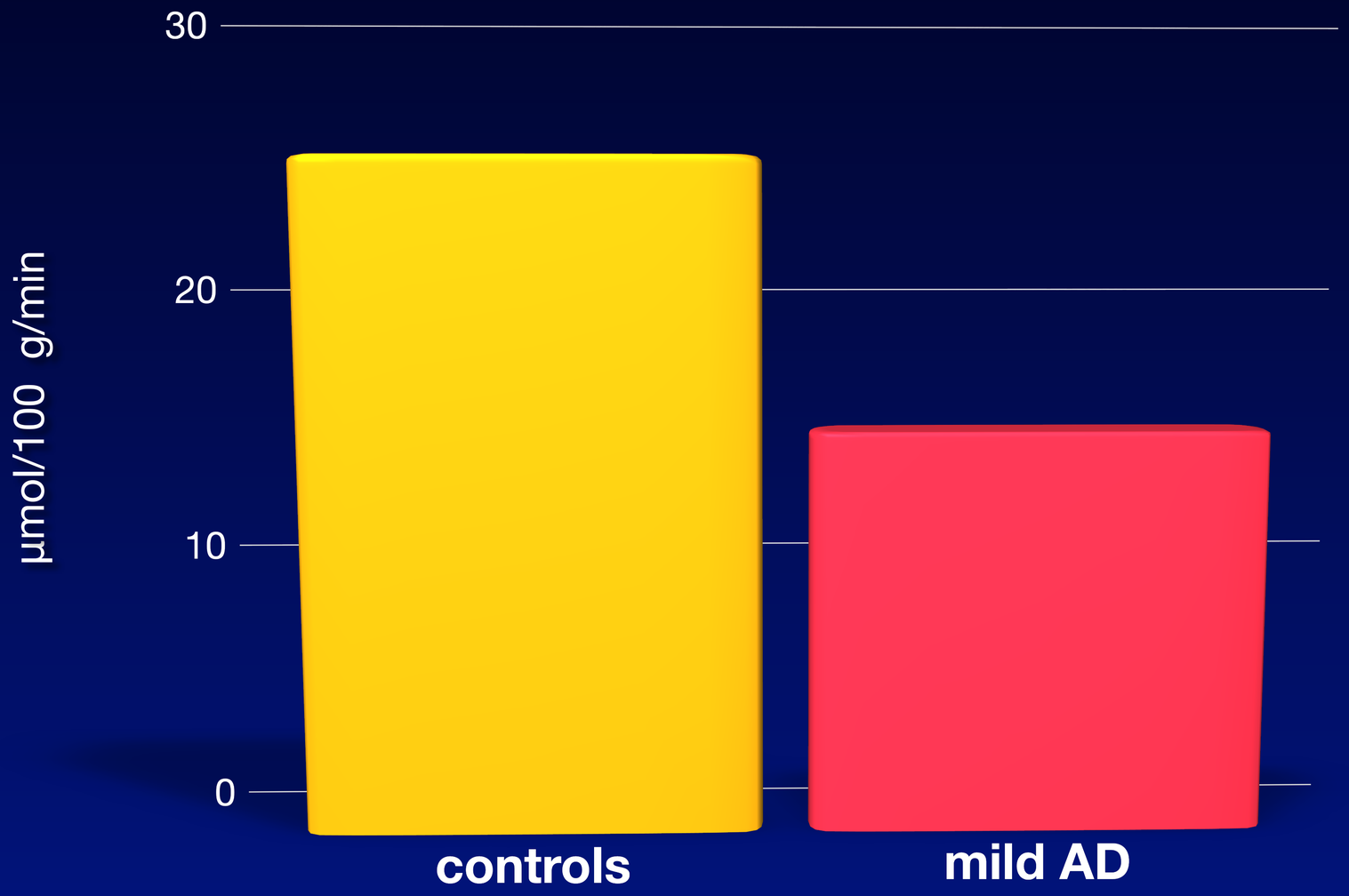
ketones

^{18} Fluorodeoxyglucose



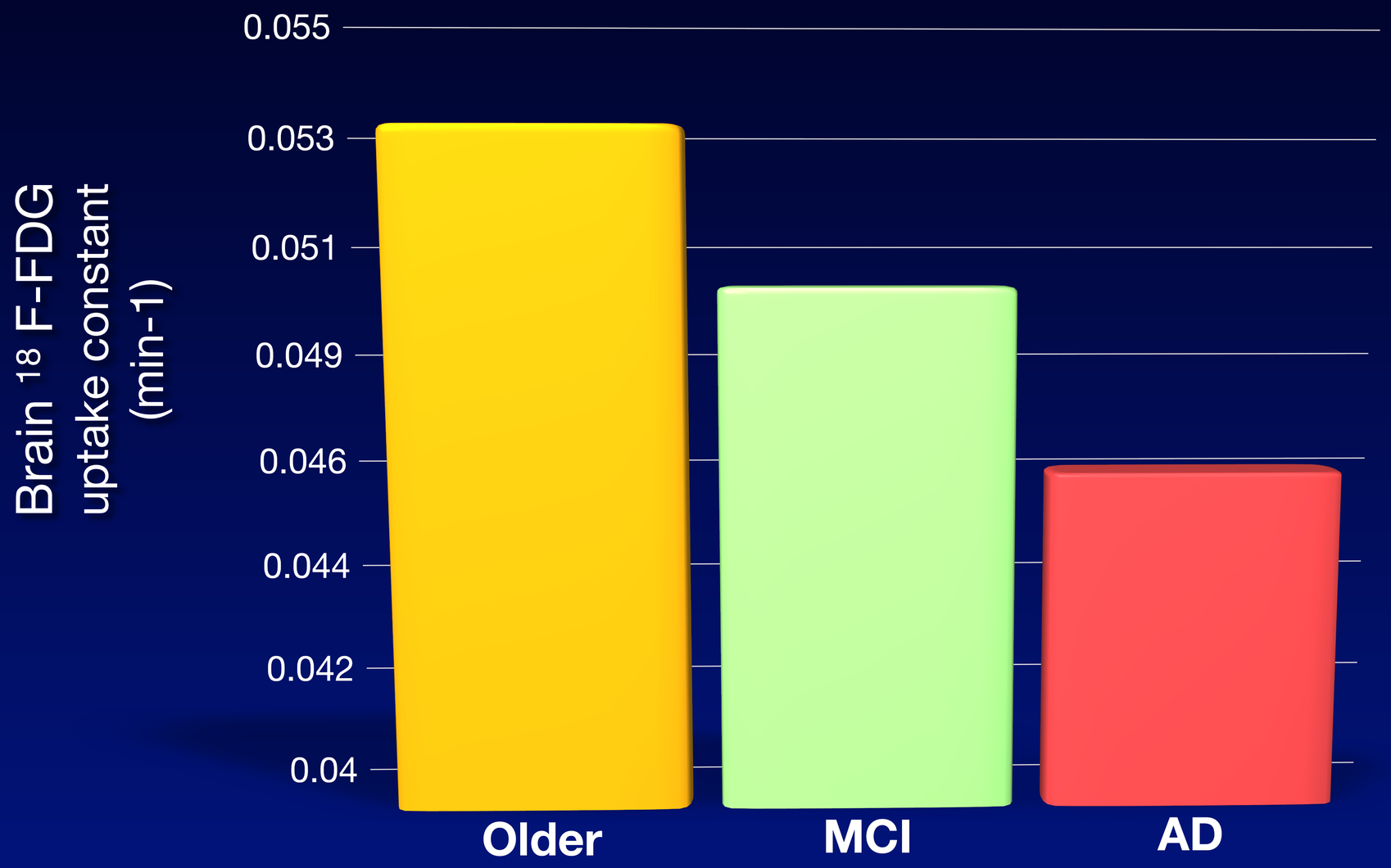
glucose

Brain Glucose Uptake



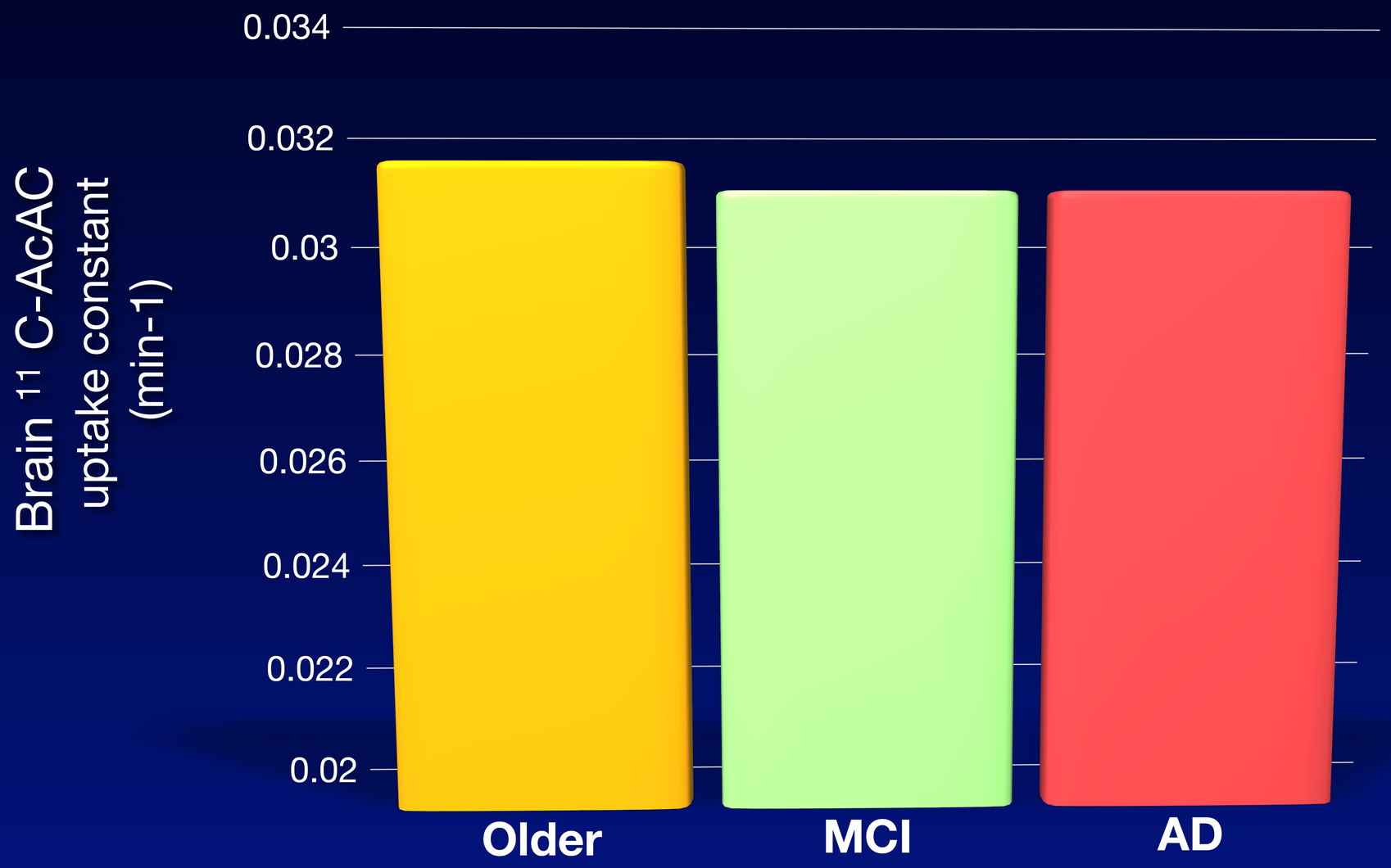
Frontiers in Molecular Neuroscience. July 8, 2016

Glucose uptake



Frontiers in Molecular Neuroscience. July 8, 2016

Ketone uptake



Frontiers in Molecular Neuroscience. July 8, 2016

Alzheimer’s Disease Is Type 3 Diabetes—Evidence Reviewed

JAMA January 8, 2020

Journal of Diabetes Science and Technology. November, 2008

Alzheimer's Disease Is Type 3 Diabetes—Evidence Reviewed

JAMA. January 8, 2020

Alzheimer's disease - characteristic abnormalities

cell loss
abundant neurofibrillary tangles
dystrophic neurites
amyloid precursor protein
amyloid-β (APP-Aβ) deposits
increased activation of prodeath genes and signaling pathways
impaired energy metabolism
mitochondrial dysfunction
chronic oxidative stress
DNA damage

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DNA damage

Disturbances in brain insulin and insulin-like growth factor (IGF) signaling mechanisms

Journal of Diabetes Science and Technology. November, 2008

In Alzheimer’s Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial

Frontiers in Aging Neuroscience. May, 2016

In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial

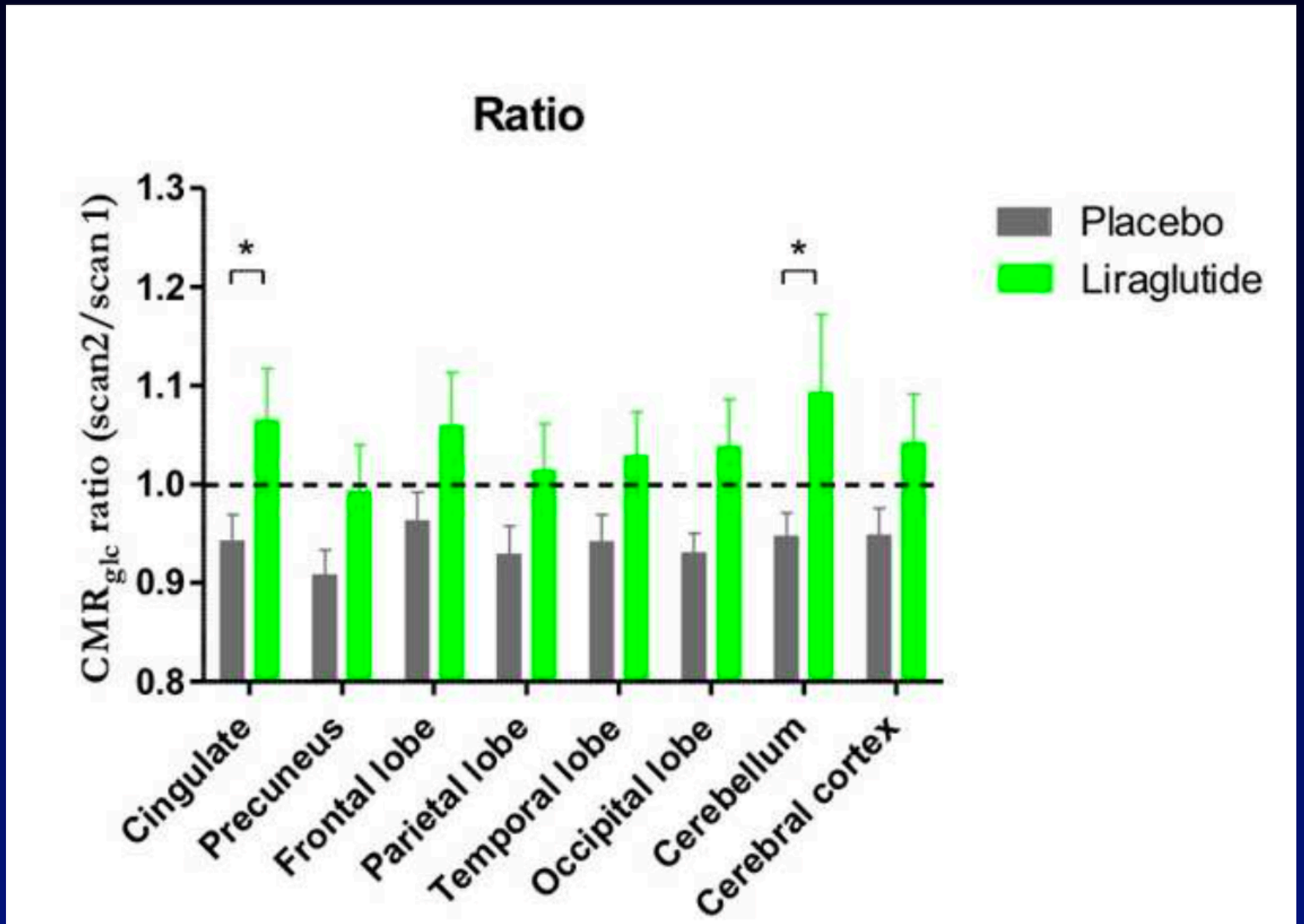
- 38 Alzheimer's participants
- Treatment 18 - placebo 20
- 26 weeks
- PET scans for beta-amyloid and glucose utilization
- Cognitive assessments

Frontiers in Aging Neuroscience. May, 2016

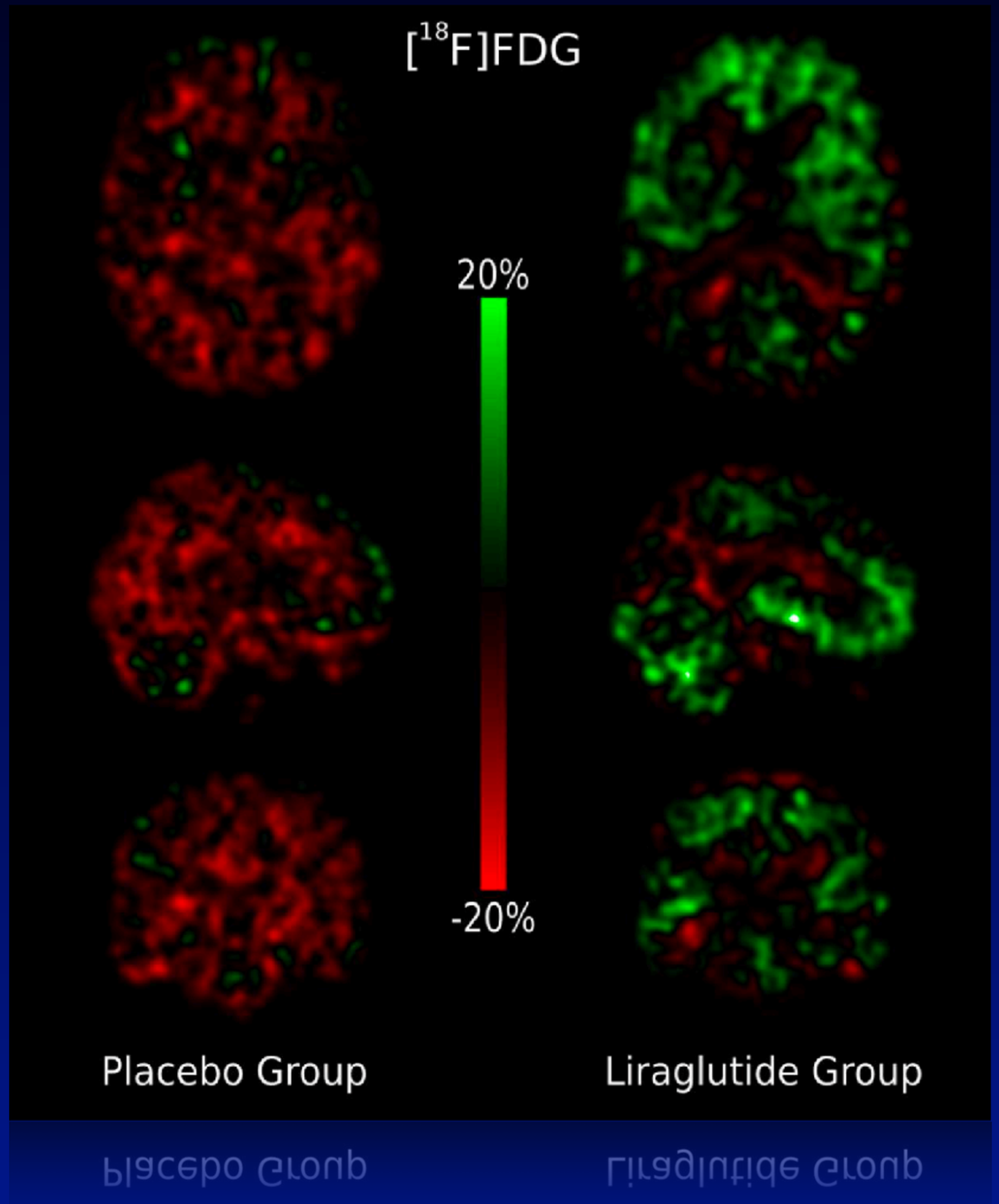
In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial

- Treatment - GLP-1 analog liraglutide

Frontiers in Aging Neuroscience. May, 2016



Frontiers in Aging Neuroscience. May, 2016



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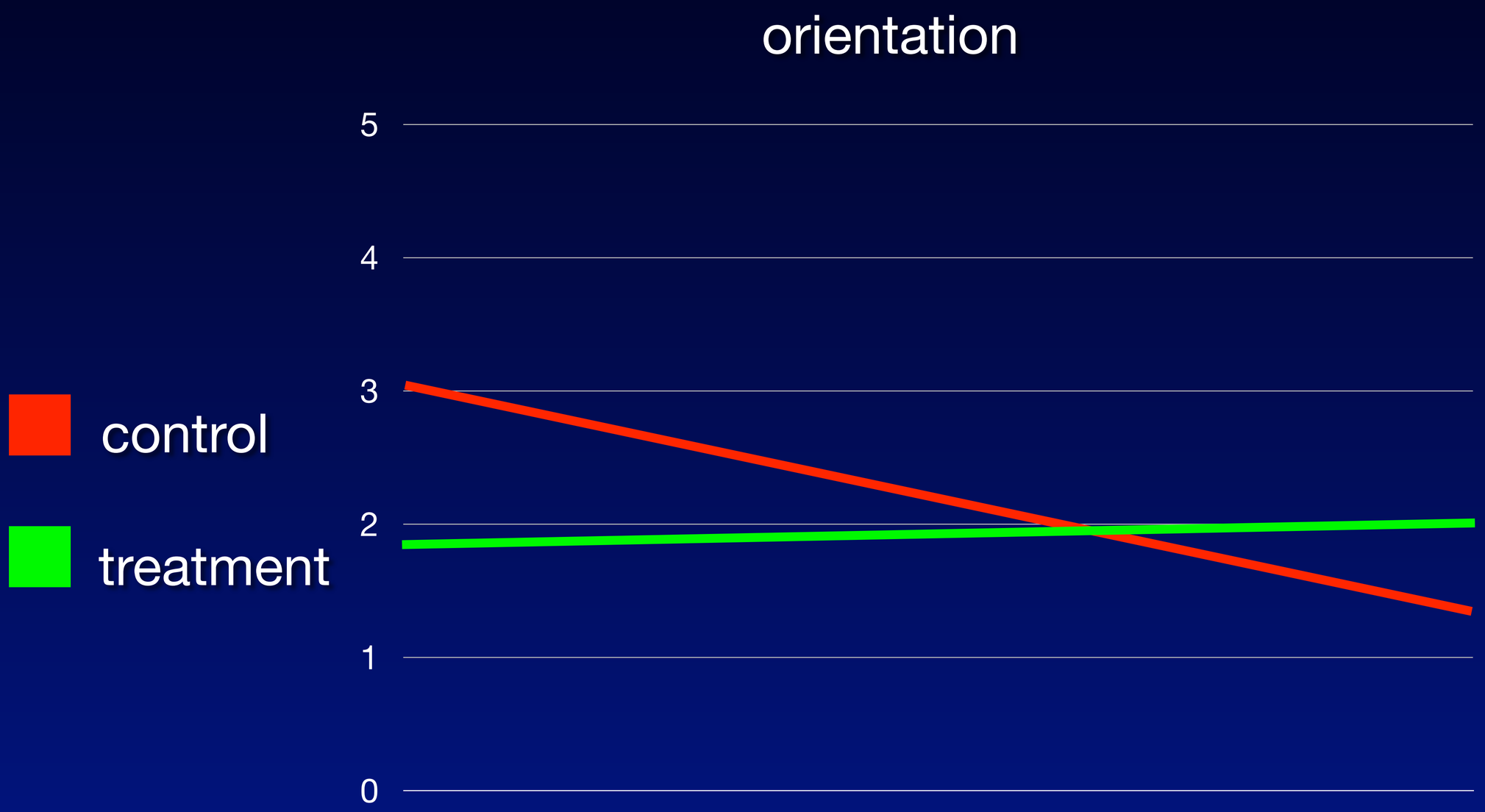
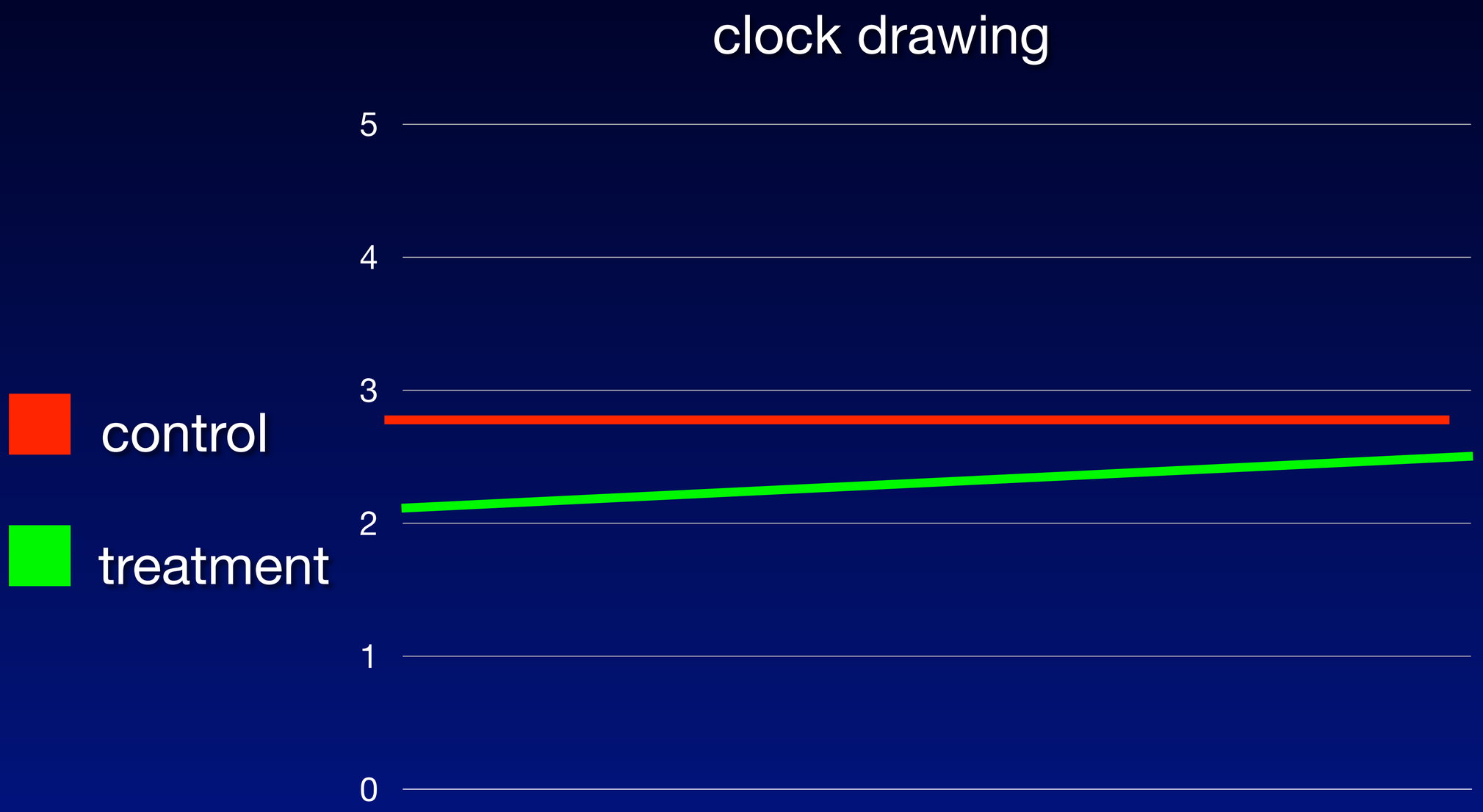


Frontiers in Aging Neuroscience. May, 2016



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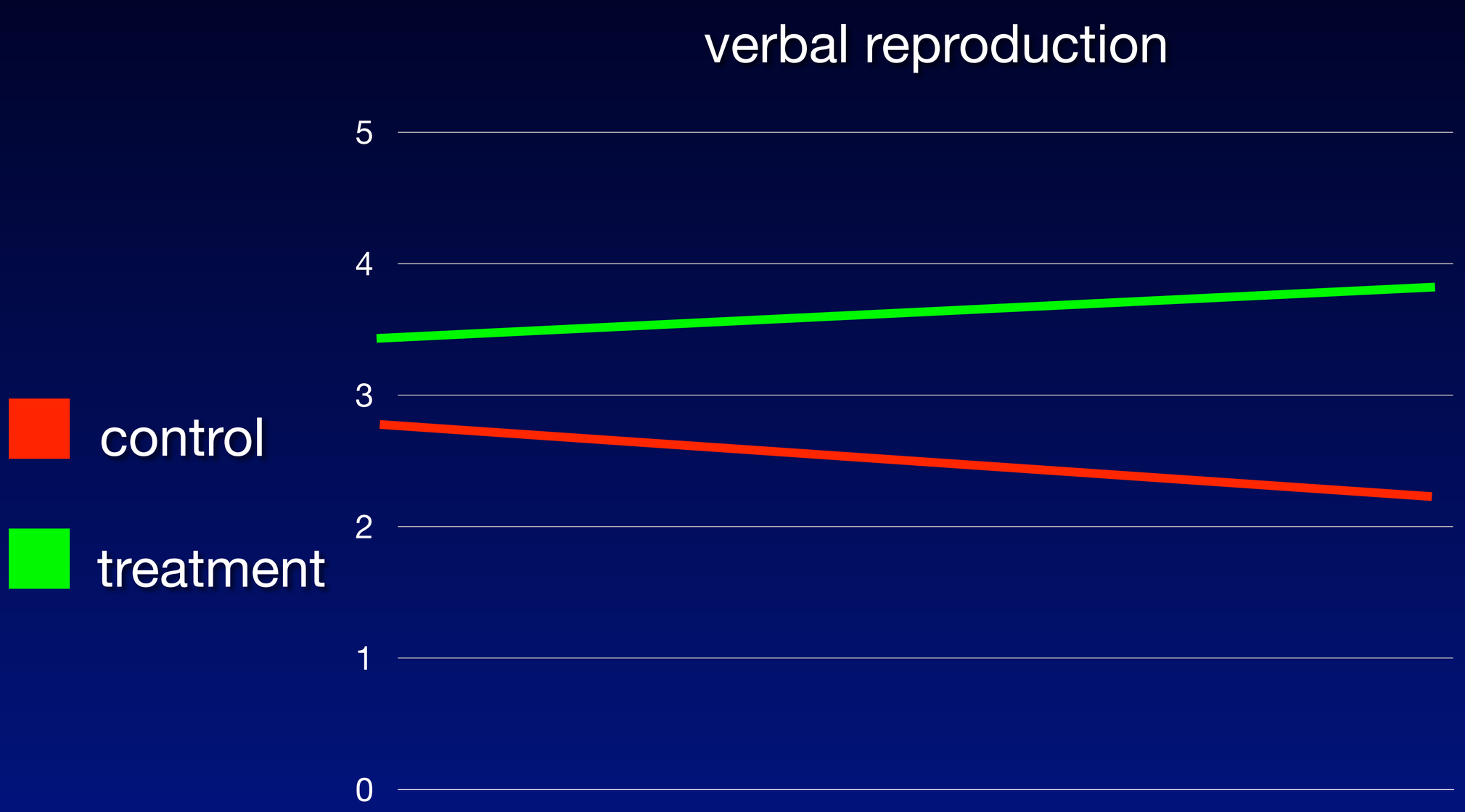


Frontiers in Aging Neuroscience. May, 2016

We conclude that the GLP-1 analog treatment prevented the decline of glucose metabolism associated with cognitive impairment, synaptic dysfunction, and disease evolution. We draw no firm conclusions from the Aβ load or cognition measures, for which the study was underpowered.

Frontiers in Aging Neuroscience. May, 2016

News & Analysis

JAMA January 8, 2020

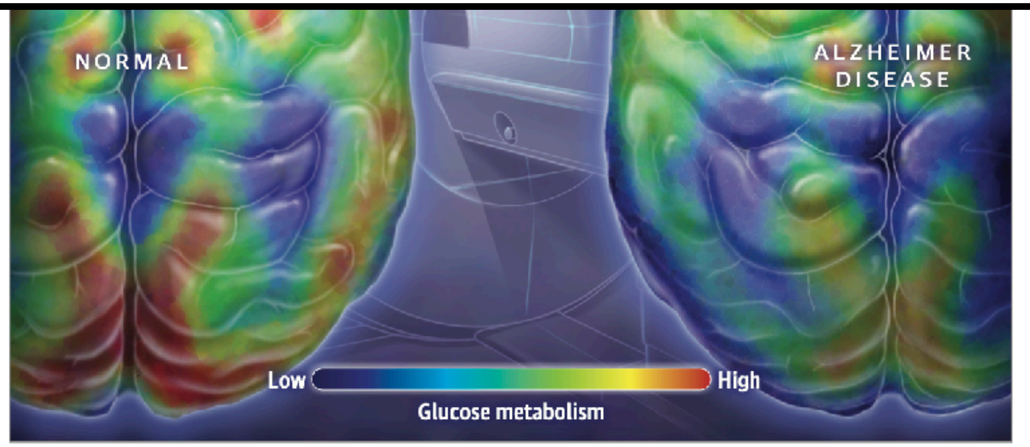
Medical News & Perspectives

In Alzheimer Research, Glucose Metabolism Moves to Center Stage

Bridget M. Kuehn, MSJ

At the same time, clinical researchers are exploring ways to slow or prevent dementia using drugs and **lifestyle modifications typically prescribed for metabolic disorders like diabetes or obesity.** These lines of inquiry have taken on new urgency as several amyloid-targeting therapies for Alzheimer disease have failed in clinical trials, leading to questions about whether the so-called amyloid hypothesis may be flawed.

recent annual meeting, several research teams presented data on mechanisms that may hamper brain energy metabolism in Alzheimer disease—and potentially contribute to cognitive decline. At the same time, clinical researchers are exploring ways to slow or prevent dementia using drugs and lifestyle modifications typically prescribed for metabolic disorders like diabetes or obesity. These lines of inquiry have taken on new urgency as several amyloid-targeting therapies for Alzheimer disease have failed in clinical trials, leading to questions about whether the so-called amyloid hypothesis may be flawed.



Diabetes clearly contributes to vascu-

tible to other conditions of aging, such as

Association between healthy lifestyle and memory decline in older adults: 10 year, population based, prospective cohort study

Our results show that a healthy lifestyle was associated with a slower rate of memory decline in cognitively normal older individuals, including in people who are genetically susceptible to memory decline.

Jia, J., et al.,*The BMJ.* January, 2023

OPEN ACCESS

Association between healthy lifestyle and memory decline in older adults: 10 year, population based, prospective cohort study

Association between healthy lifestyle and memory decline in older adults: 10 year, population based, prospective cohort study

Jianping Jia,[1] Yan Zhao,[1] Zhaojun Liu,[1] Yunlei Liang,[1] Fangyu Li,[1] Yan Li,[1] Wenying Liu,[1] Tang Li,[2] Shengliang Shi,[3] Chunkui Zhou,[4] Heyun Yang,[5] Zhengluan Liao,[6] Yang Li,[7] Huiying Zhao,[8] Jintao Zhang,[9] Kunnan Zhang,[10] Minchen Kan,[11] Shanshan Yang,[12] Hao Li,[13] Zhongling Liu,[14] Rong Ma,[15] Jihui Lv,[16] Yue Wang,[17] Xin Yan,[18] Furu Liang,[19] Xiaoling Yuan,[20] Jinbiao Zhang,[21] Serge Gauthier,[22] Jeffrey Cummings[23,24]

For numbered affiliations see end of the article

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2023;380:e072691
http://dx.doi.org/10.1136/bmj-2022-072691

Accepted: 13 December 2022

ABSTRACT

OBJECTIVE

To identify an optimal lifestyle profile to protect against memory loss in older individuals.

DESIGN

Population based, prospective cohort study.

SETTING

Participants from areas representative of the north, south, and west of China.

PARTICIPANTS

Individuals aged 60 years or older who had normal cognition and underwent apolipoprotein E (APOE) genotyping at baseline in 2009.

MAIN OUTCOME MEASURES

used to explore the impact of lifestyle factors on memory in the study sample.

RESULTS

29 072 participants were included (mean age of 72.23 years; 48.54% (n=14 113) were women; and 20.43% (n=5939) were APOE ε4 carriers). Over the 10 year follow-up period (2009-19), participants in the favourable group had slower memory decline than those in the unfavourable group (by 0.028 points/year, 95% confidence interval 0.023 to 0.032, P<0.001). APOE ε4 carriers with favourable (0.027, 95% confidence interval 0.023 to 0.031) and average (0.014, 0.010 to 0.019) lifestyles exhibited a slower memory decline than those with unfavourable lifestyles. Among people who were not carriers

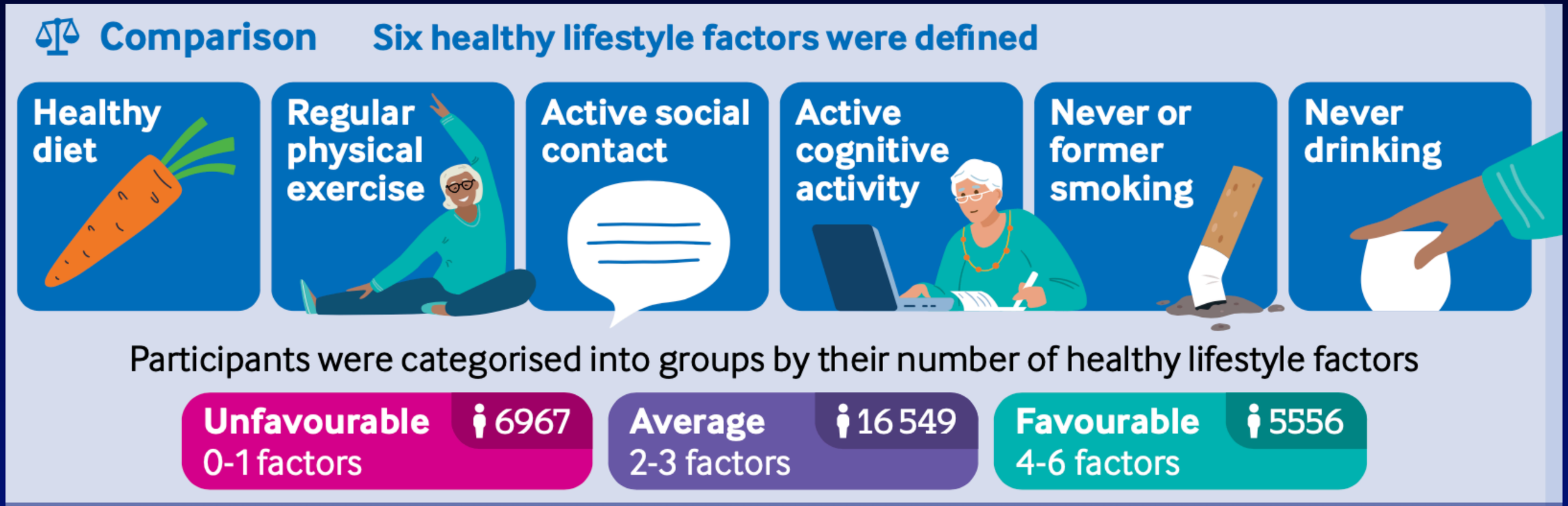
Association between healthy lifestyle and memory decline in older adults: 10 year, population based, prospective cohort study

Jia, J., et al.,*The BMJ.* January, 2023

Association between healthy lifestyle and memory decline in older adults: 10 year, population based, prospective cohort study

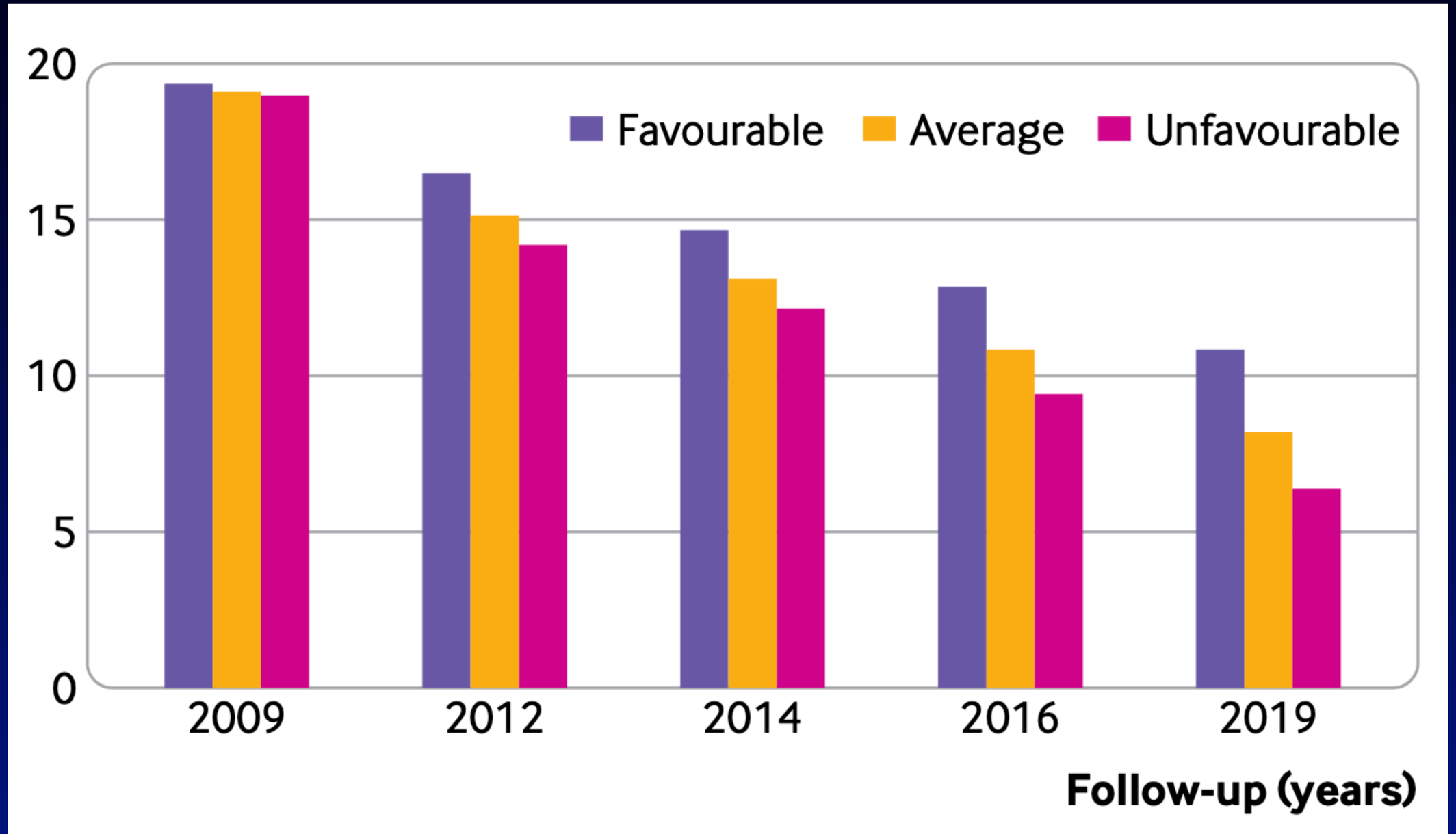
- 29,072 participants, normal cognitive function
- 46% women
- Followed 10 years
- APOE-ε4 status
- Cognitive evaluations

Jia, J., et al.,*The BMJ.* January, 2023



Jia, J., et al.,*The BMJ.* January, 2023

Mean score Auditory Verbal Learning Test



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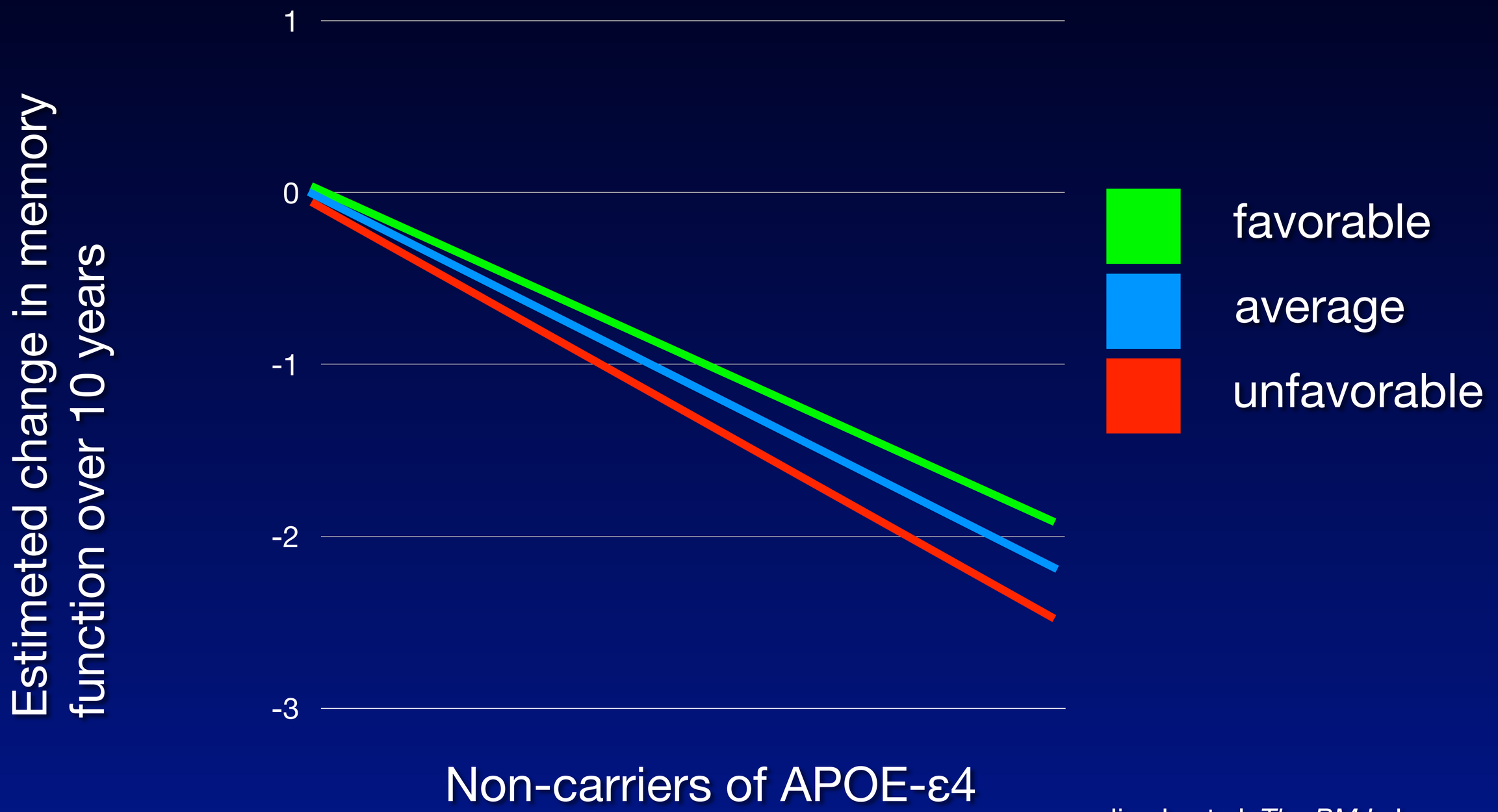

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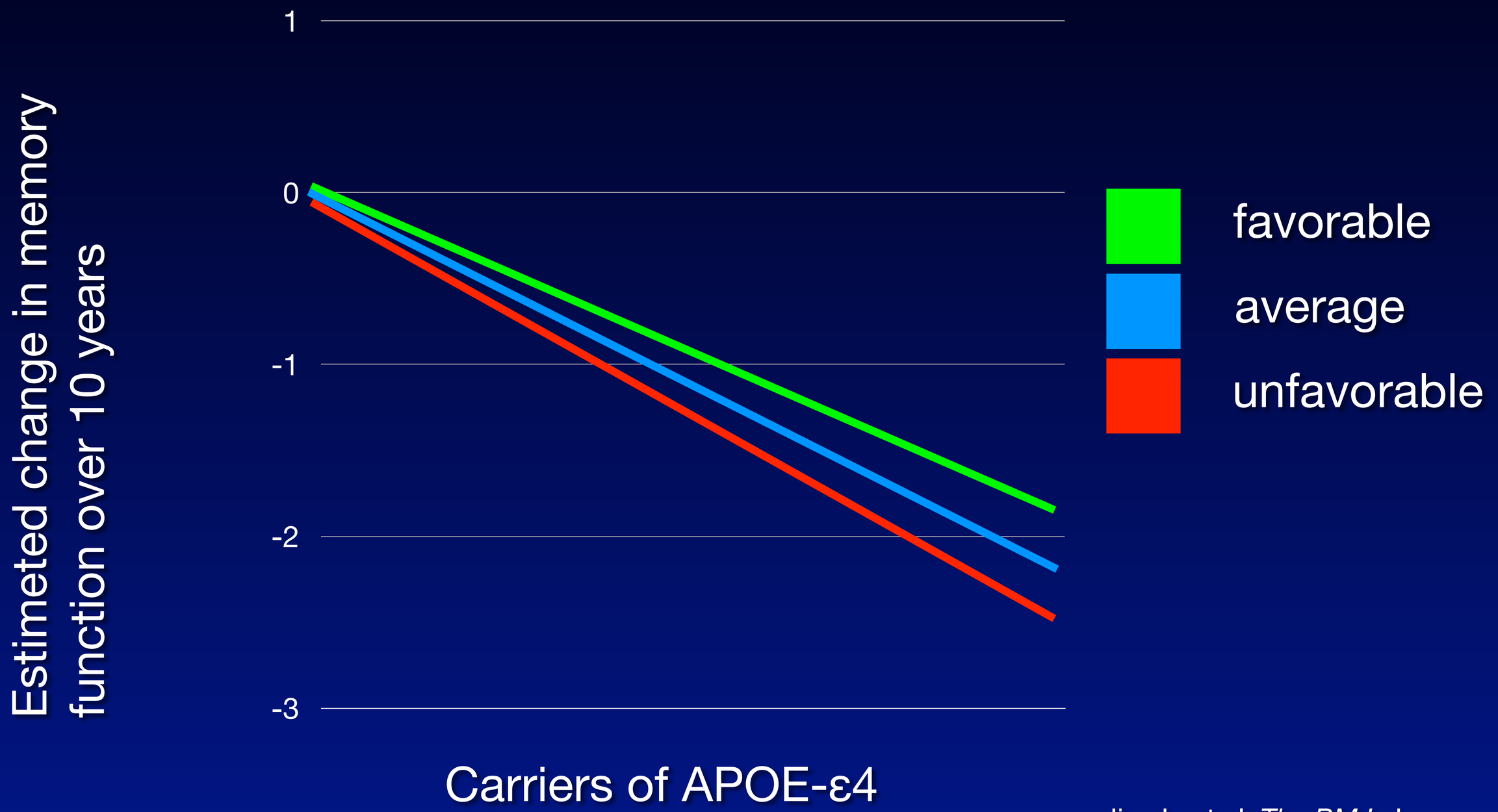

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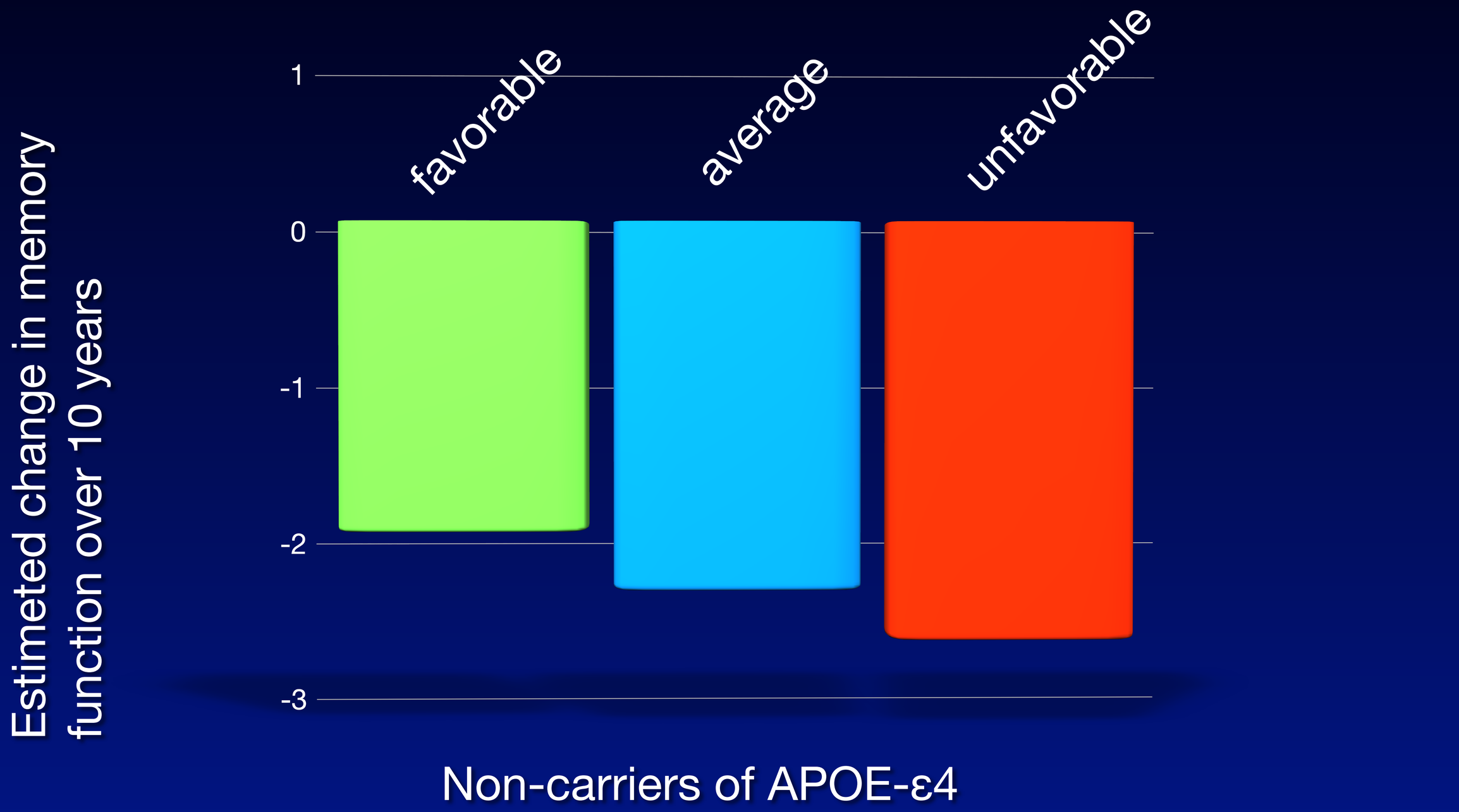
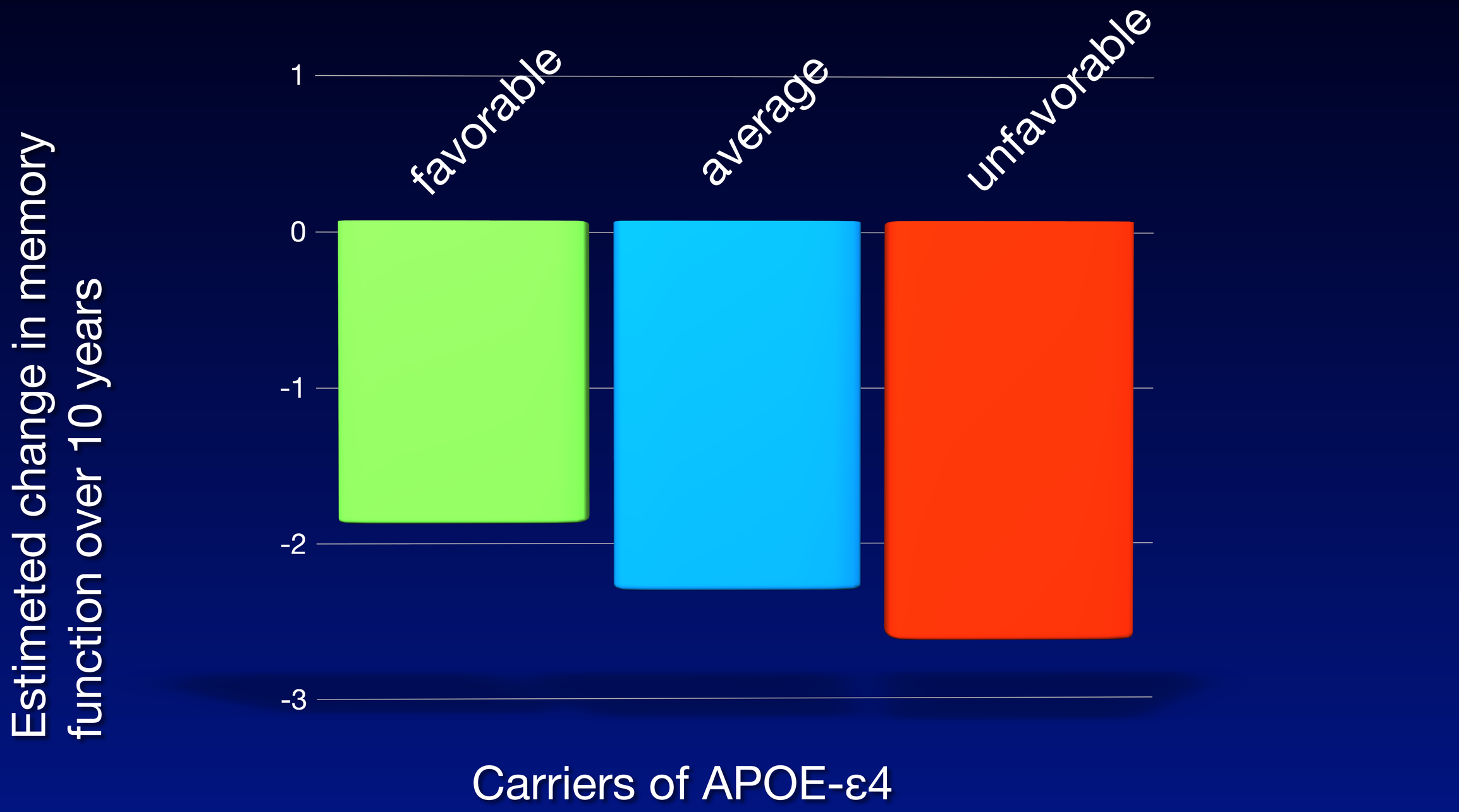


Jia, J., et al.,*The BMJ.* January, 2023



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Handgrip Strength Is Related to Hippocampal and Lobar Brain Volumes in a Cohort of Cognitively Impaired Older Adults with Confirmed Amyloid Burden

Meysami, S., et al., Journal of Alzheimer’s Disease. December, 2022

Handgrip Strength Is Related to Hippocampal and Lobar Brain Volumes in a Cohort of Cognitively Impaired Older Adults with Confirmed Amyloid Burden

- 38 Alzheimer’s patients Hand dynamometer
- Frail vs non-frail based on two-minute walk test
- Volumetric brain MRI

Meysami, S., et al., Journal of Alzheimer’s Disease. December, 2022

- Higher non-dominant handgrip strength associated with larger hippocampus
- Higher dominant handgrip strength associated with larger frontal lobe volume
- Frailty associated with reduced frontal, temporal and parietal lobe volumes

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How does the skeletal muscle communicate with the brain in health and disease?

Isaac, A., et al.,, et al., *Neuropharmacology,* August 2021

How does the skeletal muscle communicate with the brain in health and disease?

Muscle is an endocrine organ

- pituitary
- pineal
- pancreas
- adrenal
- parathyroid
- ovaries
- testes
- thyroid

Isaac, A., et al.,, et al., *Neuropharmacology,* August 2021

Myokines

Cytokines synthesized and released by muscle cells during muscular contractions. Molecular mediators of the whole body effects of exercise.

Myokinome

Isaac, A., et al.,, et al., *Neuropharmacology,* August 2021

Myokines

- Interleukin-6 (IL-6)
- Ketone bodies
- Lactate
- Irisin
- Cathepsin-B
- BDNF

Active regulators of brain metabolism

Isaac, A., et al.,, et al., *Neuropharmacology,* August 2021

Interleukin-6 (IL-6)

- Released with muscular contraction even without inflammation
- Increases glucose uptake, lipolysis and fatty oxidation in muscle
- Activates AMPK

Isaac, A., et al.,, et al., *Neuropharmacology,* August 2021

How does the skeletal muscle communicate with the brain in health and disease?

Proper muscle-to-brain signaling is an essential physiological mechanism that, once disrupted, may contribute to defective endocrine communication, and predispose individuals for brain disease.

Isaac, A., et al.,, et al., *Neuropharmacology,* August 2021

Timing of physi … r- life cognition: 30 ye … th cohort

Original research

Timing of physical activity across adulthood on later-life cognition: 30 years follow-up in the 1946 British birth cohort

Sarah-Naomi James [1], Yu-Jie Chiou,[1,2,3] Nasri Fatih,[1] Louisa P Needham,[1] Jonathan M Schott [1,4], Marcus Richards[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2022-329955).

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S-NJ and Y-JC are joint first authors.
JMS and MR are joint last authors.

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ABSTRACT

Background To assess how timing, frequency and maintenance of being physically active, spanning over 30 years in adulthood, is associated with later-life cognitive function.

Methods Participants (n=1417, 53% female) were from the prospective longitudinal cohort study, 1946 British birth cohort. Participation in leisure time physical activity was reported five times between ages 36 and 69, categorised into: not active (no participation in physical activity/month); moderately active (participated 1–4 times/month); most active (participated 5 or more times/month). Cognition at age 69 was assessed by tests of cognitive state (Addenbrooke's Cognitive Examination-III), verbal memory (word learning test) and processing speed (visual search speed).

Results Being physically active, at all assessments in adulthood, was associated with higher cognition at age 69. For cognitive state and verbal memory, the effect sizes were similar across all adult ages, and between those who were moderately and most physically active. The strongest association was between sustained cumulative physical activity and later-life cognitive state, in a dose-response manner. Adjusting for childhood cognition, childhood socioeconomic position and education largely attenuated these associations but results mainly remained significant at the 5% level.

Conclusions Being physically active at any time in adulthood, and to any extent, is linked with higher later-life cognitive state, but lifelong maintenance of physical activity was most optimal. These relationships were partly explained by childhood cognition and education, but independent of cardiovascular and mental health and APOE-E4, suggestive of the importance of education on the lifelong impacts of physical activity.

beneficial for later-life cognition,[6 7] studies often have short follow-up periods, or are at risk of reverse directionality.[8] Midlife is an important period of risk exposure for cardiovascular health on later-life cognition and brain health,[4 9 10] yet it is unclear if there are important, so-called 'sensitive', periods for physical activity exposure, or an influential role of sustained and preserved activity throughout life, on later-life cognition. Furthermore, pathways underlying the relationship between physical activity and later-life cognition are not well established. Associations observed could be explained by earlier-life confounders such as education and social class.[11 12] Implicated pathways conferring causal benefits also include better cardiovascular health[13] and better mental health.[4] There may also be a differential effect of physical activity on cognition by genetic APOE ε4 risk status.[14]

Using data from the population-based 1946 British birth cohort, which has followed people born in the same week of 1946, previous studies have demonstrated beneficial effects of midlife physical activity on midlife verbal memory[15] and search speed[16] decline. Here, we extend this work by taking a life course approach to evaluate the effects of physical activity timing, frequency and maintenance, spanning over 30 years, with later-life cognitive function. We assess three measures of later-life cognitive function including a measure of cognitive state, verbal memory and processing speed. We further aim to investigate to what extent, these effects are explained by pathways including earlier-life influences, cardiovascular health and mental health.

To investigate the effect of timing of physical

Timing of physical activity across adulthood on later- life cognition: 30 years follow-up in the 1946 British birth cohort

James, SN., et al., *Journal of Neurology, Neurosurgery and Psychiatry.* February 2023

Timing of physical activity across adulthood on later- life cognition: 30 years follow-up in the 1946 British birth cohort

- n =1417 followed over 30 years
- Reported leisure time physical activity 5 times between ages 36 and 69
- Cognitive testing at age 69 years

James, SN., et al., *Journal of Neurology, Neurosurgery and Psychiatry.* February 2023

- Being physically active, at all assessments in adulthood, was associated with higher cognition at age 69

- The strongest association was between *sustained* cumulative physical activity and later-life cognitive state, in a dose-response manner.

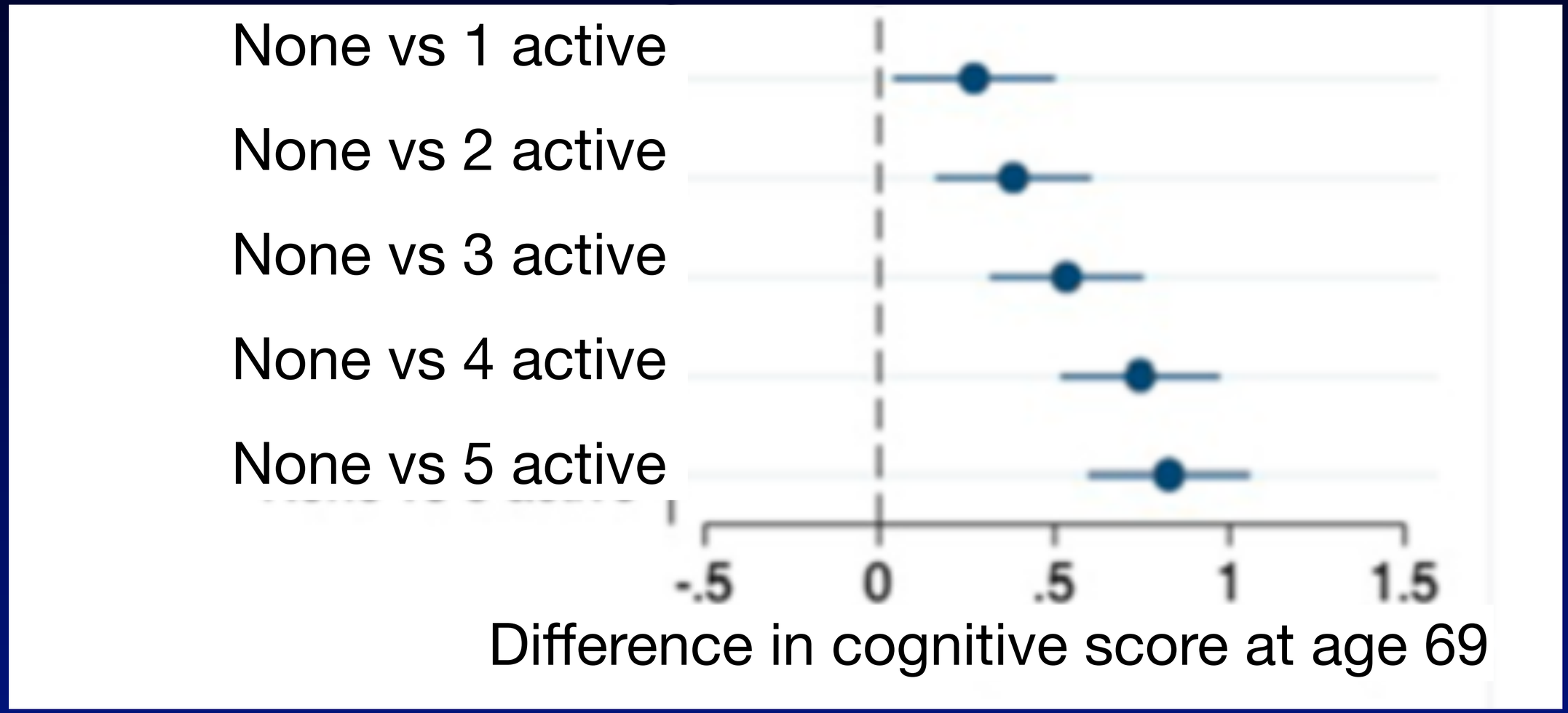
James, SN., et al., *Journal of Neurology, Neurosurgery and Psychiatry.* February 2023

- These relationships were independent of cardiovascular and mental health and APOE-E4, suggestive of the importance of education on the lifelong impacts of physical activity

James, SN., et al., *Journal of Neurology, Neurosurgery and Psychiatry.* February 2023

Adenbrooke's Cognitive Examination-III total score

Any active periods across adulthood



James, SN., et al., *Journal of Neurology, Neurosurgery and Psychiatry.* February 2023

Timing of physical activity across adulthood on later- life cognition: 30 years follow-up in the 1946 British birth cohort

Our findings support guidelines to recommend participation in any physical activity across adulthood and provide evidence that encouraging inactive adults to be more active at any time, and encouraging already active adults to maintain activity, could confer benefits on later-life cognition.

James, SN., et al., *Journal of Neurology, Neurosurgery and Psychiatry.* February 2023

JCI insight

CLINICAL MEDICINE

Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese

Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese

Stephanie Kullmann,[1,2,3] Thomas Goj,[1,2,4] Ralf Veit,[1,2] Louise Fritsche,[1,2] Lore Wagner,[1,2] Patrick Schneeweiss,[5,6] Miriam Hoene,[4] Christoph Hoffmann,[4] Jürgen Machann,[1,2,7] Andreas Niess,[5,6] Hubert Preissl,[1,2,3,8] Andreas L. Birkenfeld,[1,2,3] Andreas Peter,[1,2,4] Hans-Ulrich Häring,[1,2,3] Andreas Fritsche,[1,2,3] Anja Moller,[1,2,3] Cora Weigert,[1,2,4] and Martin Heni[1,2,3,4,9]

[1]Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany. [2]German Center for Diabetes Research (DZD e.V.), Neuherberg, Germany. [3]Department of Internal Medicine, Division of Endocrinology, Diabetology and Nephrology, Eberhard Karls University Tübingen, Tübingen, Germany. [4]Institute for Clinical Chemistry and Pathobiochemistry and [5]Department of Sports Medicine, University Hospital Tübingen, Germany. [6]Interfaculty Research Institute for Sport and Physical Activity, University of Tübingen, Tübingen, Germany. [7]Department of Radiology, Section on Experimental Radiology, University Hospital Tübingen, Germany. [8]Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany. [9]Division of Endocrinology and Diabetology, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany.

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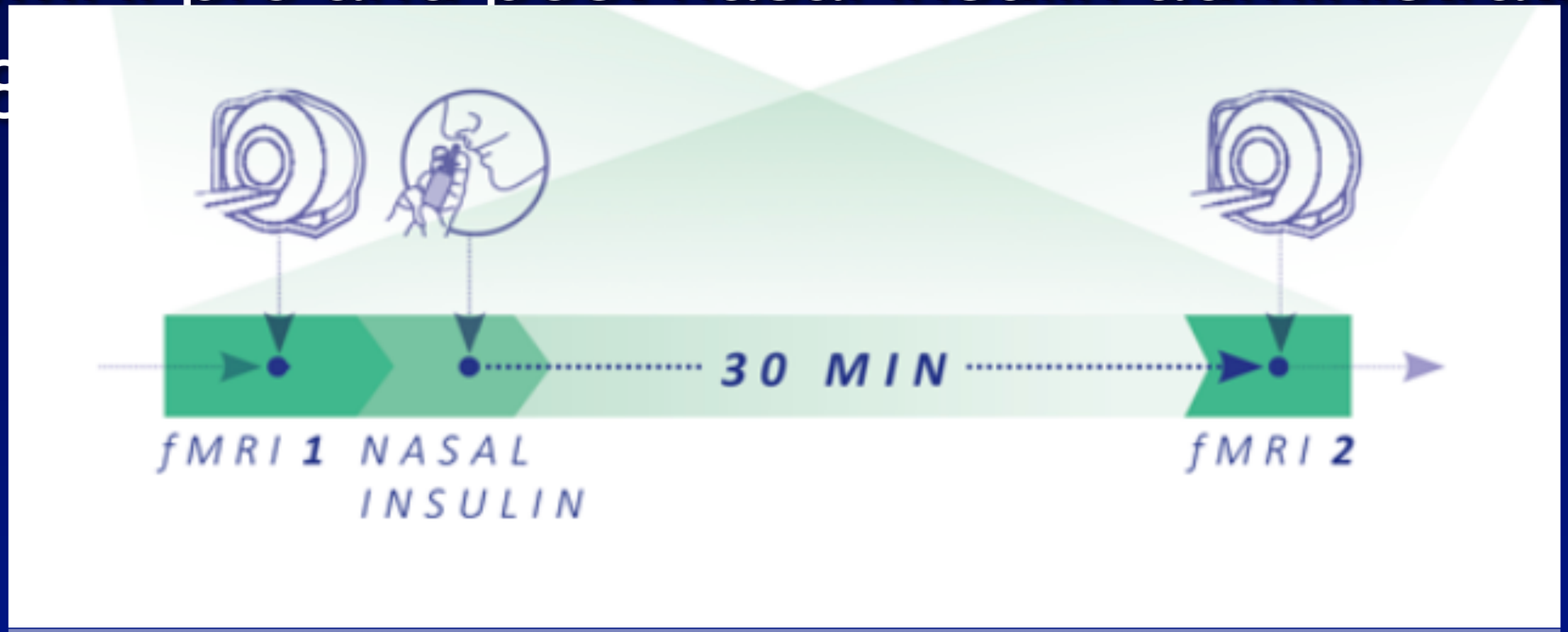

Kullmann, S., et al., *JCI Insight*. September, 2022

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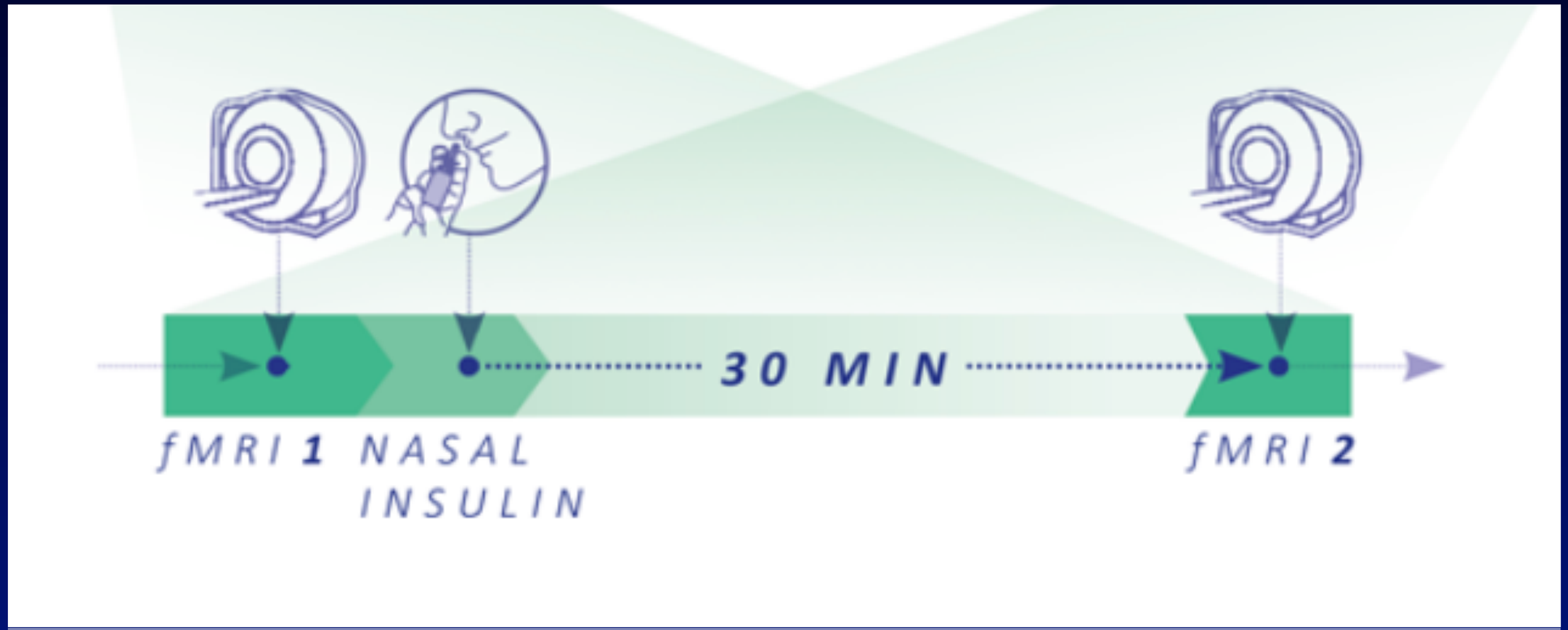
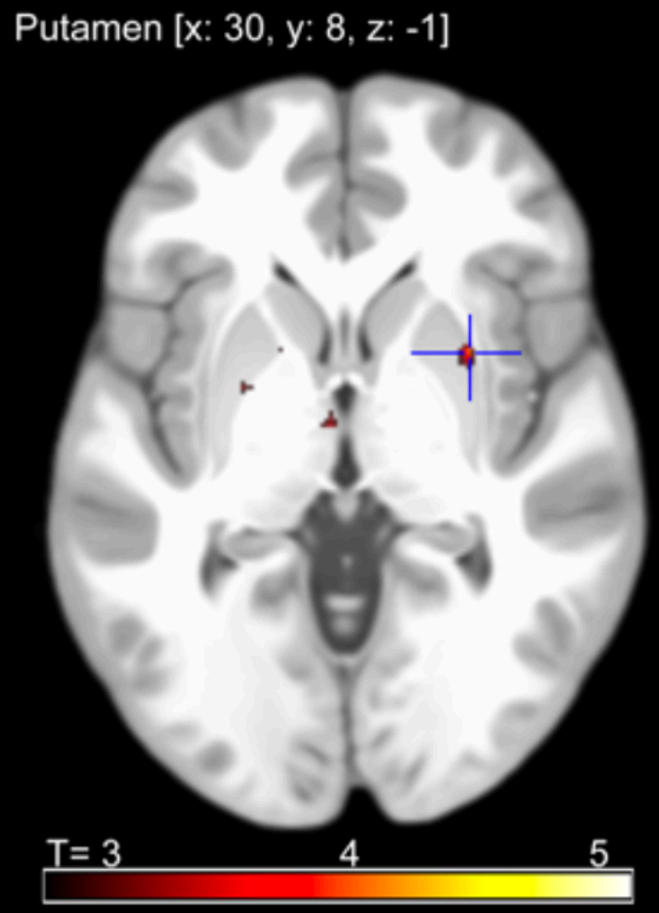
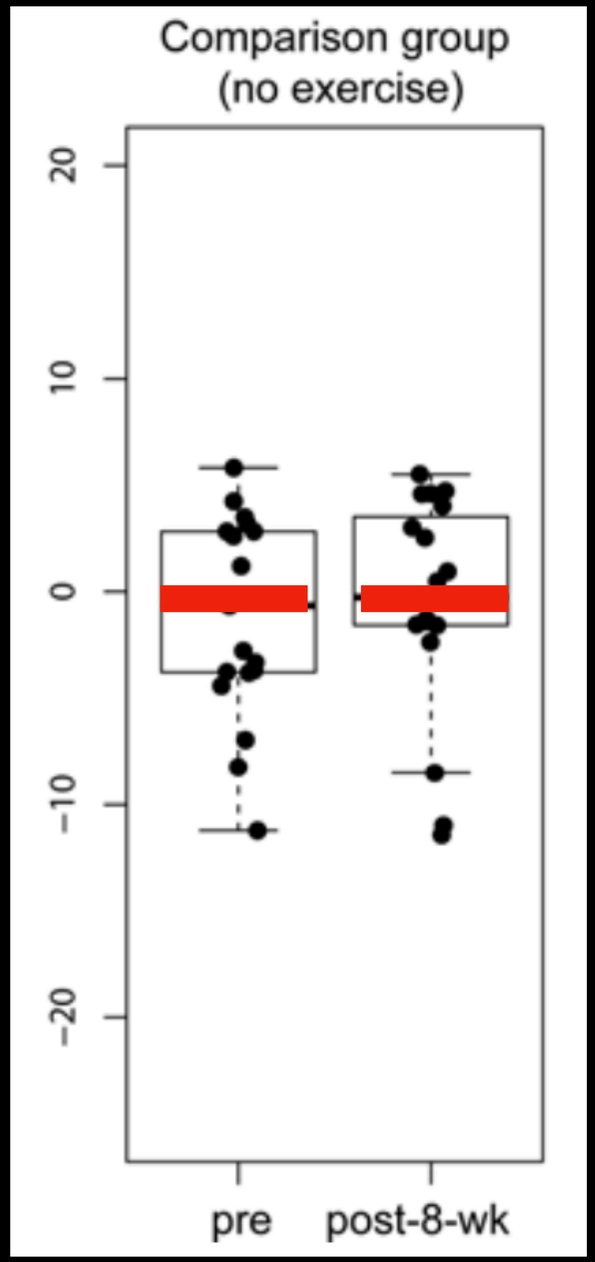
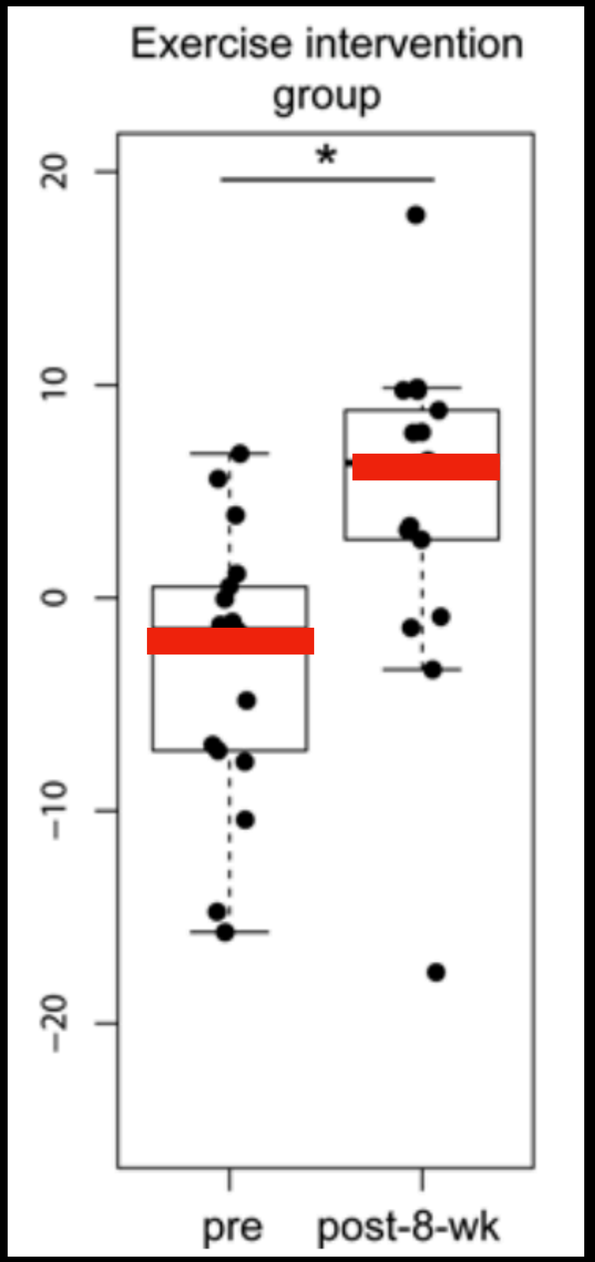


Kullmann, S., et al., *JCI Insight*. September, 2022

Δ CBF Putamen (ml/100g/min) (comparing before and after insulin)







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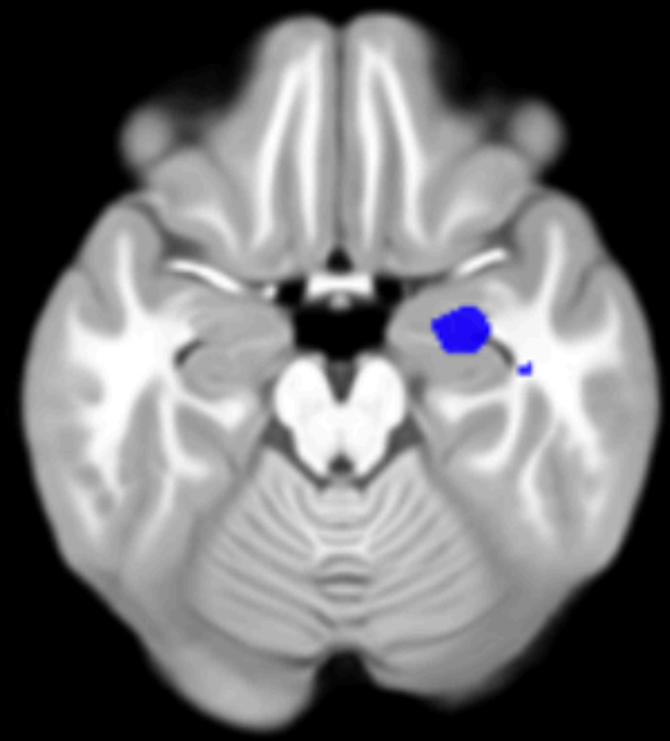
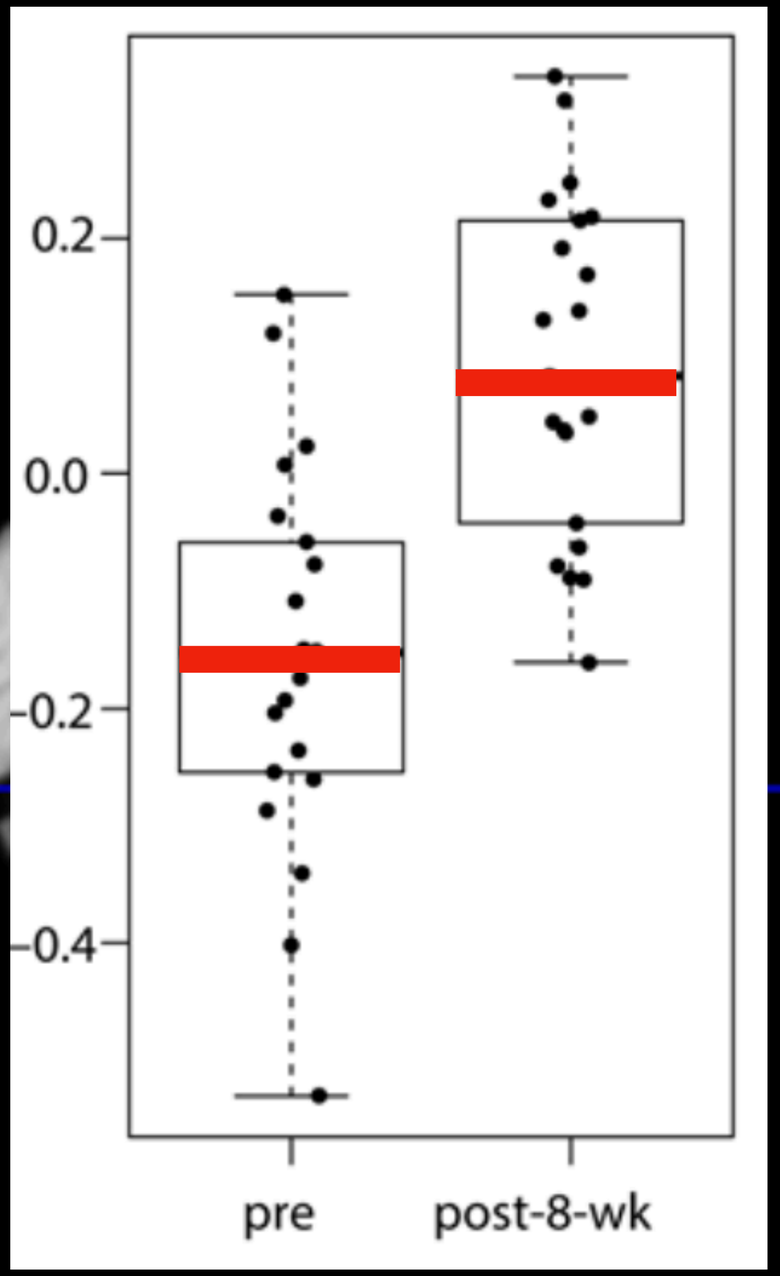
Functional Connectivity (Change)

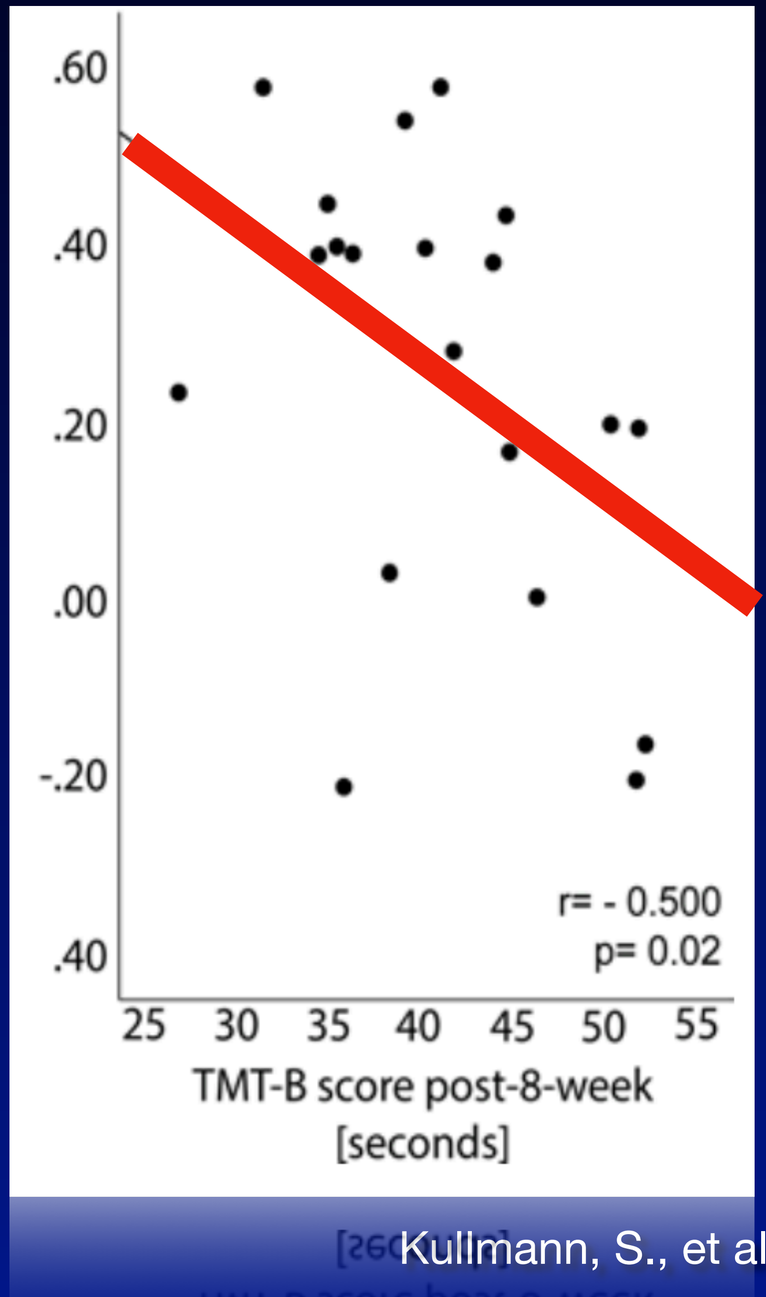


Hippocampus [x: 28, y: -8, z: -20]



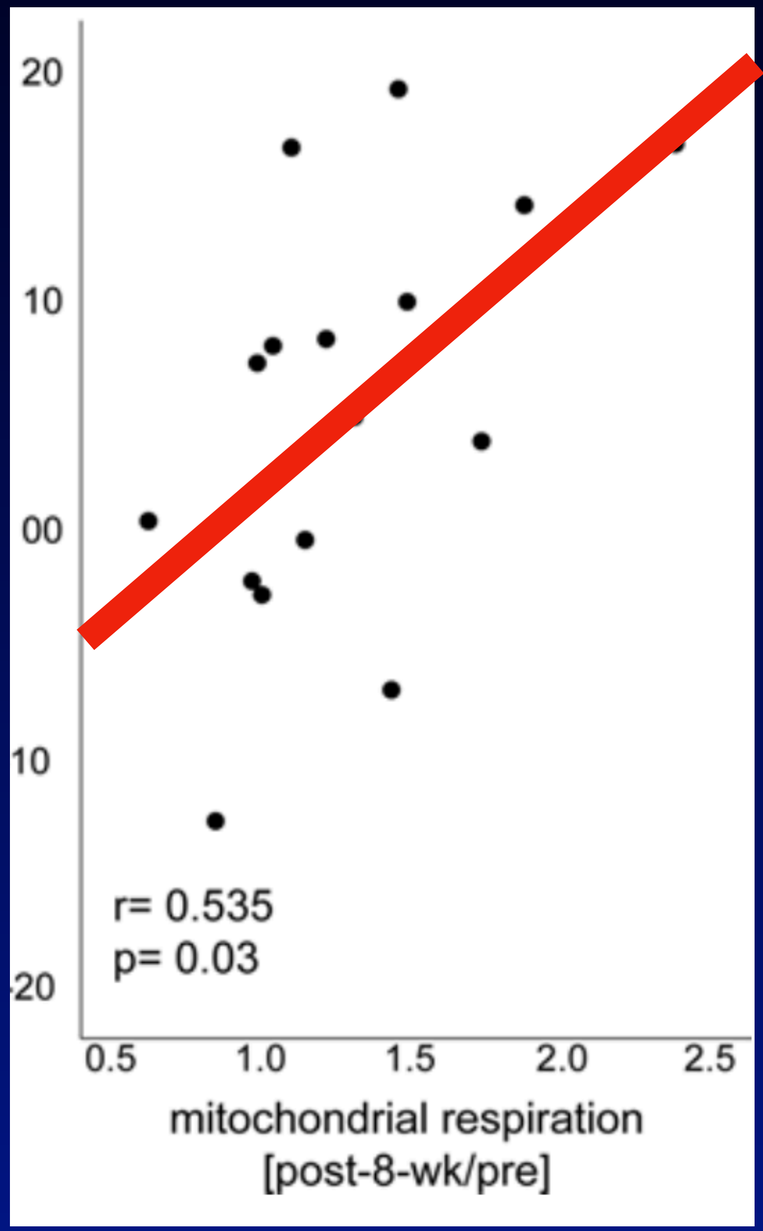
Kullmann, S., et al., *JCI Insight*. September, 2022

Change in functional connectivity (trail making test)



Kullmann, S., et al., *JCI Insight*. September, 2022

Mitochondrial respiration (fold change)



Kullmann, S., et al., *JCI Insight*. September, 2022

Blog • September 19, 2022

New Medication Associated with a 50% Risk Reduction for Dementia!

Association of Daily Step Count and Intensity With Incident Dementia in 78 430 Adults Living in the UK

- 78,430 adults (age 40-79 years)
- Followed 6.9 years
- Wrist accelerometer
- Diagnosis of dementia

del Pozo Cruz, B., et al. *JAMA Neurology*. September 6. 2022

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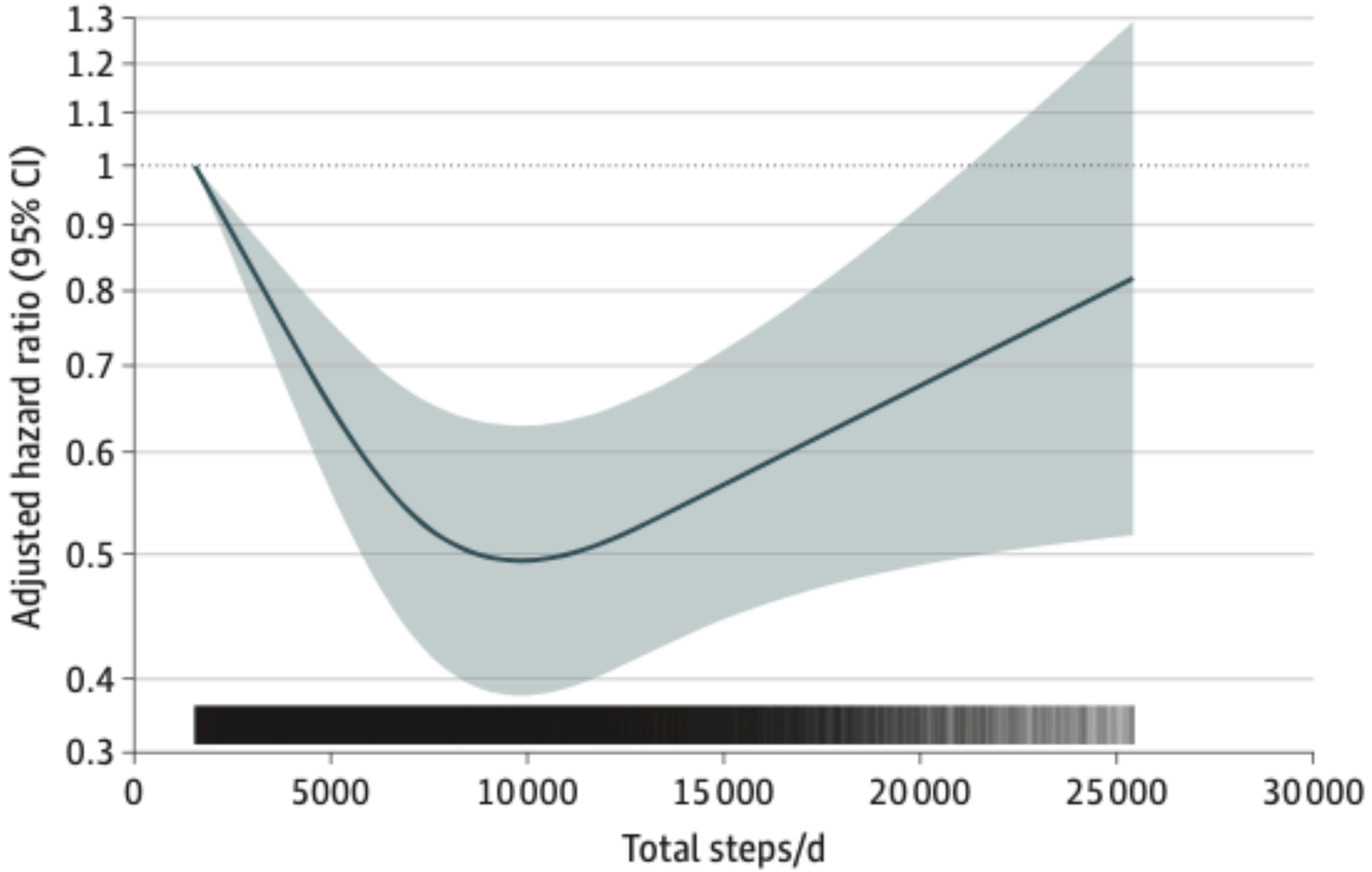
Total steps per day and incidence of all-cause dementia



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“We found no minimal threshold for the beneficial association of step counts with incident dementia. Our findings suggest that approximately 9800 steps per day may be optimal to lower the risk of dementia.”

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Vigorous, regular physical exercise may slow disease progression in Alzheimer's disease

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DOI: 10.1002/alz.12946

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

SHORT REPORT

Vigorous, regular physical exercise may slow disease progression in Alzheimer's disease

Davangere P. Devanand[1,2] | Arjun V. Masurkar[3] | Thomas Wisniewski[3,4]

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Funding information
National Institute on Aging, Grant/Award Numbers: 1R01AG055422, P30AG066512; Alzheimer's Association

Abstract

Introduction: Mild to moderate exercise may decrease Alzheimer's disease (AD) risk, but the effects of vigorous, regular physical exercise remain unclear.

Methods: Two patients with initial diagnoses of amnestic mild cognitive impairment (MCI) demonstrated positive AD biomarkers throughout 16 and 8 years of follow-up, with final diagnoses of mild AD and amnestic MCI, respectively.

Results: Patient 1 was diagnosed with amnestic MCI at age 64. Neuropsychological testing, magnetic resonance imaging (MRI), fluorodeoxyglucose–positron emission tomography (FDG-PET), amyloid imaging PET, and cerebrospinal fluid (CSF) biomarkers during follow-ups remained consistent with AD. By age 80, progression was minimal with Montreal Cognitive Assessment (MoCA) 26 of 30. Patient 2 was diagnosed with amnestic MCI at age 72. Neuropsychological testing, MRI, FDG-PET, and amyloid imaging PET during follow-ups remained consistent with AD. At age 80, MoCA was 27 of 30 with no clinical progression. Both patients regularly performed vigorous, regular exercise that increased after retirement/work reduction.

Discussion: Vigorous, regular exercise may slow disease progression in biomarker-positive amnestic MCI and mild AD.

KEYWORDS
disease progression, mild cognitive impairment, regular physical exercise, vigorous

Vigorous, regular physical exercise may slow disease progression in Alzheimer's disease

Patient 1: Age 64 → 80 years

Patient 2: Age 70 → 80 years

Devanand, D., et al.,*Alzheimer's & Dementia.* February, 2023

Vigorous, regular physical exercise may slow disease progression in Alzheimer's disease

The two patients had initial clinical diagnoses of amnestic MCI with final follow-up diagnoses of mild AD and amnestic MCI, respectively. Both patients were biomarker positive for AD with CSF markers and temporoparietal hypometabolism with FDG-PET and abnormally elevated amyloid PET SUVR values confirming an AD etiology.Global cognitive measures showed minimal to no progression during follow-up.

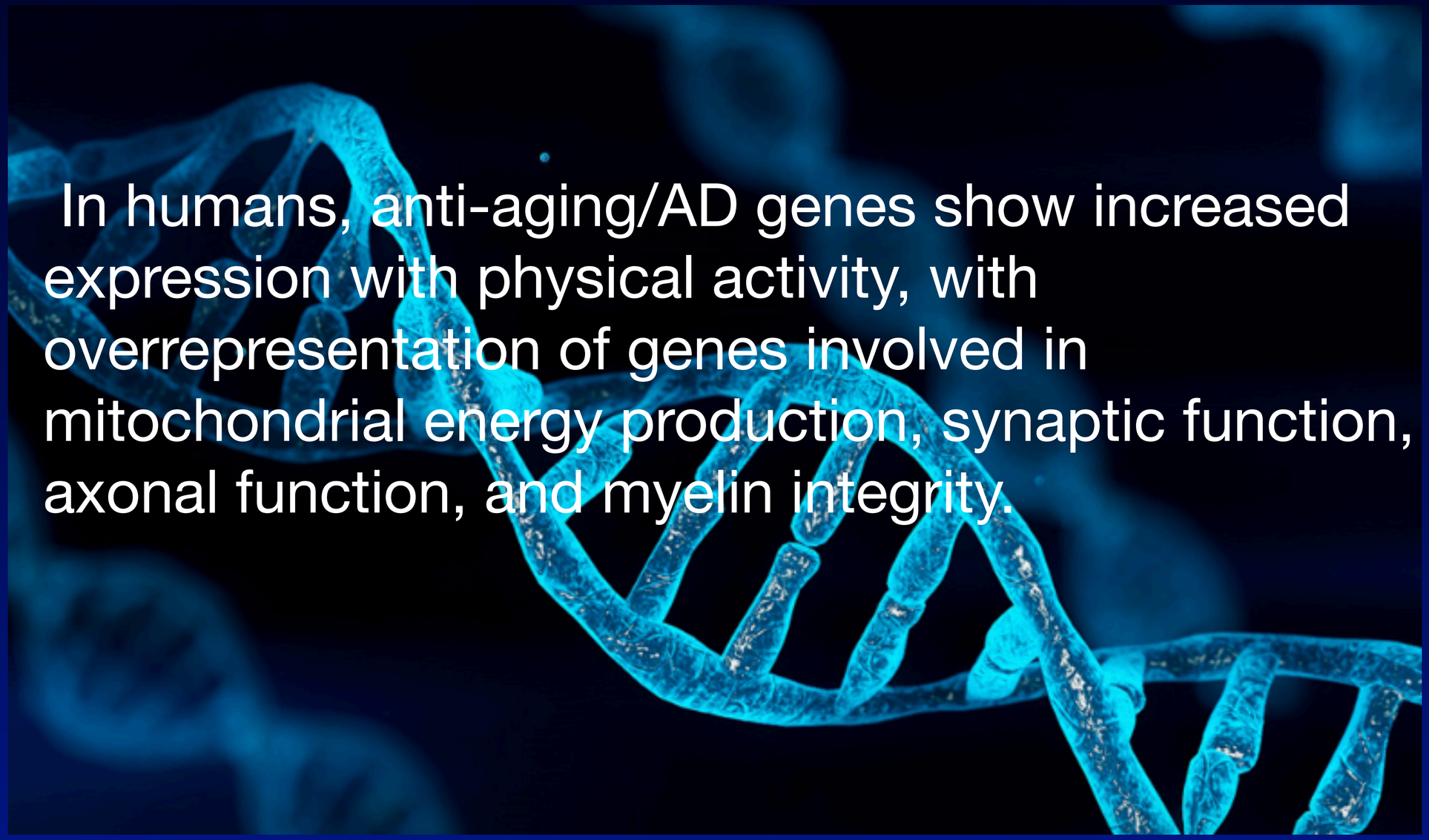
Devanand, D., et al.,*Alzheimer's & Dementia.* February, 2023

Vigorous, regular physical exercise may slow disease progression in Alzheimer's disease

Annual MMSE declines averaged 0.3 points for patient 1 and 0.125 points for patient 2, which contrasts with the average 2-point MMSE annual decline in patients with mild to moderate AD. At recent follow-ups, MoCA scores for both patients were in the normal range for age.

Devanand, D., et al.,*Alzheimer's & Dementia.* February, 2023

Vigorous, regular physical exercise may slow disease progression in Alzheimer's disease



Devanand, D., et al.,*Alzheimer's & Dementia.* February, 2023

scientific reports

Association between metabolic syndrome and uric acid: a systematic review and meta-analysis

OPEN

Association between metabolic syndrome and uric acid: a systematic review and meta-analysis

Elena Raya-Cano[1], Manuel Vaquero-Abellán[1], Rafael Molina-Luque[1,2]✉, Domingo De Pedro-Jiménez[3], Guillermo Molina-Recio[1,2] & Manuel Romero-Saldaña[1,2]

This systematic review and meta-analysis aim to provide the best evidence on the association between metabolic syndrome (MetS) and uric acid (UA) by determining the size of the effect of this biomarker on MetS. The review protocol is registered with PROSPERO (CRD42021231124). The search covered the PubMed and Scopus databases. Methodological quality was assessed with the STROBE tool, overall risk of bias with RevMan (Cochrane Collaboration) and quality of evidence with Grade Pro. Initially, 1582 articles were identified. Then, after excluding duplicates and reviewing titles and abstracts, 1529 articles were excluded from applying the eligibility criteria. We included 43 papers (56 groups) comparing UA concentrations between subjects 91,845 with MetS and 259,931 controls. Subjects with MetS had a higher mean UA of 0.57 mg/dl (95% CI 0.54–0.61) ($p < 0.00001$). Given the heterogeneity of the included studies, the researchers decided to perform subgroups analysis. Men with MetS have a higher UA concentration mg/dl 0.53 (95% CI 0.45–0.62, $p < 0.00001$) and women with MetS 0.57 (95% CI 0.48–0.66, $p < 0.00001$) compared to subjects without MetS. Assessment of UA concentration could provide a new avenue for early diagnosis of MetS, as a new biomarker and the possibility of new therapeutic targets.

JCI insight

CLINICAL MEDICINE

Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese

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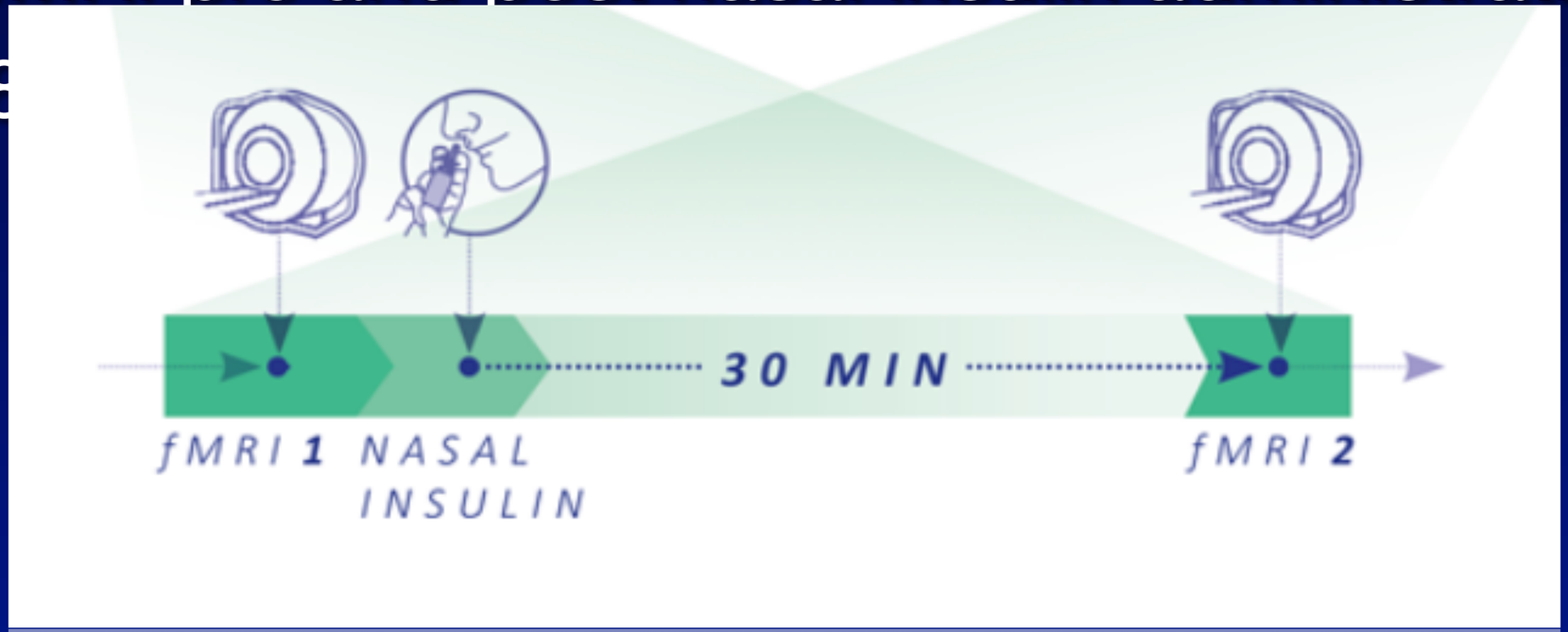

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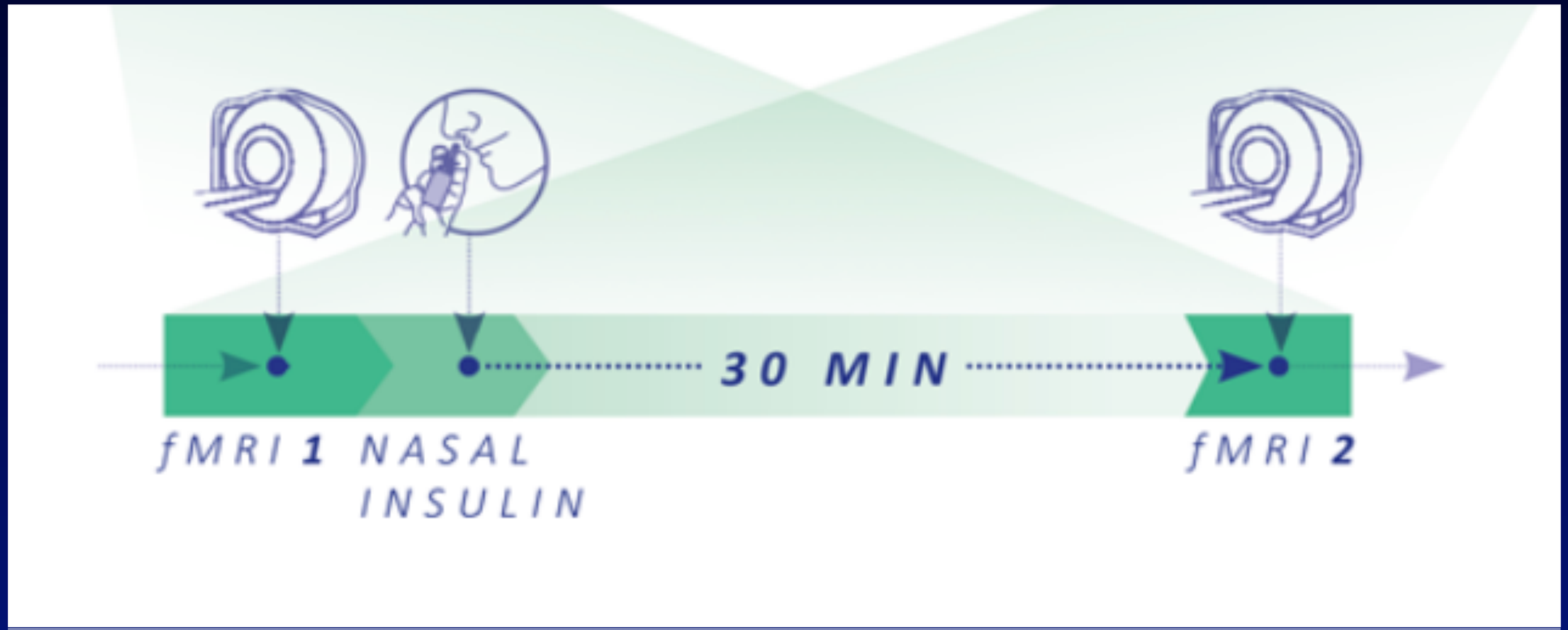

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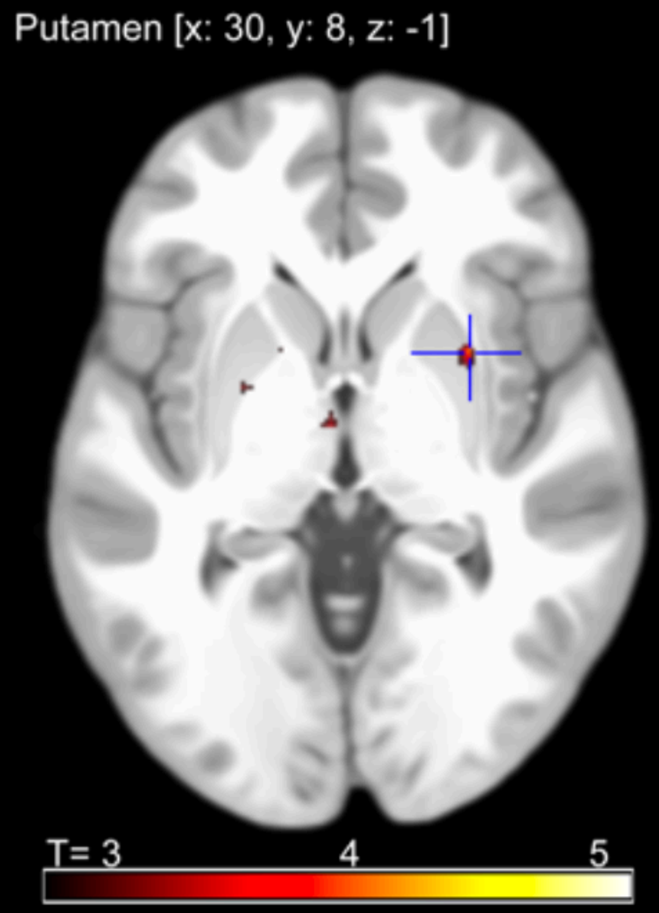

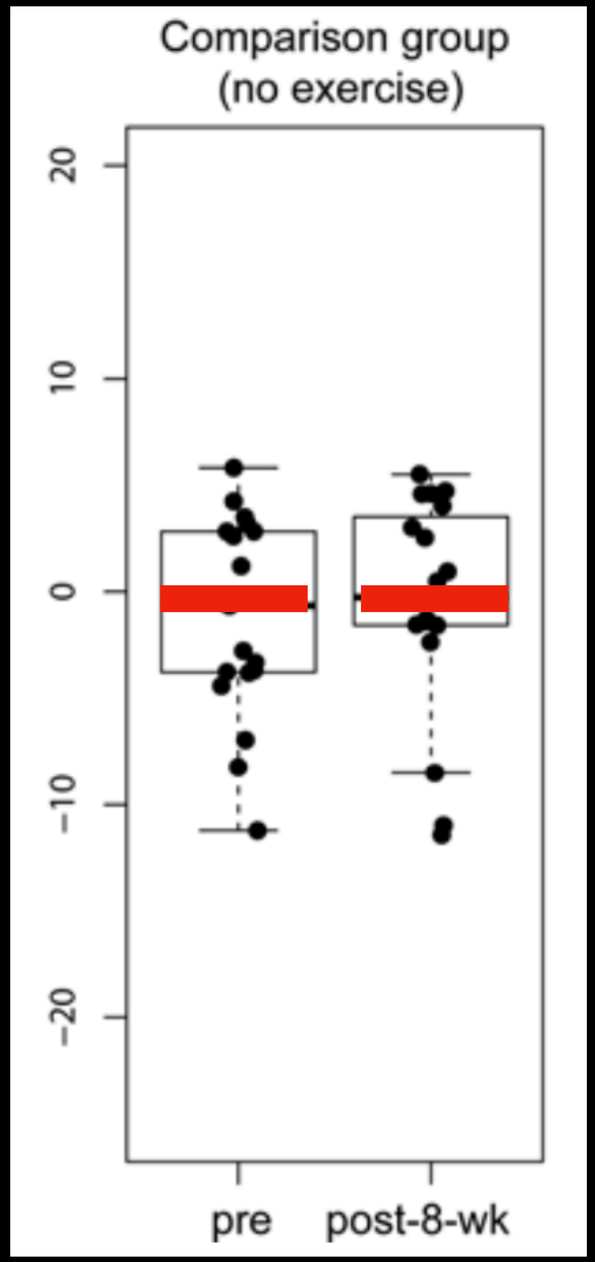

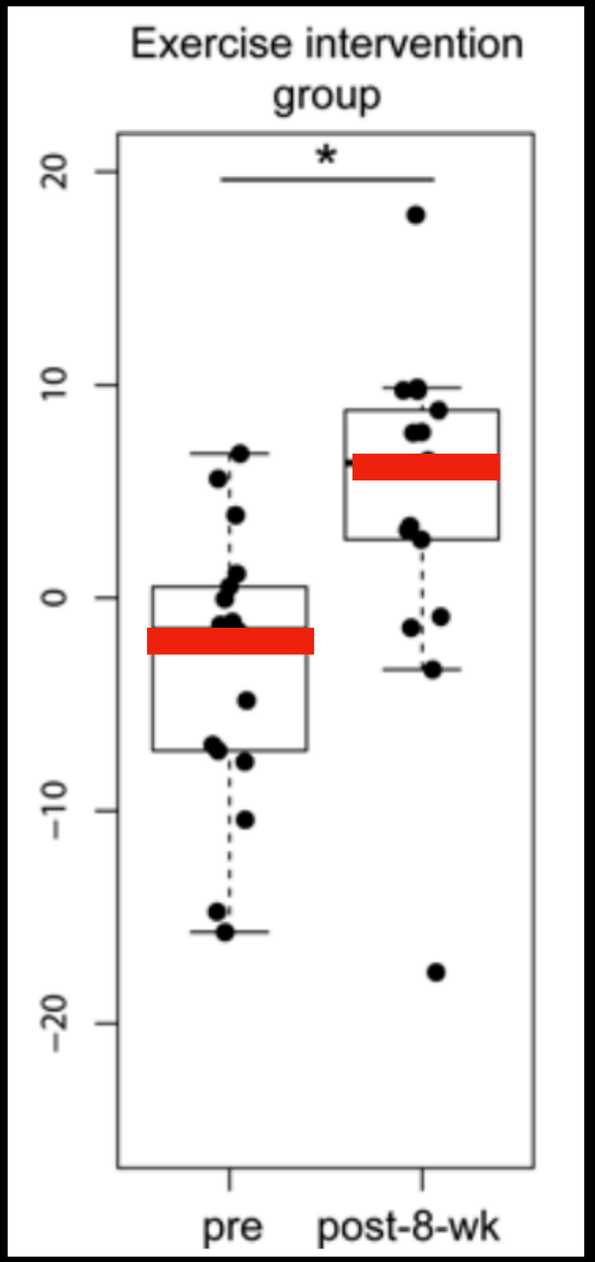

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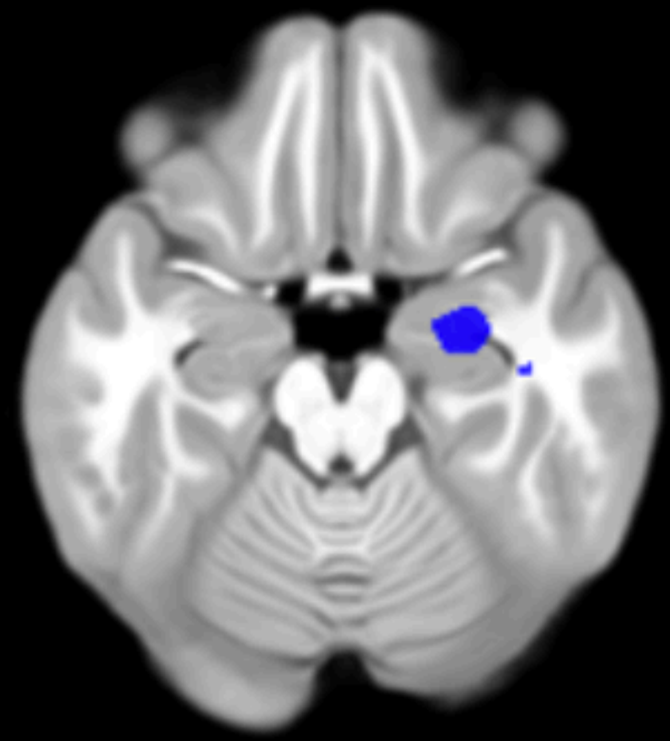

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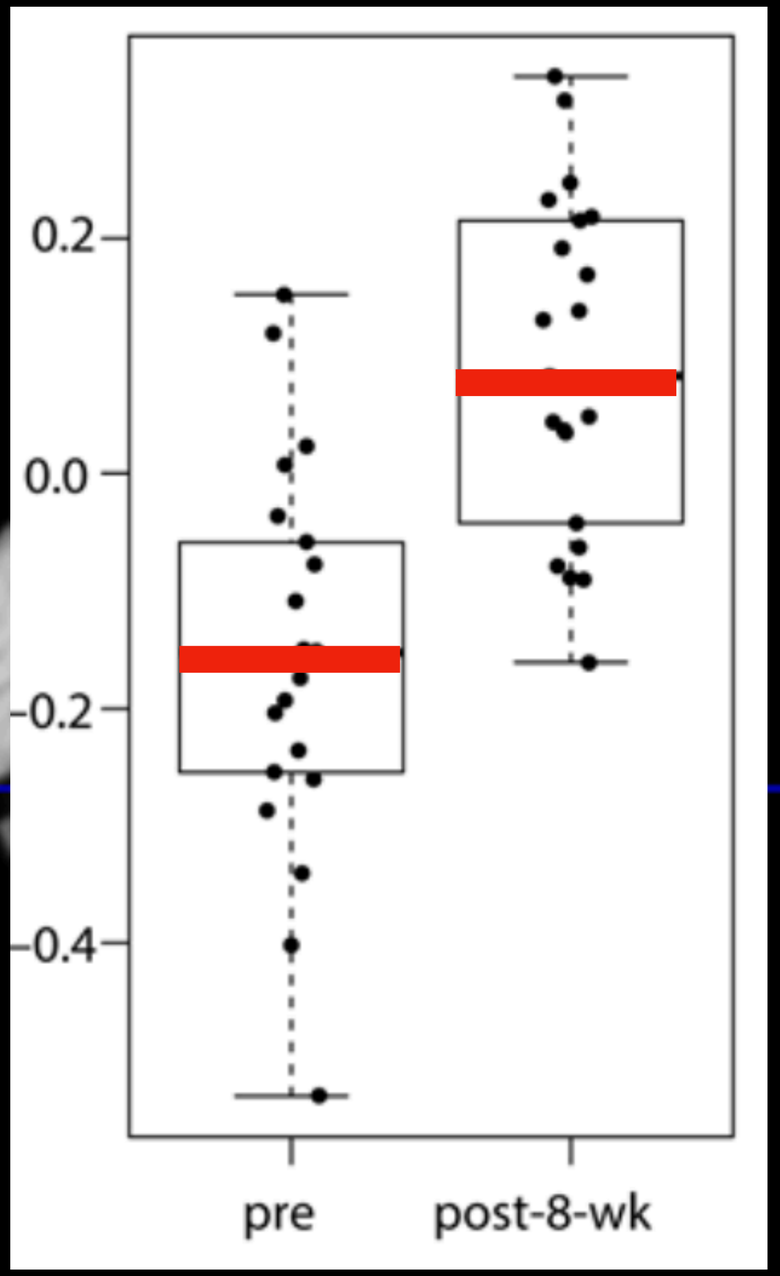
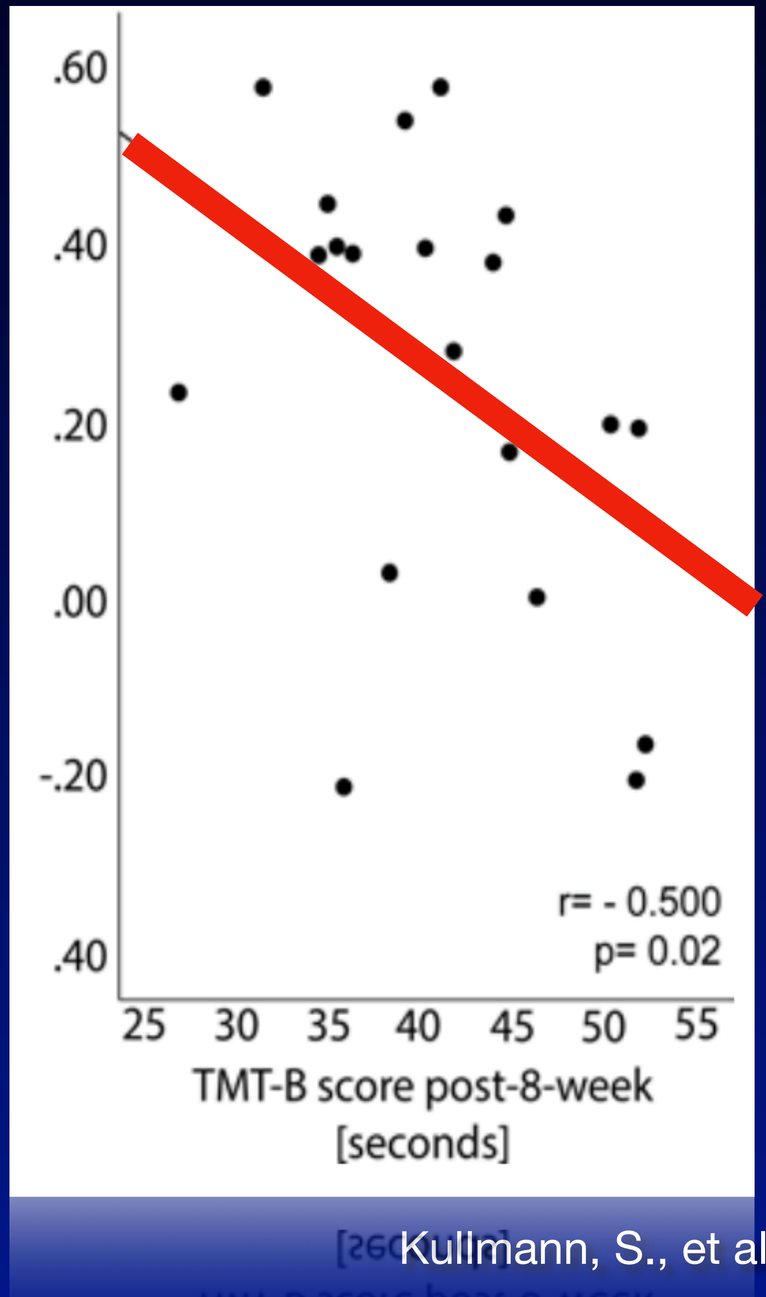


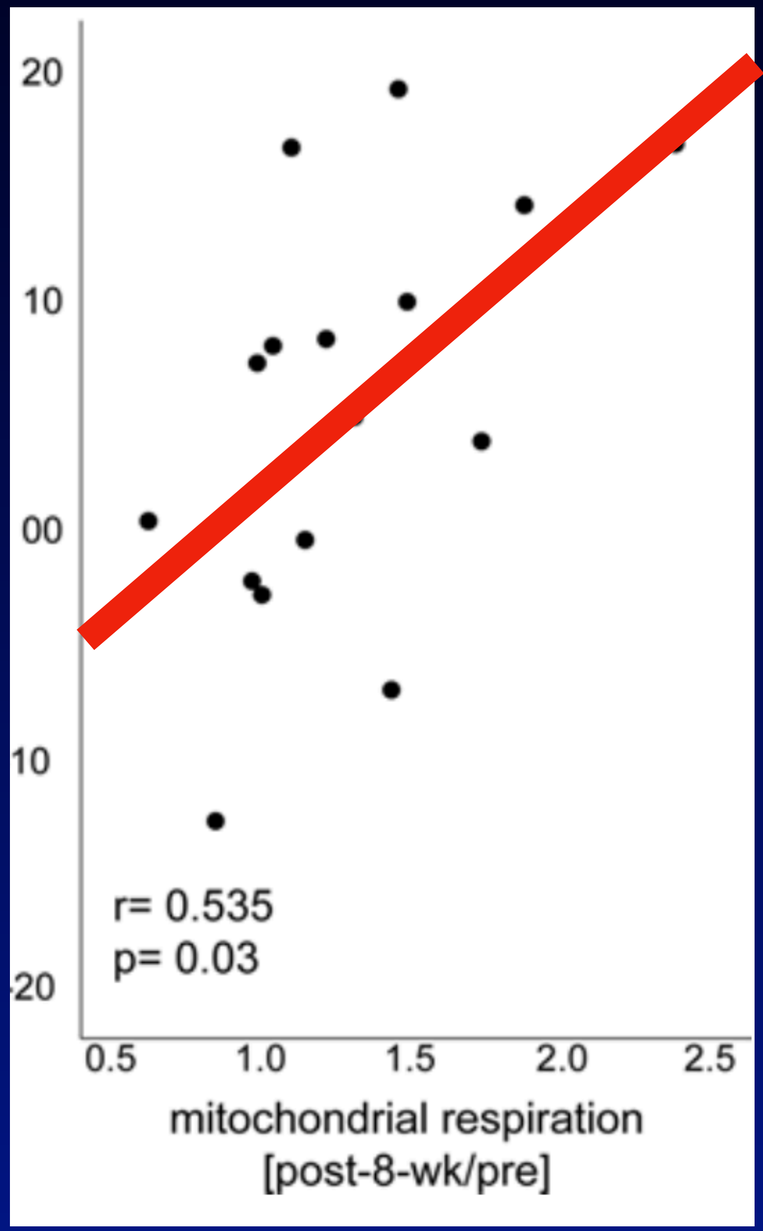
Kullmann, S., et al., *JCI Insight*. September, 2022

Change in functional connectivity (trail making test)



Kullmann, S., et al., *JCI Insight*. September, 2022

Mitochondrial respiration (fold change)



Kullmann, S., et al., *JCI Insight*. September, 2022

Over-the-counter mouthwash use and risk of pre-diabetes/diabetes

> Nitric Oxide. 2017 Dec 1:71:14-20. doi: 10.1016/j.niox.2017.09.004. Epub 2017 Sep 20.

Over-the-counter mouthwash use and risk of pre-diabetes/diabetes

Kaumudi J Joshipura [1], Francisco J Muñoz-Torres [2], Evangelia Morou-Bermudez [3], Rakesh P Patel [4]

Affiliations + expand

PMID: 28939409 PMCID: PMC6628144 DOI: 10.1016/j.niox.2017.09.004

Free PMC article

Abstract

Aims: Over-the-counter mouthwash comprises part of routine oral care for many; however, potential adverse effects of the long-term daily use have not been evaluated. Most mouthwash contain antibacterial ingredients, which could impact oral microbes critical for nitric oxide formation, and in turn predispose to metabolic disorders including diabetes. Our aim was to evaluate longitudinally the association between baseline over-the-counter mouthwash use and development of pre-diabetes/diabetes over a 3-year follow-up.

Materials and methods: The San Juan Overweight Adults Longitudinal Study (SOALS) recruited 1206 overweight/obese individuals, aged 40-65, and free of diabetes and major cardiovascular diseases; 945 with complete follow-up data were included in the analyses. We used Poisson regression models adjusting for baseline age, sex, smoking, physical activity, waist circumference, alcohol consumption, pre-hypertension/hypertension status; time between visits was included in the models as an offset.

Over-the-counter mouthwash use and risk of pre-diabetes/diabetes

Joshipura, K., et al., *Nitric Oxide.* September , 2017

Over-the-counter mouthwash use and risk of pre-diabetes/diabetes

- 945 overweight/obese adults, nondiabetic
- Frequency of mouthwash use
- Followed for 3 years

Joshipura, K., et al., *Nitric Oxide.* September , 2017

Over-the-counter mouthwash use and risk of pre-diabetes/diabetes

- Compared to nonusers, using mouthwash ≥ 2 times daily associated with 49% increased risk of pre-diabetes or diabetes.

Joshipura, K., et al., *Nitric Oxide.* September , 2017

Over the counter mouthwash use, nitric oxide and hypertensi
risk

Observational Study > Blood Press. 2020 Apr;29(2):103-112.
doi: 10.1080/08037051.2019.1680270. Epub 2019 Nov 11.

Over-the-counter mouthwash use, nitric oxide and hypertension risk

Kaumudi Joshipura [1 2], Francisco Muñoz-Torres [1], Jeanpaul Fernández-Santiago [1], Rakesh P Patel [3], Angel Lopez-Candales [4]

Affiliations + expand

PMID: 31709856 PMCID: PMC7125030 DOI: 10.1080/08037051.2019.1680270
Free PMC article

Abstract

Purpose: Mouthwash is used by a large population. Short-term clinical trials have shown that antibacterial mouthwash deplete oral nitrate-reducing bacteria, and decrease systemic nitric oxide bioavailability. Our previous publication from the San Juan Overweight Adults Longitudinal Study (SOALS) was the first to show frequent over-the-counter mouthwash use was independently associated with increased risk of prediabetes/diabetes. This manuscript evaluates whether over-the-counter mouthwash was associated with increased risk of hypertension.**Materials and methods:** SOALS recruited 40-65 year old overweight/obese individuals; baseline evaluations started in 2011 and the 3-year follow-up exam was completed by 2016. From the 1028 participants (76%) who completed follow-up, we excluded people with reported physician diagnosis of hypertension or systolic or diastolic BP at or above the hypertension cut-offs (n = 481), missing smoking (n = 1), missing physical activity (n = 1) and missing alcohol intake (n = 5) at baseline; 540 participants were included. The primary exposure was mouthwash use twice daily or more. The

Over-the-counter mouthwash use, nitric oxide and hypertension risk

Joshipura, K., et al., *Blood Pressure.* April, 2020

Over-the-counter mouthwash use, nitric oxide and hypertension risk

- 540 overweight/obese adults, nondiabetic
- Frequency of mouthwash use
- Followed for 3 years

Joshipura, K., et al., *Blood Pressure.* April, 2020

Over-the-counter mouthwash use, nitric oxide and hypertension risk

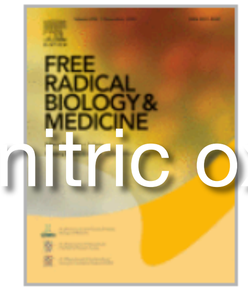
- Compared to nonusers, using mouthwash ≥ 2 times daily associated with 117% increased risk of hypertension

Joshipura, K., et al., *Blood Pressure.* April, 2020

Oral Bacteria And Your Health - with Dr. Mark Burhenne | The Empowering Neurologist EP. 162

Nitrate-responsive oral microbiome modulates nitric oxide homeostasis and blood pressure in humans

Free Radical Biology and Medicine
Volume 124, 20 August 2018, Pages 21-30

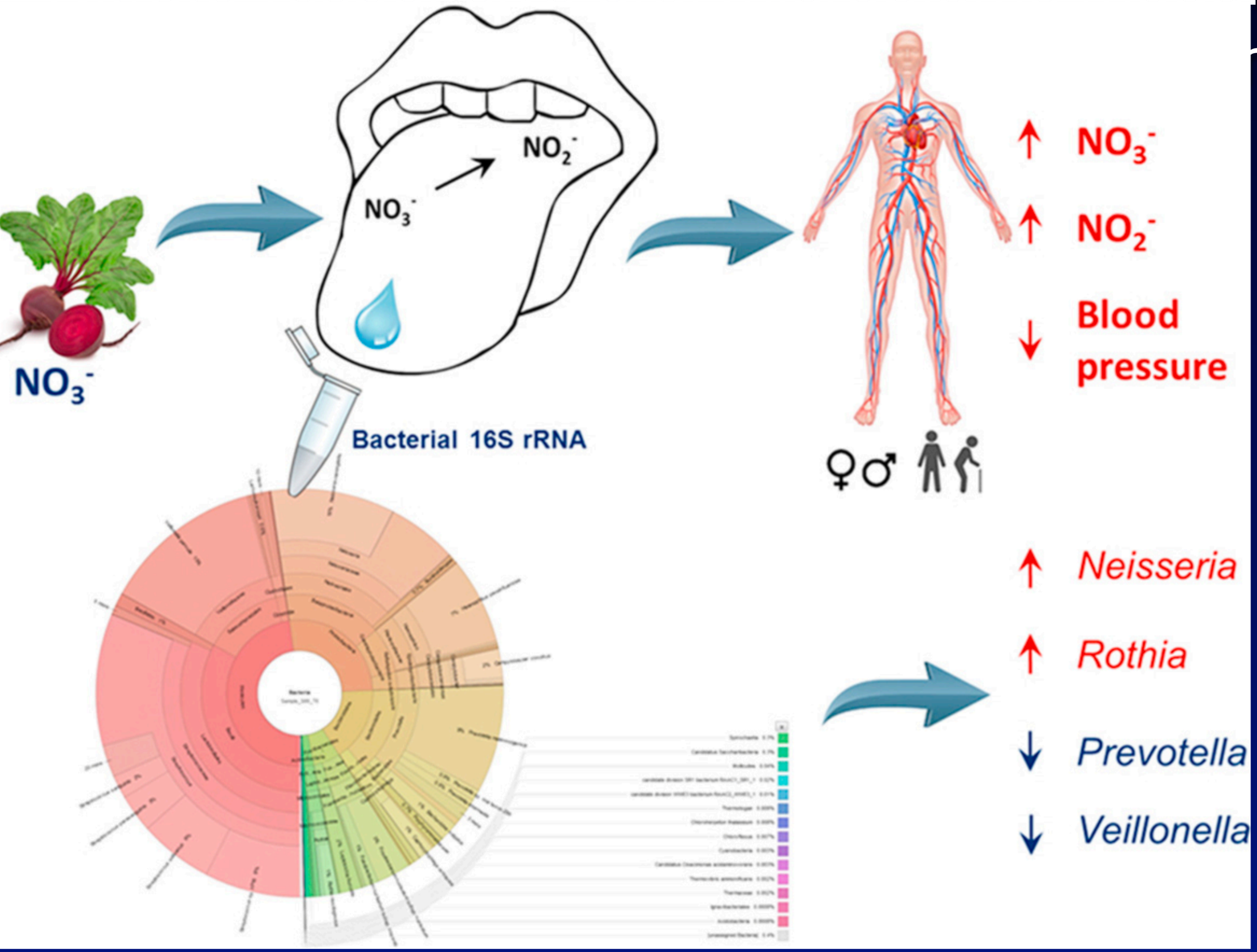


Original article

Nitrate-responsive oral microbiome modulates nitric oxide homeostasis and blood pressure in humans

Anni Vanhatalo [a], Jamie R. Blackwell [a], Joanna E. L'Heureux [a], David W. Williams [b], Ann Smith [c], Mark van der Giezen [a], Paul G. Winyard [d], James Kelly [a], Andrew M. Jones [a]

Nitrate-responsive oral microbiome modulates nitric oxide
ns



Vanhatalo, A., et al., *Free Radical Biology and Medicine.* August, 2018

Nitrate-responsive oral microbiome modulates nitric oxide homeostasis and blood pressure in humans

- Imbalance or oral microbial community associated with cardiometabolic disease
- Oral microbial community involved in converting nitrate to nitrite which generates NO
- Studied 16SrRNA evaluation oral microbiome before and after increasing available nitrate vs placebo for 10 days

Vanhatalo, A., et al., *Free Radical Biology and Medicine.* August, 2018

Nitrate-responsive oral microbiome modulates nitric oxide homeostasis and blood pressure in humans

- Nitrate supplementation caused 225% relative increase in Proteobacteria
- 5 mmHg decrease in systolic BP in 70-79 year olds

Vanhatalo, A., et al., *Free Radical Biology and Medicine.* August, 2018

Nitrate-responsive oral microbiome modulates nitric oxide homeostasis and blood pressure in humans

- The current findings indicate that the oral microbial community was malleable to change with increased dietary intake of inorganic NO_3^-, and, importantly, that the oral microbiome was related to indices of NO homeostasis and vascular health in vivo.

Vanhatalo, A., et al., *Free Radical Biology and Medicine.* August, 2018

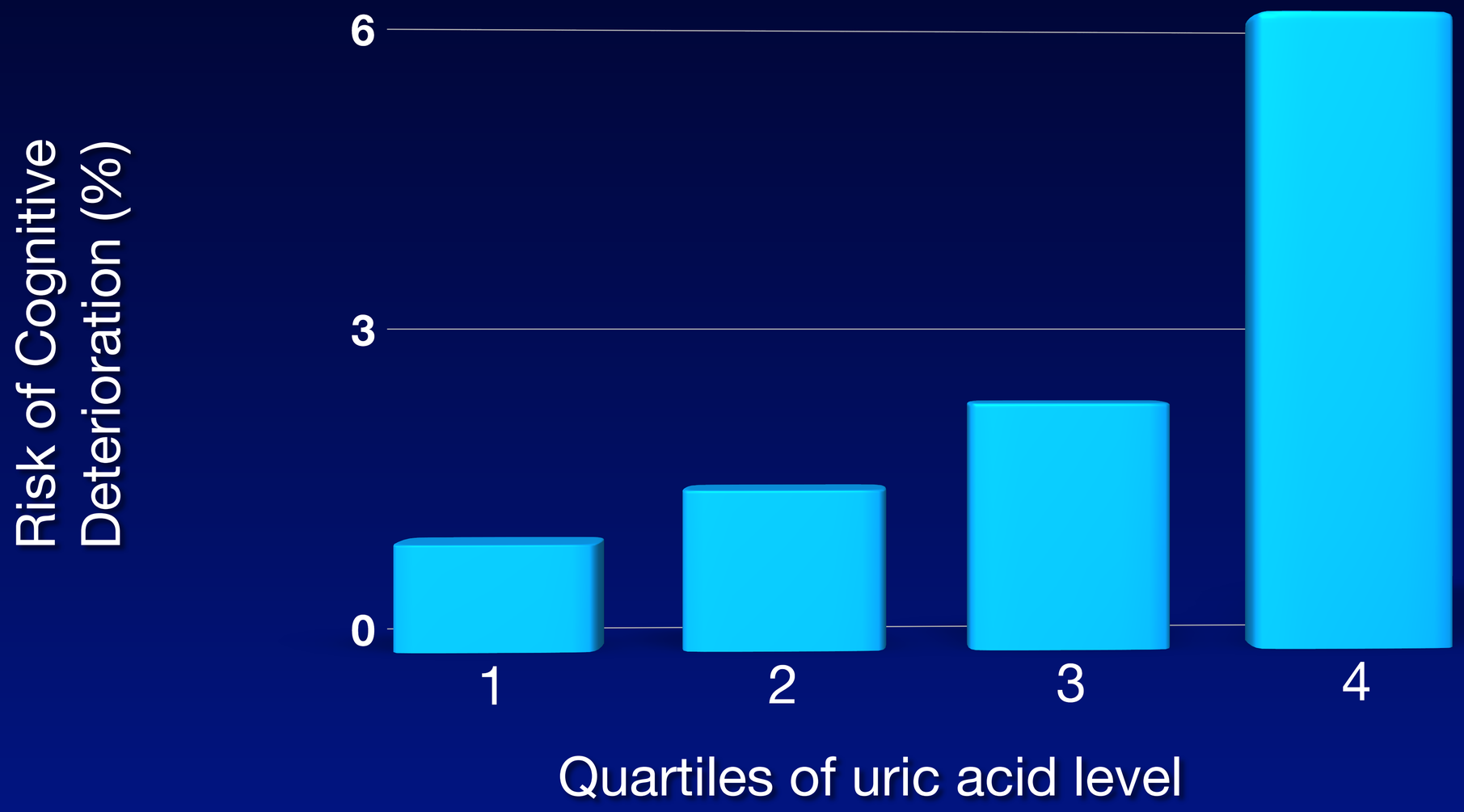
Nitric Oxide and Functional Health - with Dr. Nathan Bryan | The Empowering Neurologist EP. 166

Elevated Serum Uric Acid Levels Are Related to Cognitive Deterioration in an Elderly Japanese Population

- 228 elderly participants
- neuropsychological testing
- MRI brain scans
- Uric acid evealuation

Dementia and Geriatric Cognititve Disorders. December 22, 2016

Uric Acid and Risk for Cognitive Deterioration



Dementia and Geriatric Cognititve Disorders. December 22, 2016

Elevated Serum Uric Acid Levels Are Related to Cognitive Deterioration in an Elderly Japanese Population

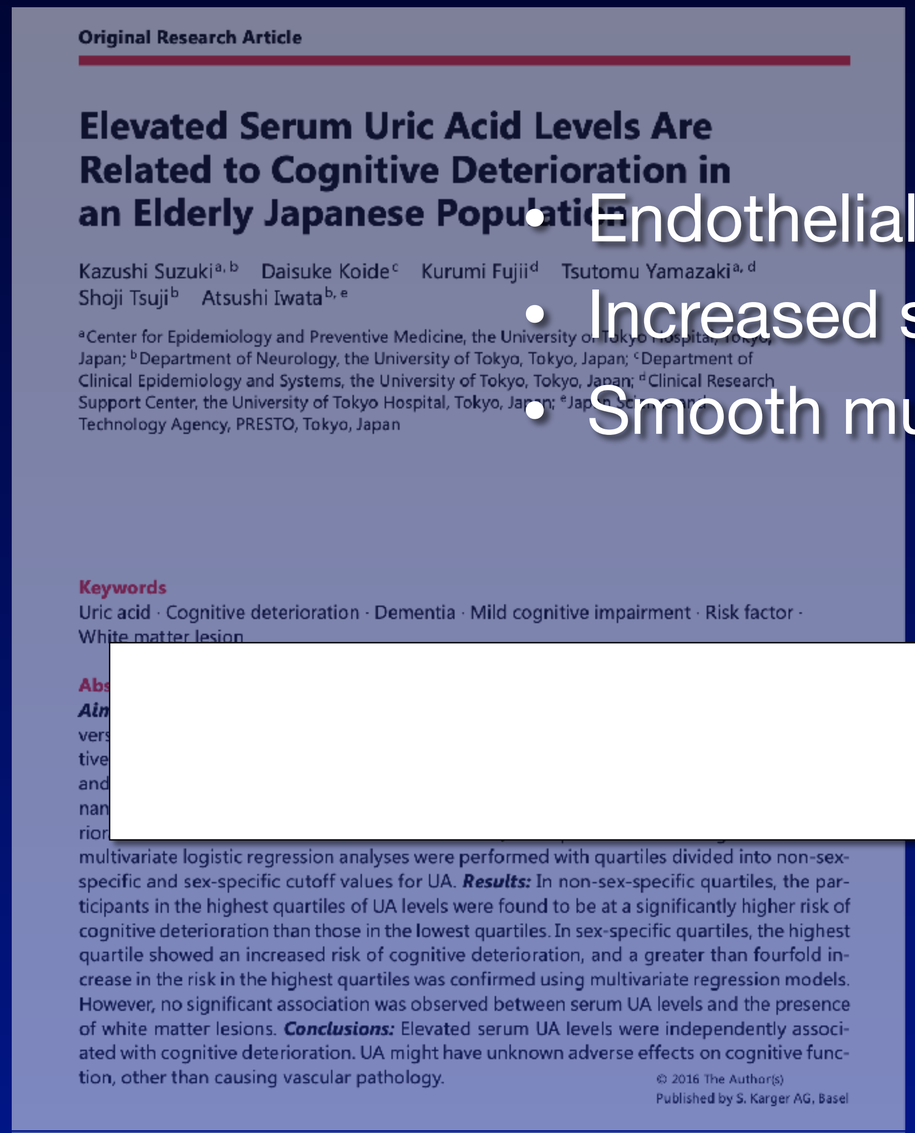
- Risk increased fourfold comparing lowest to highest uric acid level
- Uric acid elevation correleted with burden of cerebral ischemic pathology

Why? nitric oxide inhibition leads to:

- Insulin resistance
- Vascular effects

Dementia and Geriatric Cognititve Disorders. December 22, 2016

Elevated Serum Uric Acid Levels Are Related to Cognitive Deterioration in an Elderly Japanese Population



Original Research Article

Elevated Serum Uric Acid Levels Are Related to Cognitive Deterioration in an Elderly Japanese Popula

Kazushi Suzuki[a, b] Daisuke Koide[c] Kurumi Fujii[d] Tsutomu Yamazaki[a, d]
Shoji Tsuji[b] Atsushi Iwata[b, e]

[a]Center for Epidemiology and Preventive Medicine, the University of Tokyo Hospital, Tokyo, Japan; [b]Department of Neurology, the University of Tokyo, Tokyo, Japan; [c]Department of Clinical Epidemiology and Systems, the University of Tokyo, Tokyo, Japan; [d]Clinical Research Support Center, the University of Tokyo Hospital, Tokyo, Japan; [e]Japan Science and Technology Agency, PRESTO, Tokyo, Japan

Keywords
Uric acid · Cognitive deterioration · Dementia · Mild cognitive impairment · Risk factor · White matter lesion

Abs
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multivariate logistic regression analyses were performed with quartiles divided into non-sex-specific and sex-specific cutoff values for UA. ***Results:*** In non-sex-specific quartiles, the participants in the highest quartiles of UA levels were found to be at a significantly higher risk of cognitive deterioration than those in the lowest quartiles. In sex-specific quartiles, the highest quartile showed an increased risk of cognitive deterioration, and a greater than fourfold increase in the risk in the highest quartiles was confirmed using multivariate regression models. However, no significant association was observed between serum UA levels and the presence of white matter lesions. ***Conclusions:*** Elevated serum UA levels were independently associated with cognitive deterioration. UA might have unknown adverse effects on cognitive function, other than causing vascular pathology.

- Endothelial dysfunction
- Increased systemic inflammation
- Smooth muscle proliferation

Suzuki, K., et al., *Dementia and Geriatric Cognitive Disorders,* December 22, 2016

Just say NO to Alzheimer’s

NIH RESEARCH MATTERS

December 14, 2021

Viagra associated with reduced risk of Alzheimer's disease

At a Glance

- People who took the drug sildenafil were less likely to develop Alzheimer's disease.
- In cultured human neurons, sildenafil enhanced growth and reduced Alzheimer's biomarkers.
- The findings support further investigation of sildenafil as a possible treatment for Alzheimer's disease.

Alzheimer's disease (AD) is the most common form of dementia. It is expected to affect 16 million Americans by 2050. The hallmarks of AD are amyloid plaques and tau neurofibrillary tangles in the brain. Efforts to develop new drugs that directly target amyloid or tau proteins haven't yielded significant clinical benefits for patients. Another approach to developing AD treatments would be to seek existing drugs that could potentially be repurposed.

A team of researchers led by Dr. Feixiong Cheng at the Cleveland Clinic developed a computational method for identifying FDA-approved drugs that might be effective against AD. NIH's National Institute of Aging (NIA) supported the study. Results appeared in *Nature Aging* on December 6, 2021.

A study suggests that the drug sildenafil may help prevent Alzheimer's disease. *Ruslan Huzau / Shutterstock*

Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease

Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease

Fang, J., et al., *Nature Aging.* December 6, 2021

Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease

- Identified 66 drugs closely associated with Alzheimer's genes
- Top candidate was sildenafil
- Analysis of insurance claims for ~ 7 million adults x 6 years

Fang, J., et al., *Nature Aging.* December 6, 2021

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Fang, J., et al., *Nature Aging.* December 6, 2021

Top candidate was sildenafil

- Decreases neuroinflammation
- Decreases tau hyperphosphorylation
- Increases blood flow
- Increases synaptogenesis
- PGC1α activation

Fang, J., et al., *Nature Aging.* December 6, 2021

Top candidate was sildenafil

- Decreases neuroinflammation
- Decreases tau hyperphosphorylation
- Increases blood flow
- Increases synaptogenesis
- PGC1α activation
  - Increased mitochondrial biogenesis
  - Improved fatty acid metabolism
  - Improved insulin-stimulated glucose transport

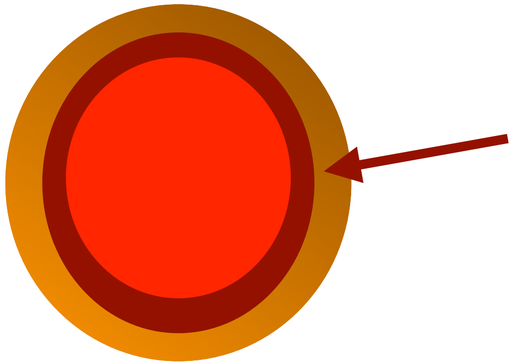
Fang, J., et al., *Nature Aging.* December 6, 2021

Endophenotype-based in silico network medicine discovery combined with insurance record data mining identifies sildenafil as a candidate drug for Alzheimer's disease

- Subjects taking sildenafil were 69% less likely to develop Alzheimer's disease (mostly men)

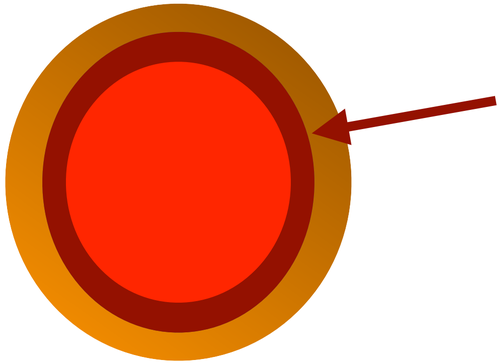
Fang, J., et al., *Nature Aging.* December 6, 2021

Uric acid normal
(nitric oxide functional)



Smooth muscle relaxed

Uric acid elevated
(nitric oxide inhibited)



Smooth muscle active

1. Reduced blood flow
2. Reduced function of insulin

Integrative Healthcare SYMPOSIUM

Thursday 9:30am - 10:30am

Plenary: Mind over Metabolism - Choosing Brain Health

Please scan this QR code on you mobile

or tablet device to access the session feedback survey

Plenary: Mind over Metabolism - Choosing Brain Health