Multidomain Interventions for the Prevention of Late in Life Alzheimer's disease and Dementia

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Dementia and Alzheimer (AD) prevention

The multidomain approach: the FINGER model

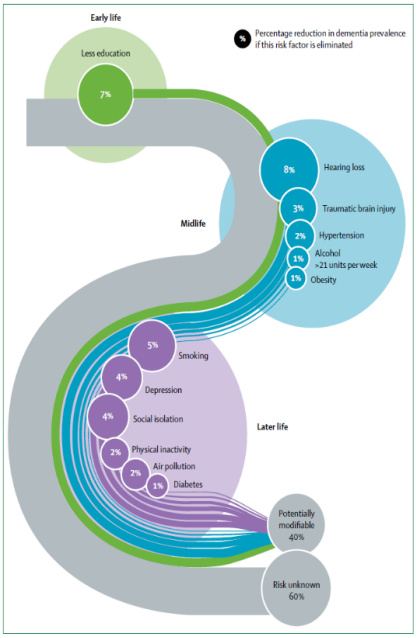
From FINGER to World-Wide FINGERS

Prevention at the time of the COVID-19 pandemic?

Future!

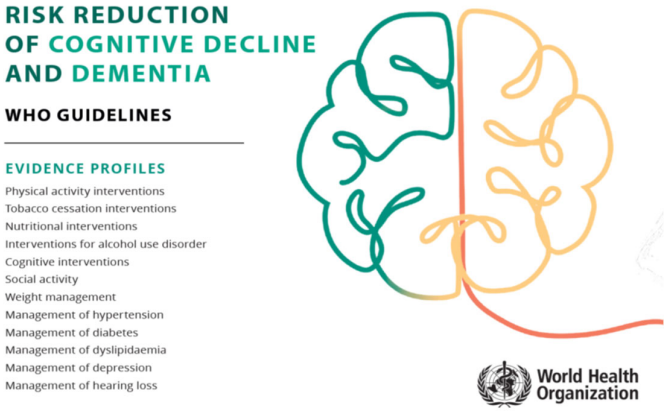
Prevention of Alzheimer´s disease and dementia

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission



Modifiable risk factors for dementia

Prevention Potential ≈ 40%



WHO 2019 (update ongoing)

Multidomain & tailored interventions

Livingston et al, Lancet Commission 2020

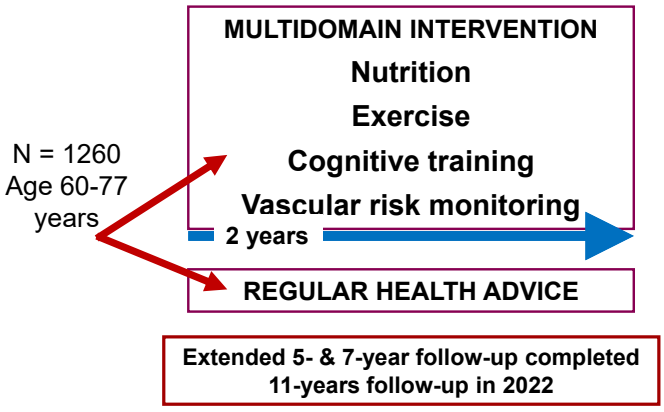
Karolinska Institutet

UNSW SYDNEY

FROM KNOWLEDGE ABOUT RISK FACTORS TO CLINICAL TRIALS AND SUSTAINABLE IMPLEMENTATION

- **Multidomain interventions: several simultaneous targets**
- **One size does not fit all! Tailor interventions: maximize the individual's prevention potential**
- **Mechanistic foundation**
- **Optimal time windows**

The FINGER model

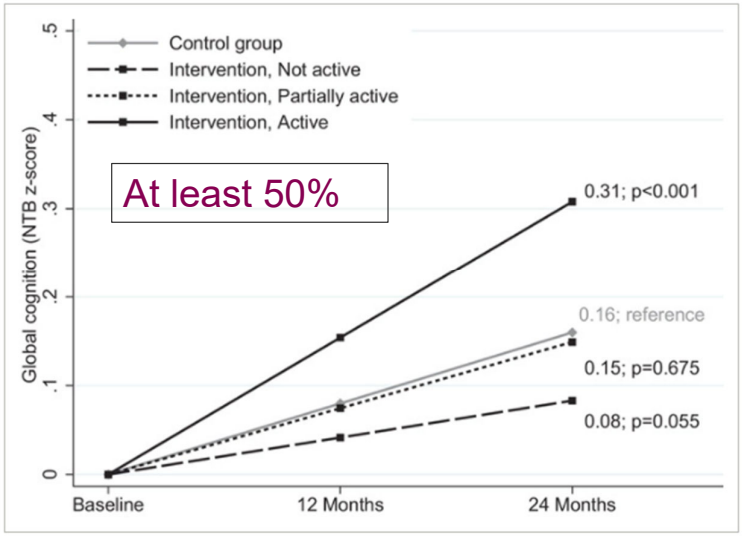


- Cognitive benefits
- 20% lower risk cardiovascular events
- 30% lower risk for functional decline
- 60% lower risk of chronic diseases
- Better health related quality of life
- Health-economical benefits

Lancet 2015; JAMA Neurology 2018, Eur Ger Med 2017, JAMDA 2017, JAGS 2019; Alzheimer's Dementia 2021; European J Cardiology 2022

The FINGER model

The effect of adherence on cognition

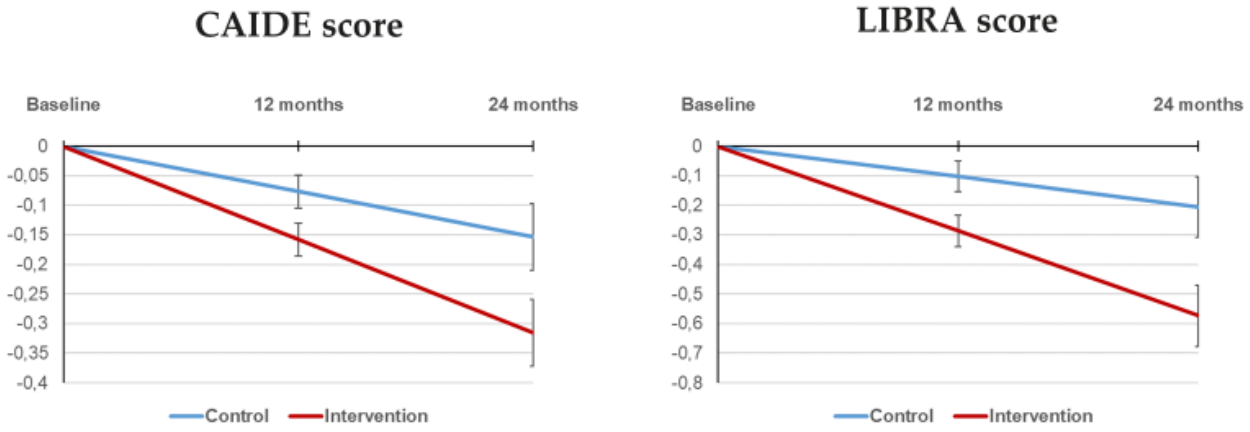


- Active participation is associated with better cognition
- Supporting adherence is essential!

Alzheimer's Dementia 2021

DEMENTIA RISK REDUCTION:
Intervention effects on change in Dementia Risk Scores

FINGER



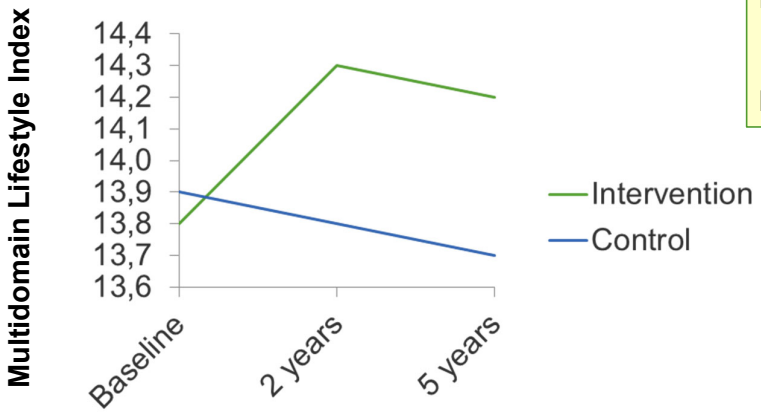
The FINGER multidomain lifestyle intervention reduced the overall dementia risk

Solomon, Kivipelto, Ngandu et al., J Alz Dis 2021, Deckers et al., Alz & Dem 2021

Long-term beneficial effects of the multidomain intervention ?

FINGER

DEMENTIA RISK REDUCTION:
Improved lifestyle changes were maintained at 5 years



Rissanen, Kivipelto et al, in preparation

thl

Mechanisms and mediating pathways?

APOE4 carriers - clear beneficial effects

FINGER

JAMA Neurology | Original Investigation April 2018 Volume 75, Number 4

Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention

A Subgroup Analysis of a Randomized Clinical Trial

Alina Solomon, MD, PhD; Heidi Turunen, BM; Tiia Ngandu, MD, PhD; Markku Peltonen, PhD; Esko Levälahti, MSc; Seppo Helisalmi, PhD; Riitta Antikainen, MD, PhD; Lars Bäckman, PhD; Tuomo Hänninen, PhD; Antti Jula, MD, PhD; Tiina Laatikainen, MD, PhD; Jenni Lehtisalo, MSc; Jaana Lindström, PhD; Teemu Paajanen, MA, Psy; Satu Pajala, PhD; Anna Stigsdotter-Neely, PhD; Timo Strandberg, MD, PhD; Jaakko Tuomilehto, MD, PhD; Hilkka Soininen, MD, PhD; Miia Kivipelto, MD, PhD

Higher AD polygenic risk score (PRS) - clear beneficial effects (prel. results)

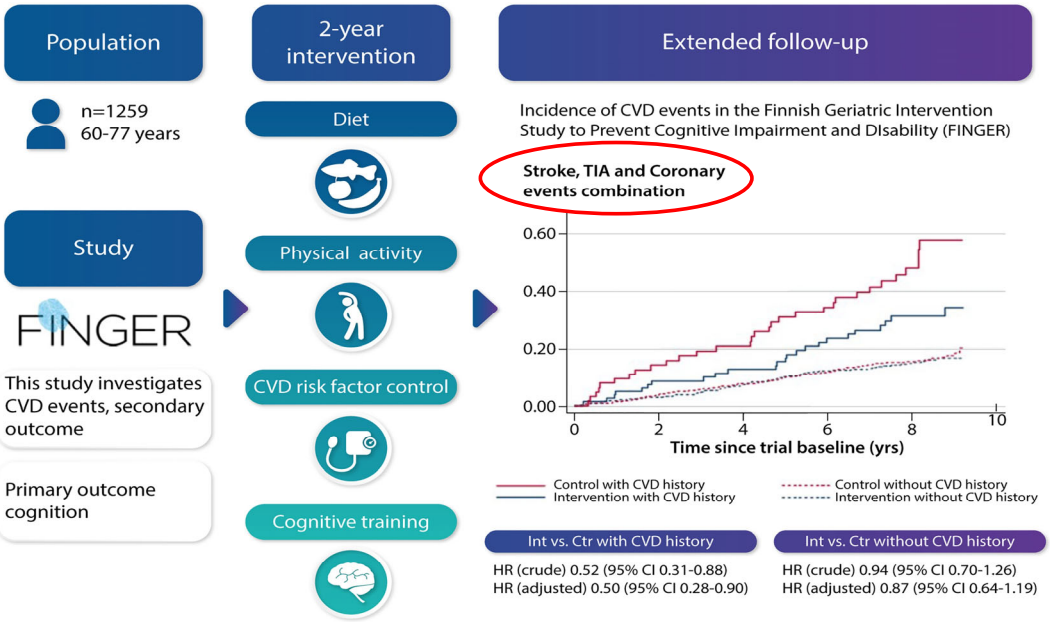
Cognitive end point	PRS	PRS without APOE			PRS with APOE		
		Difference between intervention and control groups per year		PRS*intervention*time interaction	Difference between intervention and control groups per year		PRS*intervention*time interaction
		Estimate (95% CI)	p-value	p-value	Estimate (95% CI)	p-value	p-value
NTB total score	< median	0.009 (-0.018 - 0.037)	0.515	*0.093*	0.008 (-0.019 - 0.035)	0.560	0.331
	> median	**0.038 (0.010 - 0.067)**	**0.009**		**0.042 (0.013 - 0.071)**	**0.005**	
NTB complex memory	< median	0.014 (-0.037 - 0.066)	0.582	**0.047**	0.003 (-0.047 - 0.053)	0.894	**0.031**
	> median	**0.069 (0.019 – 0.119)**	**0.006**		**0.086 (0.035 - 0.137)**	**0.001**	

*Mixed effects regression models with maximum likelihood estimation; change in cognition analyzed as a function of randomization group, time, PRS, and their interactions (group*time, PRS*time, PRS*group, PRS*group*time). Adjusted for study site, age at baseline, sex, age*time and sex*time interactions. For PRS without APOE, analyses additionally adjusted for APOEε4 and APOEε4*time interaction. p-value for PRS*intervention*time shown from models with continuous PRS.*

Solomon, Hiltunen, Kivipelto et al.., manuscript

PRS description: https://doi.org/10.1101/19012021

Incidence of cardiovascular events in the FINGER trial after a 2-year multidomain lifestyle intervention and extended follow-up stratified by the cardiovascular event history.

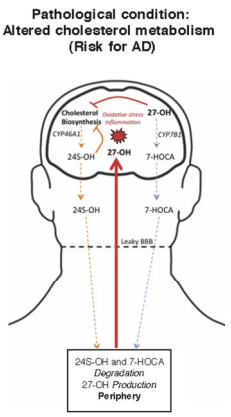


50% lower risk among those with CVD history

Eur Heart J, ehab922, https://doi.org/10.1093/eurheartj/ehab922

Other (emerging) mechanisms

- **Cholesterol and lipids**
  - **27-hydroxycholesterol (27-OH),** a possible link between peripheral hypercholesterolemia and AD
  - Higher 27-OH in the periphery is associated to poorer cognition and reduced cortical volumes
  - Improved cognition from FINGER intervention was associated with reduced 27-OH (Matton, Kivipelto et al.., Alz Research Theraphy 2021)



- **Metabolomics, Proteomics, Inflammatory markers, P-Tau, amyloid, NFL etc**
  - Ongoing analyses

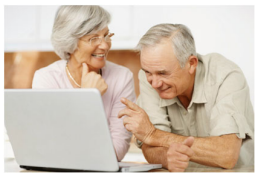
FINGER

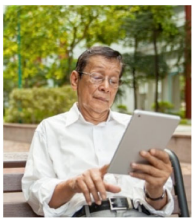
From FINGER To WW-FINGERS

WORLD-WIDE MULTIDOMAIN INTERVENTIONS FOR DEMENTIA PREVENTION

Launched 2017 PI: Miia Kivipelto

- Urgent need to expand FINGER work to test the **generalizability, adaptability, and sustainability** in diverse populations worldwide
- **Harmonize** research methods in prevention trials
- **Share** experiences and data and plan joint dementia prevention initiatives



WORLD WIDE FINGERS

Lancet 2015

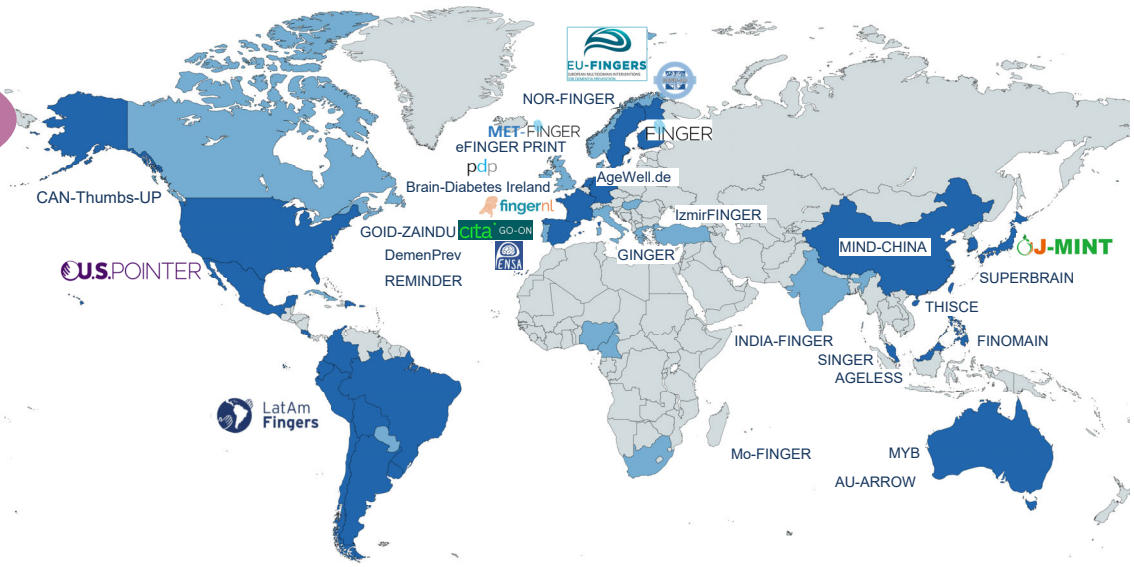
WW-FINGERS Network

WW-FINGERS
WORLD-WIDE MULTIDOMAIN INTERVENTIONS FOR DEMENTIA PREVENTION

WORLD WIDE FINGERS

Covid-19 related methodological challenges

- Countries with studies in planning stage
- Countries with ongoing studies



Participating countries 2022: 45+

Kivipelto, Mangialasche et al. World-Wide FINGERS Network: A Global Approach to Risk Reduction and Prevention of Dementia *(Alzheimer's Dement, July 6, 2020)*

SARS-CoV-2 (COVID-19) pandemic and brain health

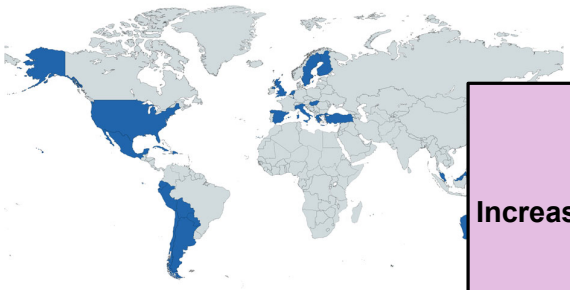
Pandemic direct and indirect effects on cognition:

- infection effects on CNS
- infection effects on organs and systems
- disruption of regular healthcare
- effects of physical distancing measures

World Health Organization

WHO collaboration: Neurology and COVID-19 global forum

World-Wide FINGERS-SARS-CoV2 survey



To assess the indirect eff
pandemic on :

- Lifestyle and risk factors
- Medical care of chronic
- Mental wellbeing

Less physical activity ~30%

Increased intake of unhealthy snacks ~25%

More sleeping problems ~25%

Experience of loneliness ~ 40%

Memory decline (self reported) ~ 15-25%

Country	Subjects N	Female %
	109	49%
	193	71%
	100	67%
ublic	15	NA
	11	NA
	735	47%
	380	56%
	100	NA
	394	65%
	600	61%
	90	NA
	100	51%
	82	54%
	215	61%
ea	152	70%
	7272	58%
Netherlands	4036	75%
Turkey	222	64%
UK	7752	53%
USA	1011	74%
Total	**23569**	

FINGERS BRAIN HEALTH INSTITUTE

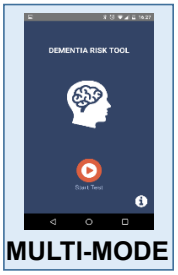
World Health Organization

WHO collaboration: Neurology and COVID-19 global forum

New technology & Digital solutions:

Personalized, Effective and Feasible, Scalable Interventions and Implementation

E-Health & M-Health tools



MULTI-MODE

HATICE

PRODEMOS

lethe
Digital Cognitive Biomarkers

eit Health

eFINGER PRINT

MAINTAIN YOUR BRAIN

Machine learning and AI

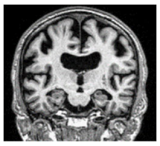
Clinical decision support

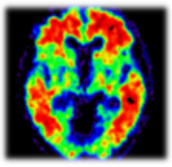
E-FINGERS

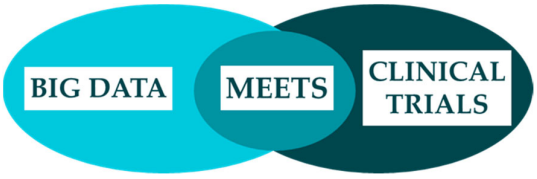
AI-FINGERS

Secure Data Sharing and Harmonization to accelerate discovery

COGNITIVE
CLINICAL
LIFESTYLE
BLOOD MARKERS
AD biomarkers Omics in clinical trials
GENETICS
GWAS in clinical trials
BRAIN IMAGING
Novel in-vivo pathology imaging
CSF MARKERS
MICROBIOME







ADDI
Alzheimer's Disease Data Initiative

Next generation of clinical trials: Combine updated FINGER lifestyle model + drugs

FINGER 2.0

MIND-AD

fingernl

MET-FINGER

JPND research

PART THE CLOUD

Alzheimer's Drug Discovery Foundation

Implementation

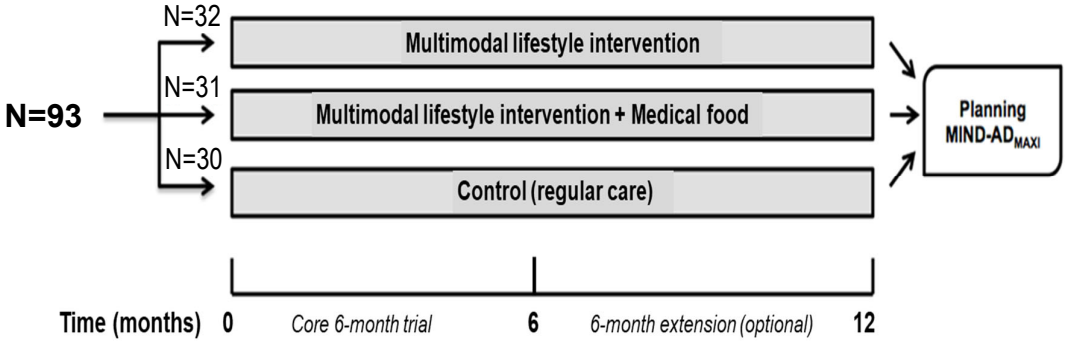
World Health Organization

Alzheimer's Disease International
The global voice on dementia

MIND-AD

Multimodal preventive trial for Alzheimer's Disease: MIND-AD$_{MINI}$

Target group: prodromal AD + vascular + lifestyle risk factors



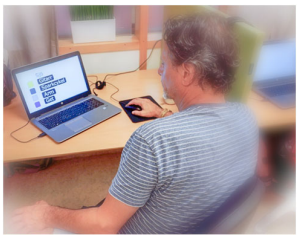
- Trial completed Dec 2019
- Electronic data entry and processing completed in Dec 2020 (delays due to Covid-19).

- Mean age 72.9 years
- MMSE 27.6 points
- Vascular and lifestyle-related risk factors were common

Kivipelto, Mangialasche et al., JPAD 2022

MIND-AD preliminary results

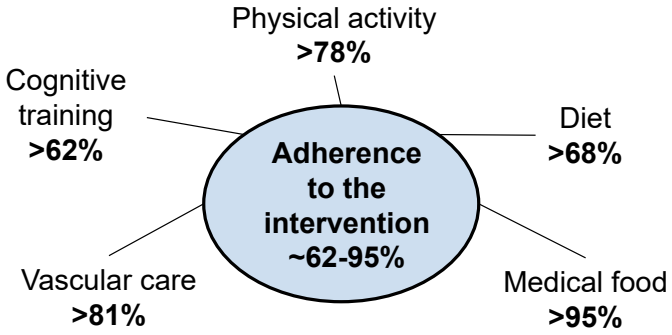
Target group: Prodromal AD
+ lifestyle + vascular risk factors



Importance of social component and adapting the intervention to the target population

Sindi, Kivipelto et al., JPAD 2022

Preliminary compliance data



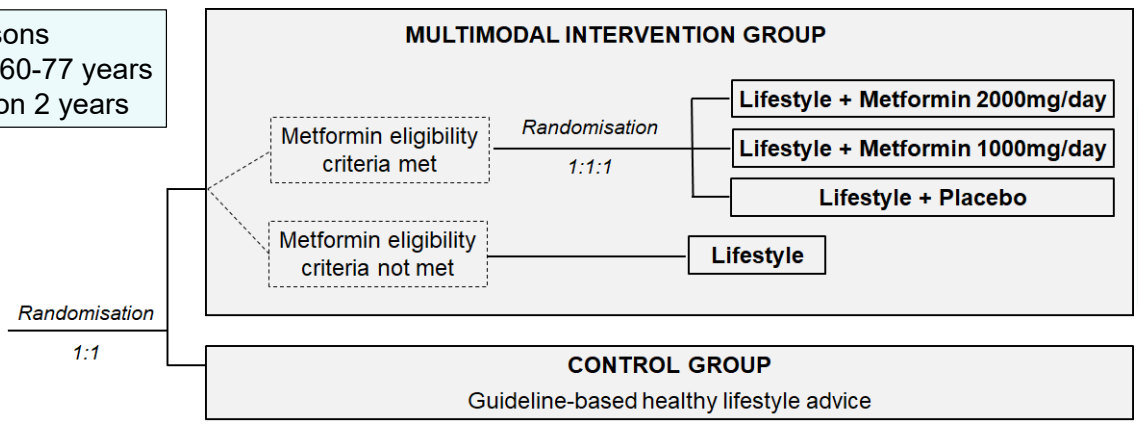
LipiDiDiet: Lancet Neurol 2017; Alz & Dem 2020

MET-FINGER study diagram

Phase 2b proof of concept trial

Diabetes medicine metformin
Repurposed drug approach

At risk persons
Age range 60-77 years
Trial duration 2 years



Outcomes:
memory and cognition
Brain scans
Alzheimer related biomarkers

Lifestyle domains: *nutrition, exercise, cognitive and social activities, cardiovascular / metabolic risk factors*

Can Dementia and Alzheimer (AD) be prevented?

- YES, a significant portion of cases can be prevented or at least delayed. Importance of the multidomain approach.
- It is never too early or too late!

From FINGER to World-Wide FINGERS

- The FINGER multidomain preventive model was feasible and effective. The model is being adapted and optimized globally to develop sustainable interventions in different settings

Prevention at the time of the COVID-19 pandemic?

- It is even more important! Requires innovative approaches and collaboration.

Future!

- Precision prevention: tailored interventions for specific at-risk profiles.
- Combination Lifestyle + Pharma + E-FINGERS.
- Implementation

Thank you for your attention!

Acknowledgements

Thank you all WW-FINGERS countries and member teams!

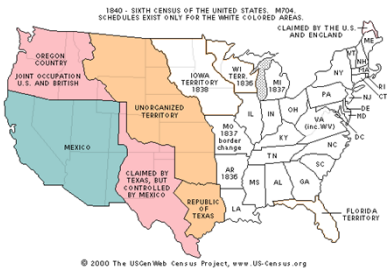
Grant support: Swedish Research Council, CIMED, Wallenberg Clinical grant, Alzheimerfonden, Hjärnfonden, Academy of Finland Alzheimer's Research and Prevention Foundation, EU 7th framework, JPND, IMI, EiT-Health, Stiftelse Stockholms Sjukhem, ALF grants, FORTE, KI-Janssen Strategic Collaboration, Imperial College ITMAT, Gates Ventures/ADDI, Alzheimer's Drug Discovery Foundation, Part the Cloud

MIND Diet for Dementia

Stacy Sattovia, MD MBA
Charlyn Fargo Ware, MS, RD, LDN
SIU School of Medicine, Culinary Medicine
May 4, 2022

Objectives

- **Identify four major points that frame challenges related to nutrition.**
- **Differentiate between *components* of nutrition and *patterns* of nutrition.**
- **Review evidence for Mediterranean, DASH, and MIND diets.**
- **Make you very hungry!**
- **No disclosures to share.**



Point #1: Human Longevity → Lifestyles Impact Health


New York Ex

Copyright, 1931, by The New York Times Company.

NEW YORK, SUNDAY, JANUARY 4, 1931.

500 Farmers Storm Arkansas Town Demanding Food for Their Children

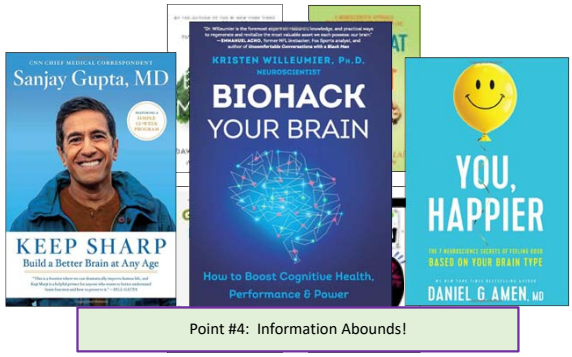
Drought Sufferers, Many Armed, Get Aid for Hungry Families

Point #2: Access to Excess

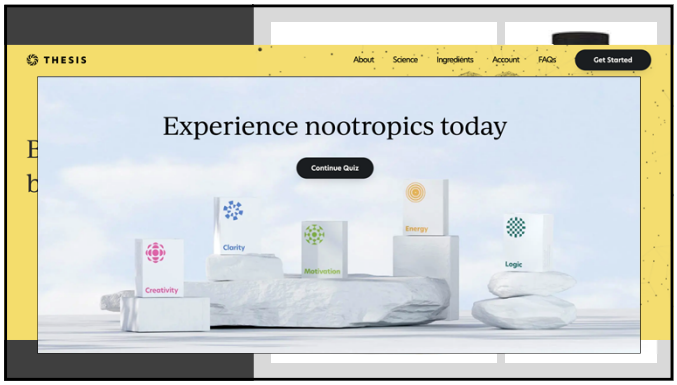
Point #3: Nutrition Research is Quite Challenging

"In an ideal world, I would take the next 1,000 children born, randomize them into two different groups, and have half of them eat nothing but fresh fruit and vegetables for the rest of their lives"

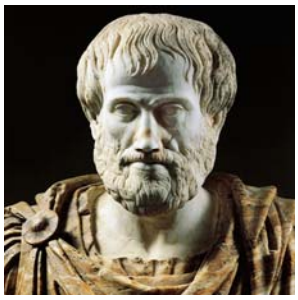
– British physician and epidemiologist, Ben Goldacre



Point #4: Information Abounds!

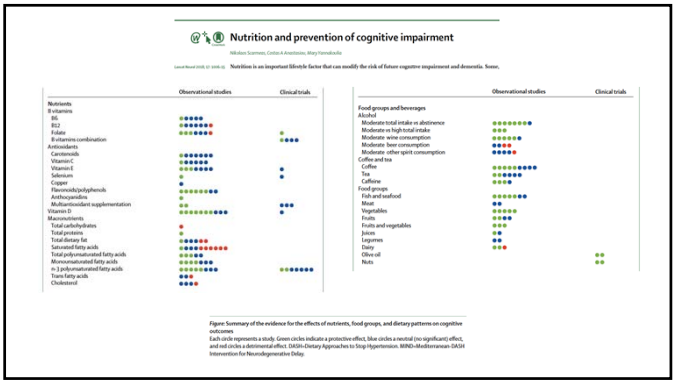


"The whole is greater than the sum of the parts."



"In the case of all things which have several parts and in which ***the totality is not, as it were, a mere heap, but the whole is something besides the parts****, there is a cause; for even in bodies contact is the cause of unity in some cases, and in others viscosity or some other such quality."*

Aristotle
Metaphysics, Book VIII, 1045a.8–10
~2370 years ago
Book VIII, 1045a.8–10



Nutrition and prevention of cognitive impairment

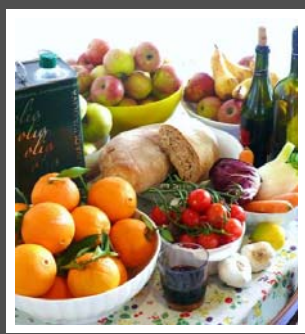
Nikolaos Scarmeas, Costas A Anastasiou, Mary Yannakoulia

Nutrition is an important lifestyle factor that can modify the risk of future cognitive impairment and dementia. Some.

Nutrients	Observational studies	Clinical trials
B vitamins		
B6		
B12		
Folate		
B-vitamins combination		
Antioxidants		
Carotenoids		
Vitamin C		
Vitamin E		
Selenium		
Copper		
Flavonoids/polyphenols		
Anthocyanidins		
Multiantioxidant supplementation		
Vitamin D		
Macronutrients		
Total carbohydrates		
Total proteins		
Total dietary fat		
Saturated fatty acids		
Total polyunsaturated fatty acids		
Monounsaturated fatty acids		
n-3 polyunsaturated fatty acids		
Trans fatty acids		
Cholesterol		

	Observational studies	Clinical trials
Food groups and beverages		
Alcohol		
Moderate total intake vs abstinence		
Moderate vs high total intake		
Moderate wine consumption		
Moderate beer consumption		
Moderate other spirit consumption		
Coffee and tea		
Coffee		
Tea		
Caffeine		
Food groups		
Fish and seafood		
Meat		
Vegetables		
Fruits		
Fruits and vegetables		
Juices		
Legumes		
Dairy		
Olive oil		
Nuts		

Figure: Summary of the evidence for the effects of nutrients, food groups, and dietary patterns on cognitive outcomes
Each circle represents a study. Green circles indicate a protective effect, blue circles a neutral (no significant) effect, and red circles a detrimental effect. DASH=Dietary Approaches to Stop Hypertension. MIND=Mediterranean-DASH Intervention for Neurodegenerative Delay.



The Seven Countries Study

Lyon Diet Heart Study

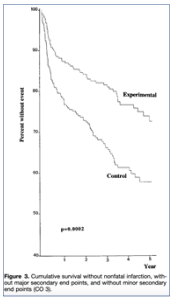


Figure 3. Cumulative survival without nonfatal infarction, without major secondary end points, and without minor secondary end points (CO 3).

This article has been retracted.

A correction has been published 1

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

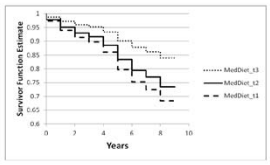
Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., María-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa María Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., et al., for the PREDIMED Study Investigators*

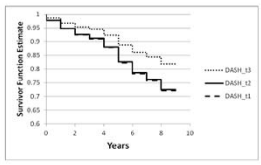
Article Figures/Media Metrics April 4, 2013
N Engl J Med 2013; 368:1279-1290

Published in final edited form as:
Alzheimers Dement. 2015 September ; 11(9): 1007–1014. doi:10.1016/j.jalz.2014.11.009.

MIND Diet Associated with Reduced Incidence of Alzheimer's Disease

Martha Clare Morris, S.D.[1], Christy C. Tangney, Ph.D.[2], Yamin Wang, Ph.D.[1], Frank M. Sacks, M.D.[3], David A Bennett, M.D.[3,4], and Neelum T. Aggarwal, M.D.[3,4]





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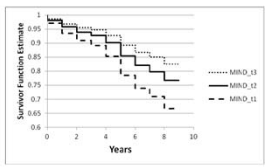


Figure 1a. – 1c.
Survivor function for incident AD by tertile of a. the MIND diet, b. the MedDiet , and c. the DASH diet based on Cox proportional hazards models adjusted for age, sex, education, APOE-ε4 (any), participation in cognitively stimulating activities, physical activity and total energy intake

DASH[d]		MedDiet[b]		MIND	
DASH components	**Max Score**	**Mediterranean Diet components**	**Max Score**	**MIND components**	**Max Score**
Total Grains ≥7/d	1	Nonrefined Grains >4/d	5	Whole Grains ≥3/d	1
Vegetables ≥4/d	1	Vegetables >4/d	5	Green Leafy ≥6/wk	1
		Potatoes >2/d	5	Other Vegetables ≥1/d	1
Fruits ≥4/d	1	Fruits >3/d	5	Berries ≥2/wk	1
Dairy ≥2/d	1	Full-fat Dairy ≤10/wk	5		
Meat, poultry & fish ≤ 2/d	1	Red meat ≤ 1/wk	5	Red Meats and products <4/wk	1
		Fish >6/wk	5	Fish ≥1/wk	1
		Poultry ≤3/wk	5	Poultry ≥2/wk	1
Nuts, seeds & legumes ≥4/wk	1	Legumes, nuts & beans >6/wk	5	Beans >3/wk	1
				Nuts ≥5 /wk	1
				Fast/fried food <1/wk	1
Total Fat ≤ 27% of kcal	1				
Saturated Fat ≤ 6% of kcal	1				
		Olive oil ≥1/d	5	Olive Oil primary oil	1
				Butter, margarine <1Tt/d	1
				Cheese<1/wk	1
Sweets ≤ 5/wk	1			Pastries, sweets <5/wk	1
Sodium ≤ 2400mg/d	1				
		Alcohol < 300mL/d but >0	5	Alcohol/wine 1/d	1
TOTAL DASH Score	10	**TOTAL MedDiet Score**	55	**Total MIND Score**	15

Nutrition and prevention of cognitive impairment

Nikolaos Scarmeas, Costas A Anastasiou, Mary Yannakoulia

Lancet Neurol 2018; 17: 1006–15 **Nutrition is an important lifestyle factor that can modify the risk of future cognitive impairment and dementia. Some,**

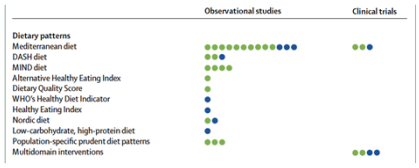
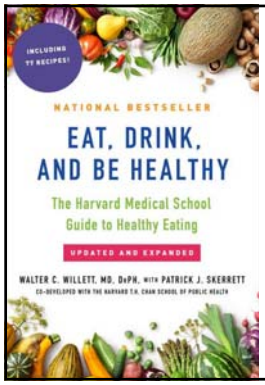


Figure: Summary of the evidence for the effects of nutrients, food groups, and dietary patterns on cognitive outcomes
Each circle represents a study. Green circles indicate a protective effect, blue circles a neutral (no significant) effect, and red circles a detrimental effect. DASH=Dietary Approaches to Stop Hypertension. MIND=Mediterranean-DASH Intervention for Neurodegenerative Delay.

To Summarize…

- Lifespan and caloric availability have increased pretty substantially over time.
- Nutrition science is challenging, producing uncertainty for patients and providers alike.
- Solid evidence to support nutritional patterns.
- Resources exist!



Resources

- OldWays: Cultural Food Traditions
  - https://oldwayspt.org/
- Harvard T.H. Chan School of Public Health, Nutrition Source
  - https://www.hsph.harvard.edu/nutritionsource/
- Goldring Center for Culinary Medicine, Culinary Medicine Certification Program
  - https://www.healthmeetsfood.com/
- Mediterranean Diet as a UNESCO Intangible Cultural Heritage of Humanity
  - https://ich.unesco.org/en/RL/mediterranean-diet-00884
- Apps of Interest
  - FoodSwitch: has a camera feature that allows you to find healthy alternatives within a category in the grocery store by scanning a bar code. Created by a Northwestern University cardiologist
  - PixFood: take a picture of something in your pantry and it will provide recipes for you!

References

- Aridi YS, Walker JL, Wright OR. The association between the Mediterranean dietary pattern and cognitive health: a systematic review. *Nutrients* 2017;9,674.
- Belluz J. I asked 8 researchers why the science of nutrition is so messy. Here is what they said. www.vox.com. August 16, 2018.
- Croll PH et al. Better diet quality relates to larger brain tissue volumes: The Rotterdam Study. *Neurology* 2018;90:e2166-e2173.
- Cutler DM, Glaeser EL, Shapiro JM. Why have Americans become more obese? *J Econ Perspectives*;17(3):93-118.
- Estruch R et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med* 2013;368:1279-1290.
- Estruch R et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra virgin olive oil of nuts. N Engl J Med 2018;378(25):e34(1)-e34(14)..
- Gabbianelli R, Damiani E. Epigenetics and neurodegeneration: role of early life nutrition. *J Nutr Biochem* 2018;57:1-13.
- Lorgeril M et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon diet heart study. *Circulation* 1999;99:779-785.
- Morris CM et al. MIND diet associated with reduced incidence of Alzheimer's Disease. *Alzheimer's Dement.* 2015;11(9):1007-1014.
- Mozaffarian D et al. History of modern nutrition science – implications for current research, dietary guidelines, and food policy. *BMJ*;2018.
- OldWays: Cultural Food Traditions, https://oldwayspt.org/
- Power R, et al. The role of nutrition for the aging population: implications for cognition and Alzheimer's disease. *Ann Rev of Food Sci Technol* 2019;10:619-639.
- Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. *Lancet Neurol* 2018;17:1006-1016.
- Soininen H et al. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomized, double blind, controlled trial. *Lancet Neurol* 2017;16:965-975.
- Willett WC, Skerrett PJ. *Eat, Drink and Be Healthy: The Harvard Medical School Guide to Healthy Eating*. New York: Free Press, 2017.

Detox the Brain with Deep Sleep

Shelley A. Tischkau, PhD

Professor and Chair
Department of Pharmacology
Department of Medical Microbiology, Immunology & Cell Biology

SIU MEDICINE
FORWARD. FOR YOU.

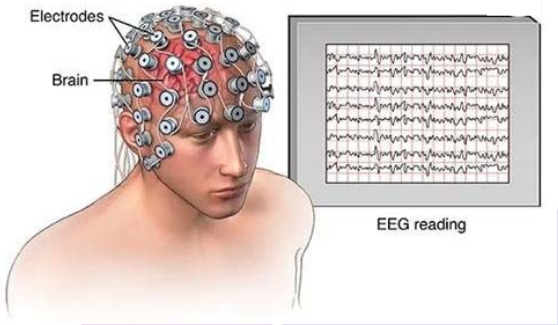
Why Sleep?

- Function unknown
  - Neuronal communication
  - Toxin removal
  - Memory consolidation
  - Immune system
- Sleep Deprivation
  - Death (Animal study)
  - Mood
  - Safety
- Poor Sleep
  - Heart Disease
  - Diabetes
  - Depression
  - Cancer
  - Colds
  - Dementia

Does sleep change with age?

- Total Sleep Time
- Sleep Latency
- Hrs Asleep/ Hrs in Bed
- Wake after Sleep Onset
- Sleep Architechture
- # Naps Duration Daytime sleepiness
- Qualitative Reports

How to measure sleep?



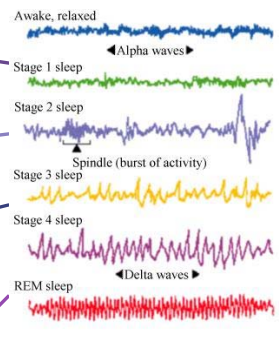
Electroencephalography

NREM
Wake Easily
Feel like no sleep
⇩ HR, RR, BP
Hypnotic Jerks

NREM
Most common 50%
Harder to wake
⇩ HR, RR, BP

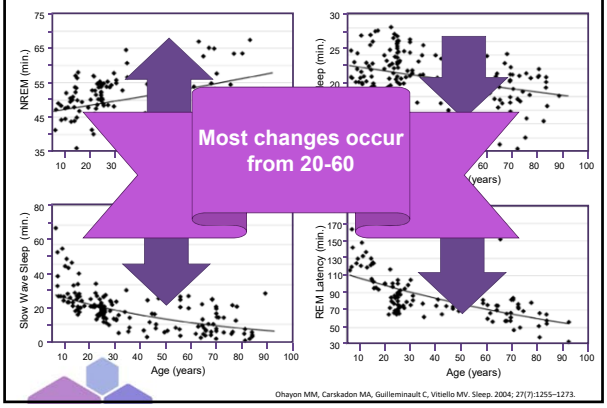
NREM Deep Sleep
35-45 min after onset
Disorient on wake
⇩ HR, RR, BP

Rapid Eye Movement
Dreaming, sleepwalking
Disoriented on wake
⇧ HR, RR, BP
⇩ Regularity
⇧ Throughout night



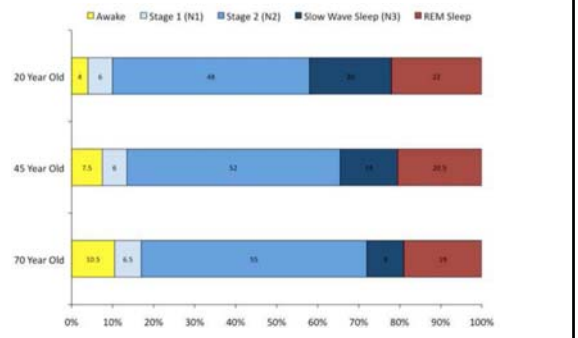
Electroencephalography (EEG)

Sleep Architecture - Aging



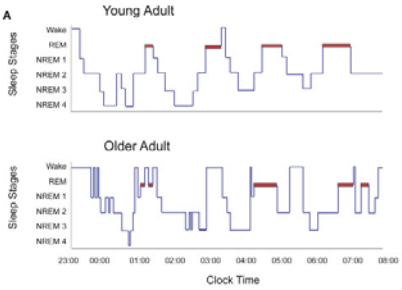
Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Sleep. 2004; 27(7):1255–1273.

Sleep Architecture

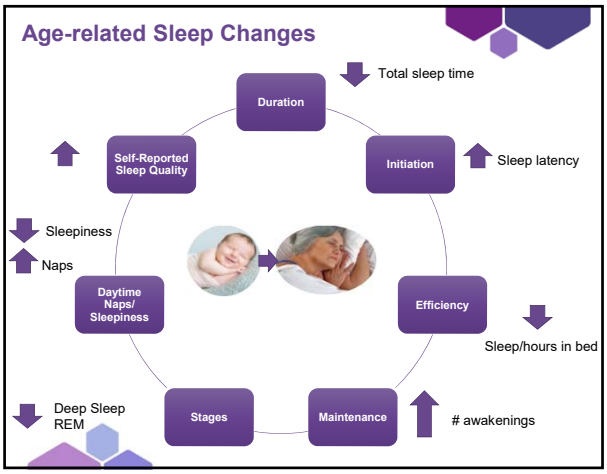


Scullin MK, Bliwise DL. Perspect Psychol Sci. 2015;10(1):97–137.

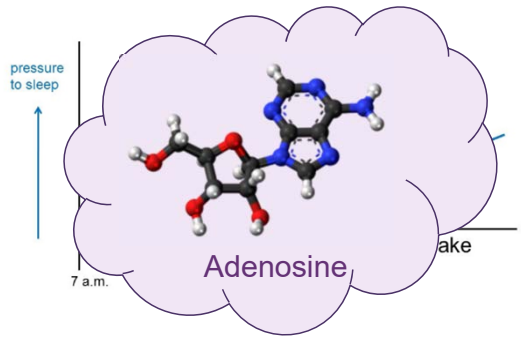
Sleep Architecture



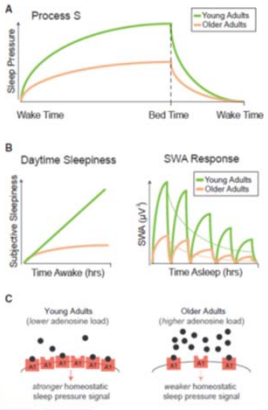
Age-related Sleep Changes



Homeostatic Sleep Drive



Homeostatic Sleep Drive



Sleep Pressure

↓

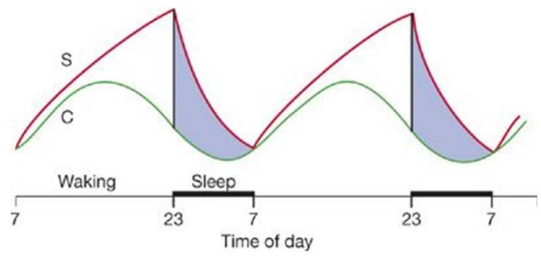
Daytime Sleepiness

&

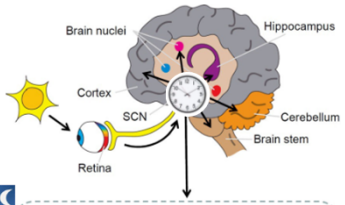
Awakenings

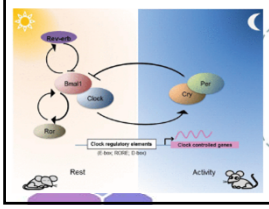
Mander BA, Winer JR, Walker MP. Neuron. 2017 Apr 5;94(1):19-36

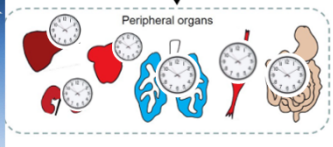
Physiological Control of Sleep/Wake Cycles



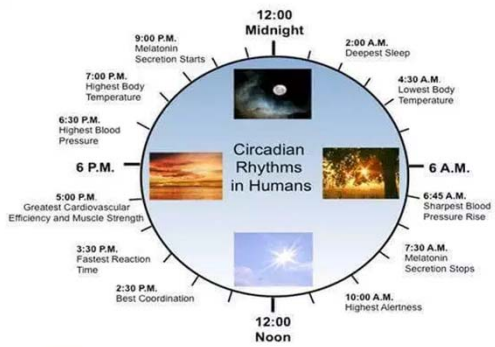
Circadian Rhythms



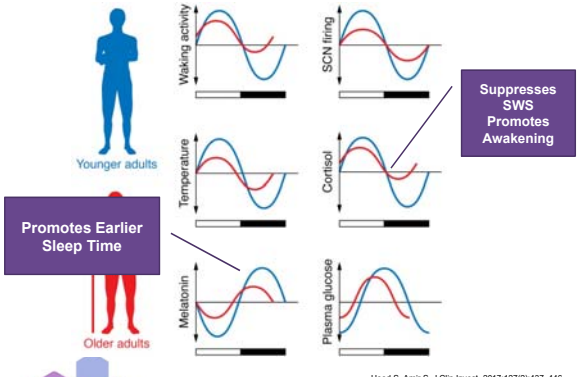




Circadian Rhythms

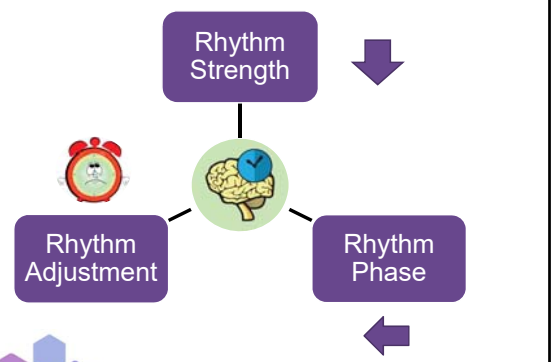


Rhythm Change - Aging

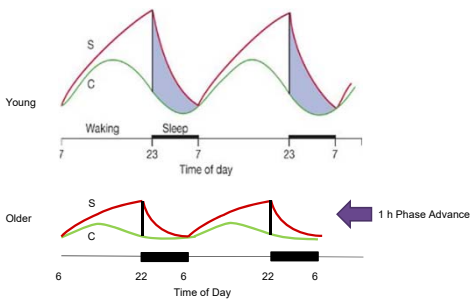


Hood S, Amir S. J Clin Invest. 2017;127(2):437–446.

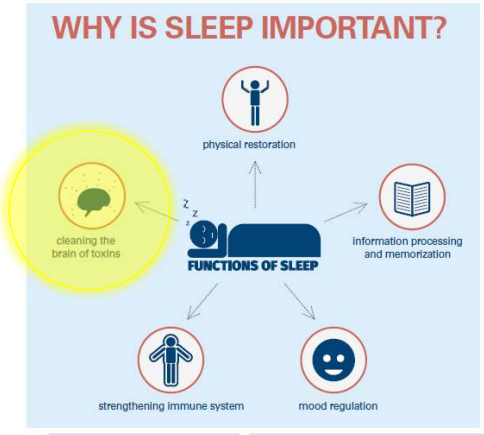
Circadian Rhythms - Aging



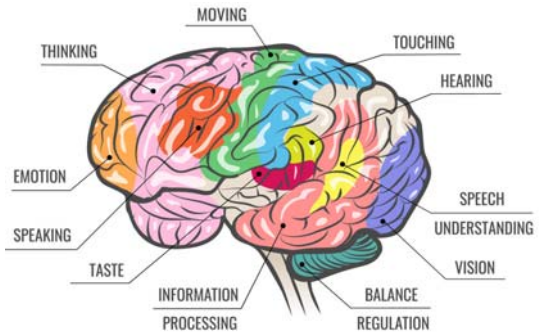
SLEEP/WAKE CYCLES



WHY IS SLEEP IMPORTANT?



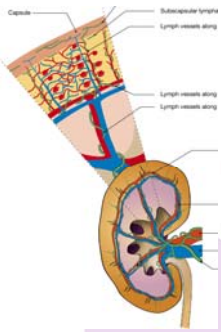
Brain Metabolic Activity



Lymphatics

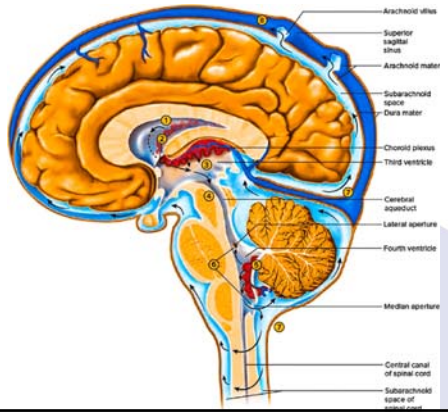
Waste Removal

Lymph System Anatomy

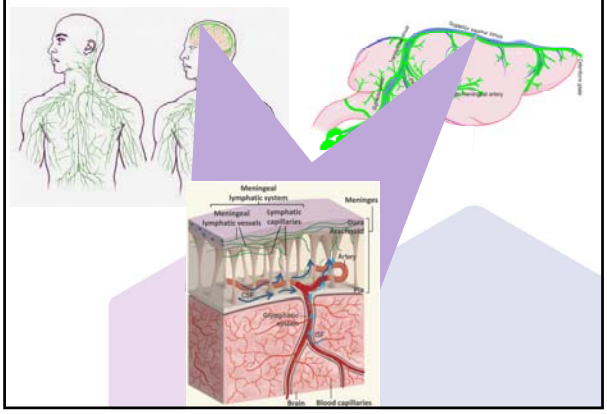


How does the brain handle waste?

CSF – the brain's lymphatic system?



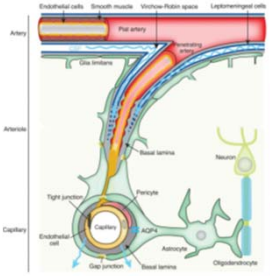
Meningeal Lymphatics

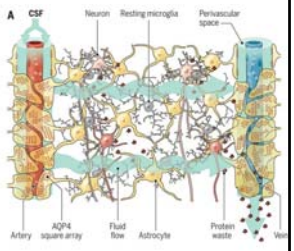


The Glymphatic System

Glial-derived lymphatic-like function

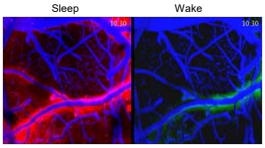
Maiken Nedergaard, MD, DMSc

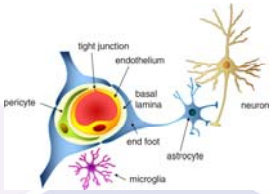


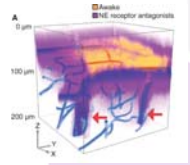


Nedergaard M, Goldman SA. Science. 2020 Oct 2;370(6512):50-56.

Glymphatic Flow during Sleep

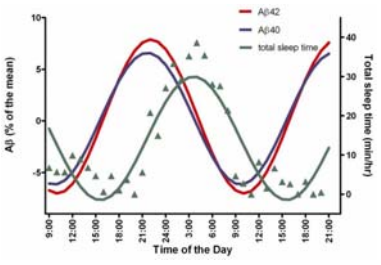






Xie L, Kang H, Xu Q, et al. Science. 2013;342(6156):373-377.

Sleep Removes Aβ from CSF



Aβ production = wakefulness due to increased neuronal activity

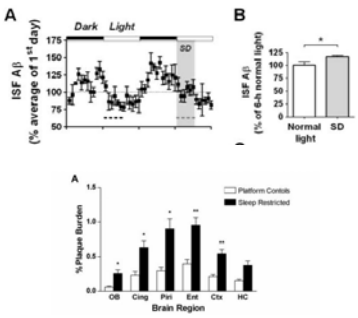
Aβ production reduced during SWS

Aβ cleared by glymphatic flow during sleep

Huang Y, Potter R, Sigurdson W, et al. Arch Neurol. 2011;69(1):51–58.

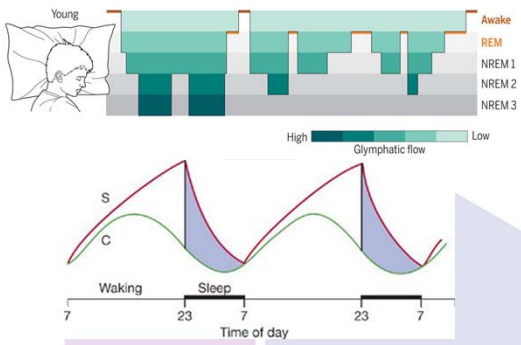
Sleep Deprivation Increases Plaque Burden and CSF Aβ

- Tg2576 Mice
- 5-fold increase in Aβ40 and a 10- to 15-fold increase in Aβ42/43
- 6 h sleep deprivation



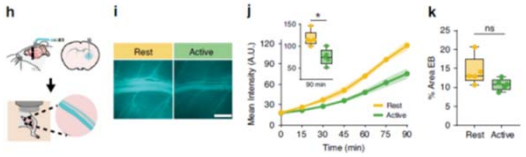
Kang JE, Lim MM, Bateman RJ, et al. Science. 2009;326(5955):1005–1007.

Sleep Promotes Glymphatic Flow



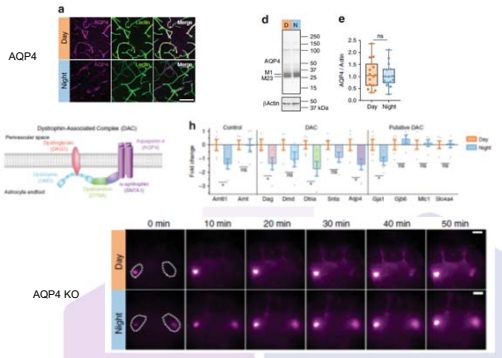
Nedergaard M, Goldman SA. Science. 2020 Oct 2;370(6512):50-56

Circadian Control of Glymphatics



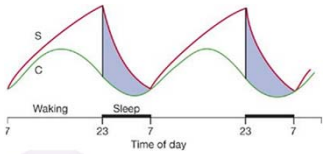
Hablitz LM, Plá V, Giannetto M, Vinitsky HS, Stæger FF, Metcalfe T, Nguyen R, Benrais A, Nedergaard M. Nat Commun. 2020 Sep 2;11(1):4411.

Circadian Control of Glymphatics



Hablitz LM, Plá V, Giannetto M, Vinitsky HS, Stæger FF, Metcalfe T, Nguyen R, Benrais A, Nedergaard M. Nat Commun. 2020 Sep 2;11(1):4411.

Circadian Control of Glymphatics



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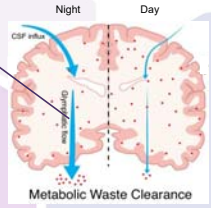
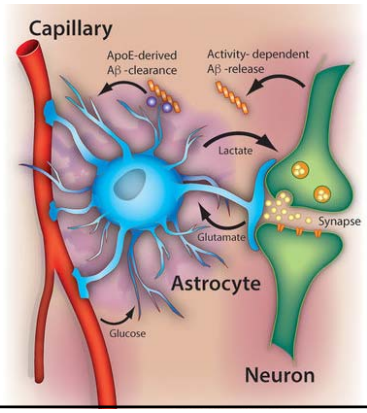


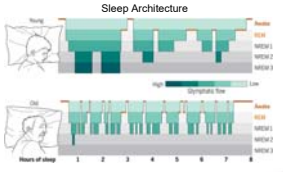
Hauglund, N., Pavan, C. & Nedergaard, M. 2020. Current Opinion in Physiology, 15: 1-6.

Sleep and Circadian Regulation of Astrocytes



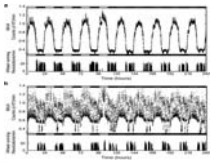
Glymphatics and Aging

Sleep Architecture

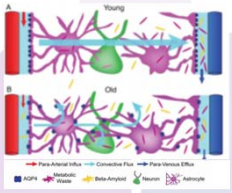


Nedergaard M, Goldman SA. Science. 2020 Oct 2;370(6512):50-56. doi: 10.1126/science.abb8739.

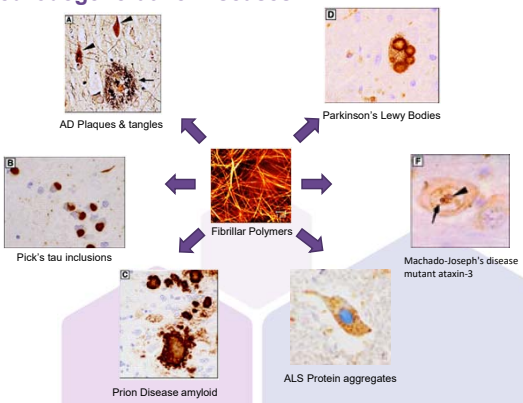
Circadian Clock Function



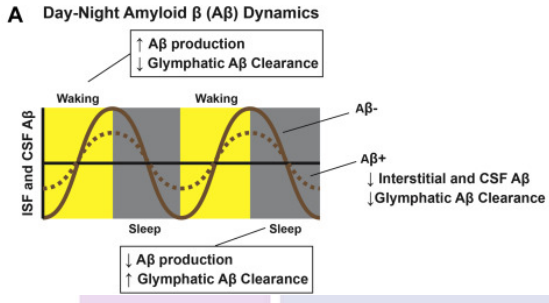
Nakamura, T.J., Takasu, N.N. & Nakamura, W. 2016. J Physiol Sci 66, 367–374



Neurodegenerative Diseases

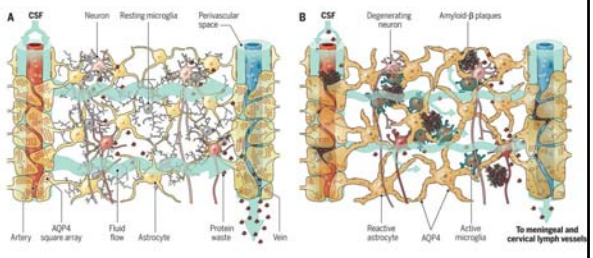


Amyloid Beta Dynamics



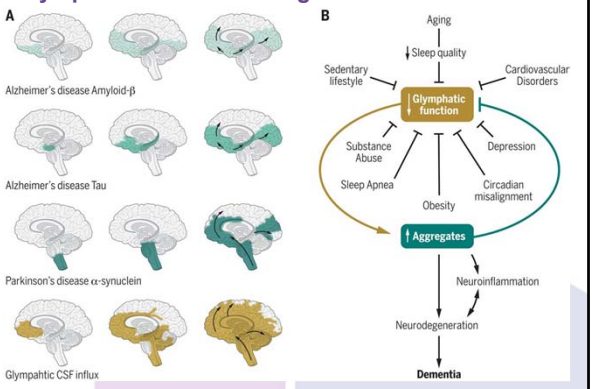
Boespflug EL, Iliff JJ. Biol Psychiatry. 2018 Feb 15;83(4):328-336.

Fluid Transport in Alzheimer's Disease



Nedergaard M, Goldman SA. Science. 2020 Oct 2;370(6512):50-56.

Glymphatics and Neurodegenerative Disease



Nedergaard M, Goldman SA. Science. 2020 Oct 2;370(6512):50-56.

References

- Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep. 2004 Nov 1;27(7):1255-73. doi: 10.1093/sleep/27.7.1255. PMID: 15586779.
- Scullin MK, Bliwise DL. Sleep, cognition, and normal aging: integrating a half century of multidisciplinary research. Perspect Psychol Sci. 2015 Jan;10(1):97-137. doi: 10.1177/1745691614556680. PMID: 25620997; PMCID: PMC4302758.
- Mander BA, Winer JR, Walker MP. Sleep and Human Aging. Neuron. 2017 Apr 5;94(1):19-36. doi: 10.1016/j.neuron.2017.02.004. PMID: 28384471; PMCID: PMC5810920.
- Hood S, Amir S. The aging clock: circadian rhythms and later life. J Clin Invest. 2017 Feb 1;127(2):437-446. doi: 10.1172/JCI90328. Epub 2017 Feb 1. PMID: 28145903; PMCID: PMC5272178.
- Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. Science. 2020 Oct 2;370(6512):50-56. doi: 10.1126/science.abb8739. PMID: 33004510; PMCID: PMC8186542.
- Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013;342(6156):373-377. doi:10.1126/science.1241224. PMID: 24136970.
- Huang Y, Potter R, Sigurdson W, Santacruz A, Shih S, Ju YE, Kasten T, Morris JC, Mintun M, Duntley S, Bateman RJ. Effects of age and amyloid deposition on Aβ dynamics in the human central nervous system. Arch Neurol. 2012 Jan;69(1):51-8. doi: 10.1001/archneurol.2011.235. Epub 2011 Sep 12. PMID: 21911660; PMCID: PMC3254706.
- Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, Fujiki N, Nishino S, Holtzman DM. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science. 2009 Nov 13;326(5955):1005-7. doi: 10.1126/science.1180962. Epub 2009 Sep 24. PMID: 19779148; PMCID: PMC2789838.
- Hablitz LM, Plá V, Giannetto M, Vinitsky HS, Stæger FF, Metcalfe T, Nguyen R, Benrais A, Nedergaard M. Circadian control of brain glymphatic and lymphatic fluid flow. Nat Commun. 2020 Sep 2;11(1):4411. doi: 10.1038/s41467-020-18115-2. PMID: 32879313; PMCID: PMC7468152.
- Hauglund, N., Pavan, C. & Nedergaard, M. 2020. Cleaning the sleeping brain – the potential restorative function of the glymphatic system. Current Opinion in Physiology, 15: 1-6.
- Nakamura, T.J., Takasu, N.N. & Nakamura, W. The suprachiasmatic nucleus: age-related decline in biological rhythms. J Physiol Sci 66, 367–374 (2016). https://doi.org/10.1007/s12576-016-0439-2
- Boespflug EL, Iliff JJ. The Emerging Relationship Between Interstitial Fluid-Cerebrospinal Fluid Exchange, Amyloid-β, and Sleep. Biol Psychiatry. 2018 Feb 15;83(4):328-336. doi: 10.1016/j.biopsych.2017.11.031. Epub 2017 Dec 7. PMID: 29279202; PMCID: PMC5767516.
- Nedergaard EuroPhysiology conference talk: https://www.youtube.com/watch?v=He6HMnMbxAc

May 4 and 5, 2022

Pharmacologic Treatments

FDA-approved and dietary supplements

Tom Ala, MD

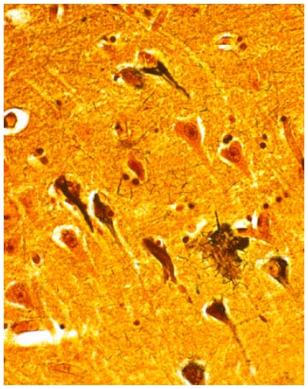
SIU MEDICINE
FORWARD. FOR YOU.

OBJECTIVES TODAY

- What is Alzheimer's disease?
- Explain its disease trajectory.
- Explain how the FDA-approved drugs affect its trajectory.
- Review donepezil, rivastigmine, galantamine, and memantine.
- Review aducanumab and three similar drugs.
  - lecanemab, donanemab, gantenerumab
- Explain what dietary supplements are.

ALZHEIMER'S IS A DEGENERATIVE DISEASE

- The brain cells are dying off.
- The patient's thinking ability fades away.
- The exact cause is uncertain.
- There are no treatments proven to stop or slow the degeneration.



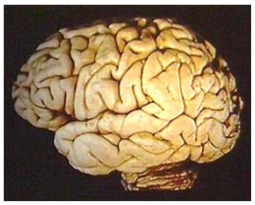
Neurofibrillary tangles

Amyloid plaques

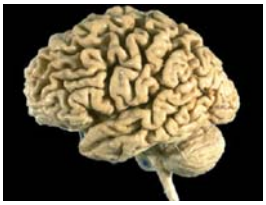
Loss of brain cells

Neurotransmitter imbalances

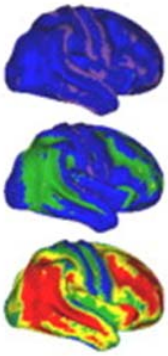
BRAIN ATROPHY



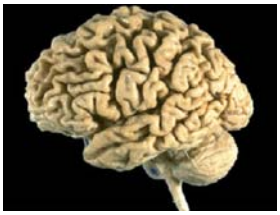
Normal brain



Alzheimer's brain

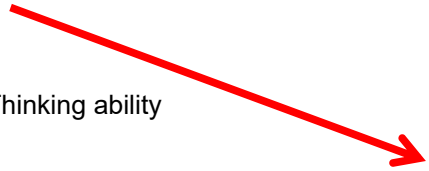


The protein amyloid accumulates in the brain.



PMID: 22108203
Vlassenko. *Biochimica Biophysica Acta* 2012;1822:370

THE TRAJECTORY OF ALZHEIMER'S DISEASE



Thinking ability

Without treatment

MEDICATIONS TO TREAT ALZHEIMER'S

?

MEDICATIONS TO TREAT ALZHEIMER'S

- Symptomatic drugs
- Disease-modifying drugs

SYMPTOMATIC DRUGS

- treat the **symptoms**

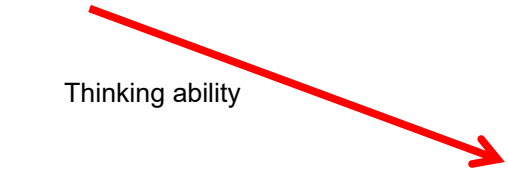
SYMPTOMS OF ALZHEIMER'S

- Memory loss
- Behavioral problems
  - Delusions
  - Hallucinations
  - Anxiety
  - Depression
  - Agitation
  - Apathy
- Disordered sleep
- Etc.

DISEASE-MODIFYING DRUGS

- treat the disease itself

THE TRAJECTORY OF ALZHEIMER'S DISEASE



Thinking ability

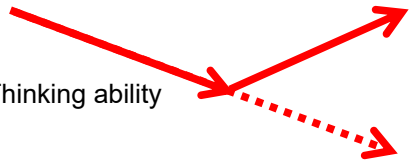
Without treatment

THE TRAJECTORY OF ALZHEIMER'S DISEASE

Thinking ability

With **disease-modifying** treatment

THE TRAJECTORY OF ALZHEIMER'S DISEASE



Thinking ability

We wish!

TREATMENT OF ALZHEIMER'S

- Up until 2021, there had been no new FDA-approved drugs to treat AD in the past 18 years.

FDA-APPROVED DRUGS FOR ALZHEIMER'S DISEASE

donepezil	Aricept donepezil HCl
rivastigmine	Exelon
galantamine	Razadyne ER
memantine	Namenda
donepezil + memantine	Namzaric

FDA-APPROVED DRUGS FOR ALZHEIMER'S DISEASE

- donepezil
- rivastigmine
- galantamine

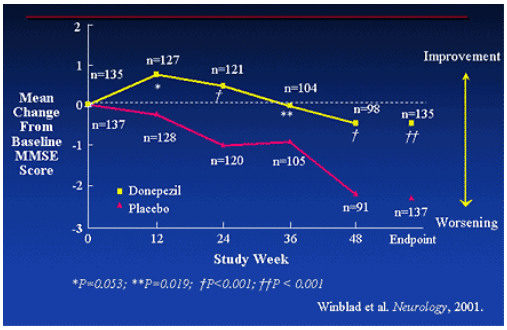
} increase acetylcholine acetylcholine esterase inhibitors (AChEIs)

- memantine — interferes with glutamate

FDA-APPROVED DRUGS FOR ALZHEIMER'S

- Alter the balance of neurotransmitters in the brain
  - donepezil (Aricept®)
  - galantamine (Razadyne®)
  - rivastigmine (Exelon®)
  - memantine (Namenda®)

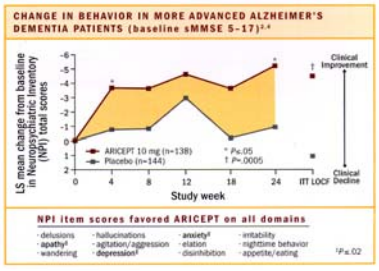
THESE DRUGS CAN IMPROVE COGNITION IN ALZHEIMER'S



PMID: 11502918

Winblad. *Neurology* 2001:14:489

THESE DRUGS CAN IMPROVE **BEHAVIOR** IN ALZHEIMER'S

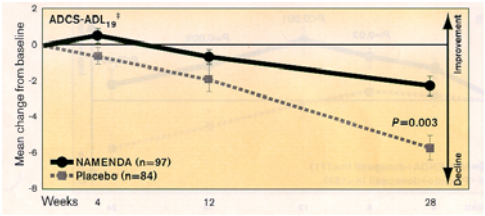


Neuropsychiatric Inventory Scale

PMID: 11524468

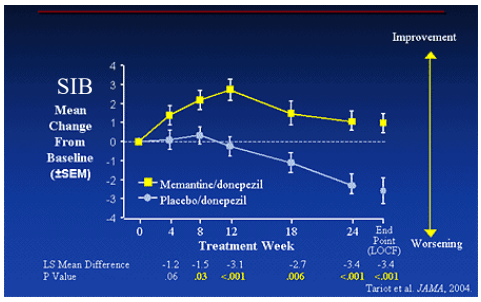
Feldman. *Neurology* 2001;57:613

THESE DRUGS CAN IMPROVE ACTIVITIES OF DAILY LIVING IN ALZHEIMER'S



PMID: 12672860
Reisberg. *NEJM* 2003;348:1333

COMBINATION THERAPY

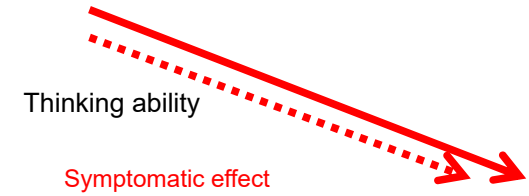


PMID: 14734594
Tariot. *JAMA* 2004;291:317

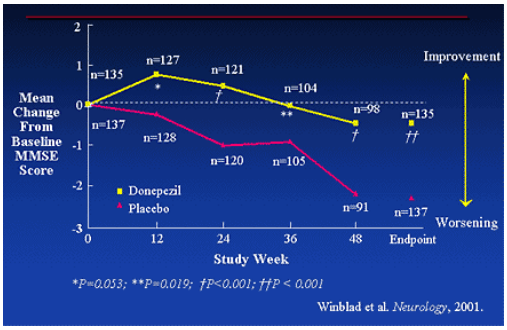
TREATMENT OF ALZHEIMER'S

- Up until 2021, there had been no new FDA-approved drugs to treat AD in the past 18 years.
- The drugs that had been approved offer modest *symptomatic* benefit.
- They do not slow or stop the progression of Alzheimer's.

THE TRAJECTORY OF ALZHEIMER'S DISEASE



THESE DRUGS CAN IMPROVE COGNITION IN ALZHEIMER'S



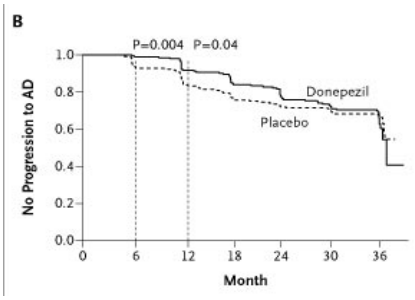
PMID: 11502918

Winblad. *Neurology* 2001:14:489

THE BENEFIT OF THESE DRUGS

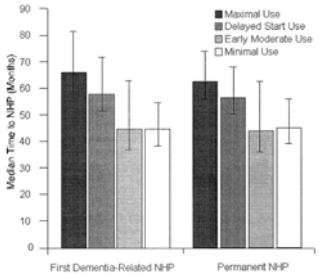
- The average patient functions a little better.
- A few patients do significantly better.
- They delay the conversion to Alzheimer's disease.
- They help keep the patient out of the nursing home.

DELAYING CONVERSION TO ALZHEIMER'S



PMID: 15829527
Petersen. *NEJM* 2005;352:2379

DELAYING NURSING HOME PLACEMENT

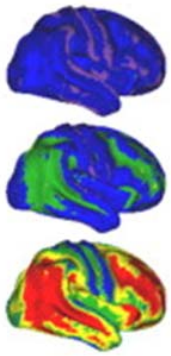


When donepezil was taken at an effective dose for at least 9 to 12 months, conservative estimates of the time gained before NHP were 21.4 months for first dementia-related NHP and 17.5 months for permanent NHP.

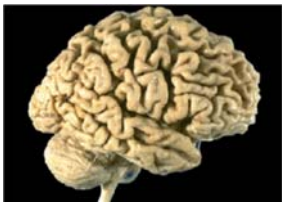
PMID: 12834513
Geldmacher. *JAGS* 2003;51:937

THE BENEFIT OF THESE DRUGS

Like using a crutch if we have severe leg pain...



The protein amyloid accumulates in the brain.

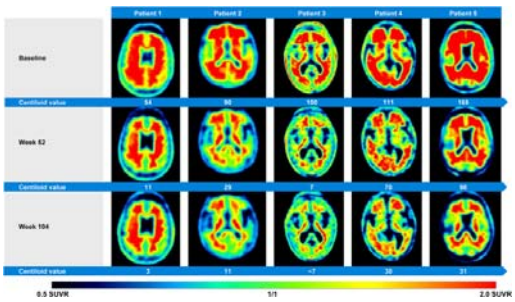


PMID: 22108203
Vlassenko. *Biochimica Biophysica Acta* 2012;1822:370.

DISEASE-MODIFYING DRUGS?

- aducanumab (Aduhelm)
- donanemab
- lecanemab
- gantenerumab

Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease



PMID: 31831056
Klein. *Alz Res Ther* 2019;11:101

BUT DOES REMOVAL OF THE AMYLOID PROTEIN AFFECT THE THINKING ABILITY OF THE PATIENT?

Does removal of the amyloid slow the degeneration of the brain cells?

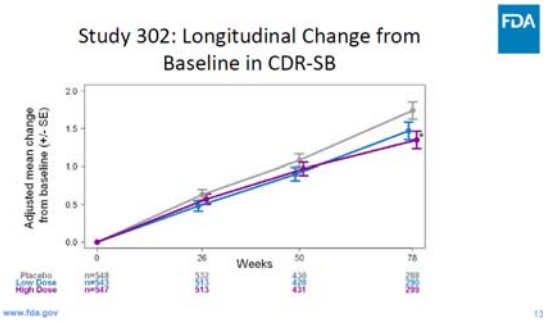
U.S. FOOD & DRUG ADMINISTRATION

Aducanumab for the Treatment of Alzheimer's Disease: Clinical Overview of Efficacy

Kevin M. Krudys, PhD
Clinical Efficacy Reviewer
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

https://www.fda.gov/media/143504/download

ADUCANUMAB



https://www.fda.gov/media/143504/download

Evidence of Effectiveness

- Study 302 provides primary evidence of effectiveness
- Results of Study 103 are appropriately viewed as supportive evidence of the effectiveness of aducanumab
- Study 301 does not contribute to the evidence of effectiveness
  - Analyses allow for independent consideration of Study 302 and do not represent evidence that aducanumab is ineffective

www.fda.gov 35

https://www.fda.gov/media/143504/download

ADUCANUMAB

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761178Orig1s000

CLINICAL REVIEW(S)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf

Clinical Review
Kevin Krudys, PhD
BLA 761178
Aduhelm (aducanumab)

FDA CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761178
Priority or Standard	Priority
Submit Date(s)	02/20/2020, 05/15/2020, 07/07/2020
Received Date(s)	07/07/2020
PDUFA Goal Date	06/07/2021
Division/Office	Division of Neurology 1/Office of Neuroscience
Reviewer Name(s)	Kevin Krudys, PhD
Review Completion Date	06/06/2021
Established/Proper Name	aducanumab-avwa
(Proposed) Trade Name	Aduhelm
Applicant	Biogen Inc.
Dosage Form(s)	Solution for injection
Applicant Proposed Dosing Regimen(s)	10 mg/kg as an intravenous infusion every four weeks
Applicant Proposed Indication(s)/Population(s)	To delay clinical decline in patients with Alzheimer's disease
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of Alzheimer's disease

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf

ADUCANUMAB

- Aduhelm™ (brand name).
- Very controversial: many experts disagree about its benefit and whether it should be prescribed.
- Administered by monthly intravenous infusions.
- Very expensive, $28,000 per year for the drug itself, not including the cost of the infusions.
- At present Medicare will only cover the cost if the patient is in an approved study.
- Patient must have a test that shows that amyloid is accumulating in the brain, either by a spinal tap or an amyloid PET scan.
- Patient must have relatively mild Alzheimer's or only significant memory impairment.
- 20-43% of patients may experience some degree of brain swelling or microhemorrhages.
- Unknown at this time how long the drug should be administered

DISEASE-MODIFYING DRUGS?

- aducanumab (Aduhelm)
- donanemab
- lecanemab
- gantenerumab

HAVE YOU SEEN ANY ADVERTISEMENTS FOR MEMORY PILLS LATELY?

ADS I HAVE SEEN IN THE PAST FEW MONTHS

- Prevagen
- Neuriva
- Focus factor
- Cognimax
- Cognium
- Ceremin
- Neuronol
- Neuro enhancer
- Brain Awake

THERE ARE MANY MORE…

- Procera AVH
- Alpha Brain
- NAD+OVIM
- Brainjuice
- Cebria
- Excelerol
- NooCube
- US Doctor's Clinical Brain Power Advances
- Genius Consciousness
- Healthycell Pro
- Lumonol
- Brain Awake
- Brain Armor
- brainMD (Brain & Memory Power Boost, Neurovite Plus)
- Clarity Brain Health Formula
- Percepta
- Qualia Mind
- Luein
- Etc, etc, etc

INGREDIENTS OF THE DIETARY SUPPLEMENTS

- Apoaequorin
- Huperzine A
- Vitamin B Complex
- L-Tyrosine
- L-Theanine
- Alpha Lipoic Acid
- Guarana
- Ginkgo Biloba
- Brahmi (Bacopa monnieri)
- Bacopa Extract (Bacopa monnlerl)
- Rhodiola Rosea
- S-Adenosyl Methionine
- Cat's claw
- CoQ-10
- Omega-3 fatty acids (e.g., DHA and EPA)
- St. John's Wort
- l-Glutamine,
- DMAE Bitartrate
- Green Tea Extract
- Oolong Tea Extract
- Caffeine
- Vitamin B12
- Acetyl-L-Carnitine
- Phosphatidylserine
- Creatine
- Resveratrol
- Coffee Cherry Extract
- Choline
- Etc, Etc, Etc

The apoaequorin Chewables Year Supply Sweepstakes x2

Enter for a chance to win a year supply of apoaequorin Chewables for you and a friend!

ENTER NOW

https://prevagen.com/

What is apoaequorin?

apoaequorin was originally discovered in jellyfish. Apoaequorin is safe and uniquely supports brain function.*

® Selected as the **#1 Pharmacist Recommended Memory Support Brand in 2021** Pharmacy Times annual survey for third year in a row.

https://prevagen.com/

Apoaequorin is an over-the-counter supplement for healthy brain function and memory improvement.

Based on a clinical study of subgroups of individuals who were cognitively normal or mildly impaired.

https://prevagen.com/

Apoaequorin

Madison Memory Study

In a double-blinded, placebo-controlled trial, apoaeq..demonstrated the ability to improve aspects of cognitive function in subgroups of participants with either normal cognitive aging or very mild impairment, as determined by pre-trial screening. The group of participants taking apoaeq..improved certain aspects of cognitive function according to computer-based testing. The adults were over 40 years old and took one capsule daily (10 mg) for 90 days.

PMID: 26878676

Moran. *Adv Mind Body Med* 2016;30:4

https://prevagen.com/

Apoaequorin

Study details

A total of 218 participants, ages 40 to 91, with self-reported memory concerns were enrolled in the study. Two hundred and eleven (211) participants completed the study.

Adverse Events

The Experimental and Control substances were very well tolerated. Two participants experienced adverse events during the study. Each group had a single adverse event, and there were no serious adverse events (SAEs) in the study.

https://prevagen.com/

AD8 test

AD8 Dementia Screening Interview

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	YES, A change	NO, No change	N/A, Don't know
1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)			
2. Less interest in hobbies/activities			
3. Repeats the same things over and over (questions, stories, or statements)			
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)			
5. Forgets correct month or year			
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)			
7. Trouble remembering appointments			
8. Daily problems with thinking and/or memory			
TOTAL AD8 SCORE			

Apoaequorin

Table 1 Cognitive Measurement Tests

Task	Cognitive Domain Measured
International Shopping List (ISL)	Verbal Learning
International Shopping List - Delayed Recall (ISRL)	Memory
Groton Maze Learning (GML)	Executive Function
Groton Maze Learning - Delayed Recall (GMR)	Memory
Detection (DET)	Psychomotor Function
Identification (IDN)	Attention
One Card Learning (OCL)	Visual Learning
One Back (ONB)	Working Memory
Two Back (TWOB)	Working Memory

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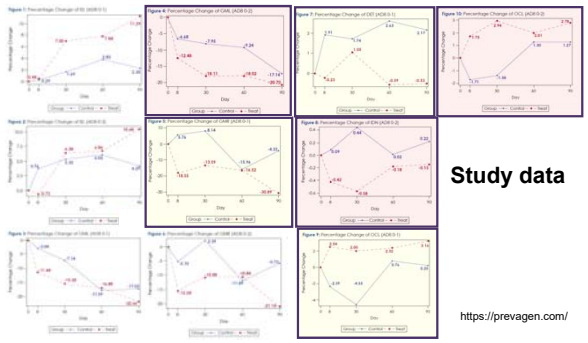
Apoaequorin



Study data

https://prevagen.com/

https://prevagen.com/

Apoaequorin

Study results

Table 3 The Score Differences in the Two Groups Before and After Treatment (AD8 0-1)

Tasks	Placebo		Within p	Apoaequorin		Within p	Between Group P value			
	Day 0	Day 90	value	Day 0	Day 90	value	Group	Time	Group x Time	Base
ISL	24.62 ± 3.499	25.19 ± 5.163	0.373	24.48 ± 6.162	27.25 ± 5.106	0.002*	0.125	0.040*	0.279	<.0001*
ISRL	8.208 ± 2.449	8.904 ± 2.947	0.030*	8.702 ± 2.654	9.277 ± 2.614	0.091	0.704	0.134	0.897	<.0001*
GML	61.83 ± 21.54	51.00 ± 21.54	0.003*	57.64 ± 18.97	44.58 ± 13.69	<0.0001*	0.103	<.0001*	0.491	<.0001*
GMR	9.208 ± 4.211	8.809 ± 5.182	0.296	9.324 ± 4.870	6.444 ± 3.691	0.000*	0.011*	0.065	0.078	<.0001*
DET	2.503 ± 0.066	2.557 ± 0.096	0.005*	2.543 ± 0.095	2.530 ± 0.082	0.561	0.015*	0.146	0.021*	<.0001*
IDN	2.733 ± 0.066	2.727 ± 0.059	0.965	2.725 ± 0.069	2.723 ± 0.059	0.854	0.246	0.979	0.460	<.0001*
OCL	1.016 ± 0.103	1.018 ± 0.119	0.836	1.017 ± 0.103	1.049 ± 0.093	0.057	0.010*	0.330	0.193	<.0001*
ONB	1.313 ± 0.145	1.404 ± 0.160	0.015*	1.356 ± 0.156	1.397 ± 0.145	0.214	0.220	0.013*	0.388	<.0001*
TWOB	1.220 ± 0.168	1.321 ± 0.157	0.021	1.244 ± 0.148	1.312 ± 0.134	0.019*	0.747	0.004*	0.474	<.0001*

Notes on Table 3
1 Time is the number of visits since the initial Baseline visit and was coded as a categorical variable

https://prevagen.com/

Apoaequorin

Study results

Table 4 The Score Differences in the Two Groups Before and After Treatment (AD8 0-2)

Tasks	Placebo		Within p	Apoaequorin		Within p	Between Group P value			
	Day 0	Day 90	value	Day 0	Day 90	value	Group	Time	Group x Time	Base
ISL	24.45 ± 4.075	25.50 ± 5.474	0.090	25.01 ± 5.434	27.68 ± 4.634	<0.0001*	0.324	0.000*	0.039*	<.0001*
ISRL	8.275 ± 2.385	9.000 ± 2.908	0.012*	8.762 ± 2.336	9.482 ± 2.400	0.002*	0.465	0.015*	0.703	<.0001*
GML	60.37 ± 21.08	50.02 ± 22.43	0.000*	58.59 ± 23.45	46.46 ± 18.78	<0.0001*	0.040*	<.0001*	0.463	<.0001*
GMR	9.400 ± 5.424	8.861 ± 5.938	0.229	8.898 ± 4.470	7.017 ± 4.722	0.001*	0.107	0.092	0.367	<.0001*
DET	2.500 ± 0.081	2.537 ± 0.099	0.045*	2.534 ± 0.104	2.533 ± 0.100	0.675	0.250	0.165	0.365	<.0001*
IDN	2.726 ± 0.068	2.732 ± 0.064	0.267	2.729 ± 0.072	2.725 ± 0.061	0.815	0.037*	0.780	0.108	<.0001*
OCL	1.005 ± 0.113	1.018 ± 0.121	0.292	1.013 ± 0.107	1.041 ± 0.100	0.046*	0.020*	0.437	0.357	<.0001*
ONB	1.298 ± 0.185	1.421 ± 0.156	<.0001*	1.356 ± 0.163	1.397 ± 0.140	0.081	0.944	0.000*	0.223	<.0001*
TWOB	1.223 ± 0.164	1.317 ± 0.176	0.002*	1.251 ± 0.114	1.302 ± 0.127	0.028*	0.934	0.000*	0.290	<.0001*

Notes on Table 4
1 Time is the number of visits since the initial Baseline visit and was coded as a categorical variable

https://prevagen.com/

CONCLUSION

apoaequorin demonstrated the ability to improve aspects of cognitive function in older participants with either normal cognitive aging or very mild impairment, as determined by AD8 screening.

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HMMMM….

This looks half-way decent!


The Medical Letter

LEGAL ACTIONS – In the 2012 FDA letter, the agency warned the manufacturer of apoaeq about making false therapeutic claims.[1] In November 2020, a nationwide class-action settlement required the company to refund consumers who had purchased the product and change misleading marketing claims. A lawsuit has been filed against Quincy Bioscience by the Federal Trade Commission and the New York State Attorney General that alleges the company made false claims that their product improves memory and brain functioning.

CONCLUSION – There is no acceptable evidence that apoaequorin is effective for memory improvement. Patients should be advised not to take it.

PMID: 35085208
Med Lett Drugs Ther 2021;63:175

CONCLUSION

- There is no acceptable evidence that apoaequorin is effective for memory improvement. Patients should be advised not to take it.

PMID: 35085208

Med Lett Drugs Ther 2021;63:175

DIFFERENCE BETWEEN FDA-APPROVED DRUGS AND DIETARY SUPPLEMENTS.

- In order for a drug to be approved by the FDA, it must be proven to be safe and effective.
  - data on the drug's effects have been reviewed by the Center for Drug Evaluation and Research, and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population.
- Unlike new drugs, dietary supplements are not reviewed and approved by the FDA based on their safety and effectiveness.
- When public health concerns arise about a dietary supplement after the product is on the market, the FDA evaluates the product's safety through research and adverse event monitoring.
- Promotional information about the supplement must include the phrase, "These statements have not been evaluated by the FDA and are not intended to diagnose, treat, cure or prevent any disease or health condition."

https://www.fda.gov/consumers/consumer-updates/it-really-fda-approved

What is apoaequorin?

apoaequorin was originally discovered in jellyfish. Apoaequorin is safe and uniquely supports brain function.*

® Selected as the **#1 Pharmacist Recommended Memory Support Brand in 2021** Pharmacy Times annual survey for third year in a row.

These statements have not been evaluated by the FDA and are not intended to diagnose, treat, cure or prevent any disease or health condition

https://prevagen.com/

https://healthreview.org/brain-supplements/neuronol/?gclid=EAIaIQobChMIwqW_tueg9wIV9vTjBx10tgPOEAAYASAAEgIfqfD_BwE

These statements have not been evaluated by the FDA and are not intended to diagnose, treat, cure or prevent any disease or health condition.

https://healthreview.org/brain-supplements/neuronol/?gclid=EAIaIQobChMIwqW_tueg9wIV9vTjBx10tgPOEAAYASAAEgIfqfD_BwE

ALZHEIMER'S ASSOCIATION STATEMENT

- One of the biggest problem areas for unsubstantiated claims are dietary supplements, foods and products that claim to be beneficial for Alzheimer's or other dementia symptoms.
- These products are not approved by the FDA, and little is known about their effectiveness, quality and safety.
- But that hasn't stopped some outlets from touting their benefits for cognitive health.
- In the past five years, the FDA has issued more than 40 warning letters to companies illegally marketing over 80 products claiming to prevent, treat or cure Alzheimer's disease.

Alz.org

DON'T FALL FOR FALSE HEALTH CLAIMS

YOU DON'T NEED TO BE A SCIENTIST TO THINK LIKE ONE — USE THESE TIPS TO NAVIGATE THE CONFUSING WORLD OF RESEARCH

- Be savvy
  - review research news with a critical eye.
- Supplement your awareness
  - Talk to your doctor.
  - Look for FDA-approved treatments.
- Be your own advocate
  - "The most important thing you can do is to demand evidence rigorously backed in science"
- Think like a scientist
  - Is there sufficient evidence?
  - Who conducted the research?
  - How was the research conducted?
  - Does it sound too good to be true?
  - Where was the research announced?

Alz.org

BOTTOM LINE…

- Not recommended.
- But use your judgment; it's up to you.
  - Can you afford it?
  - Is it OK with your primary MD?
  - No side effects?

Cognitive Impacts of COVID-19

KEVIN N. HASCUP, PHD
ASSISTANT PROFESSOR
SOUTHERN ILLINOIS UNIVERSITY SCHOOL OF MEDICINE
• NEUROSCIENCE INSTITUTE
• DALE AND DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH AND TREATMENT (CARE)
• DEPARTMENTS OF NEUROLOGY, PHARMACOLOGY, & MMICB

4TH MAY 2022

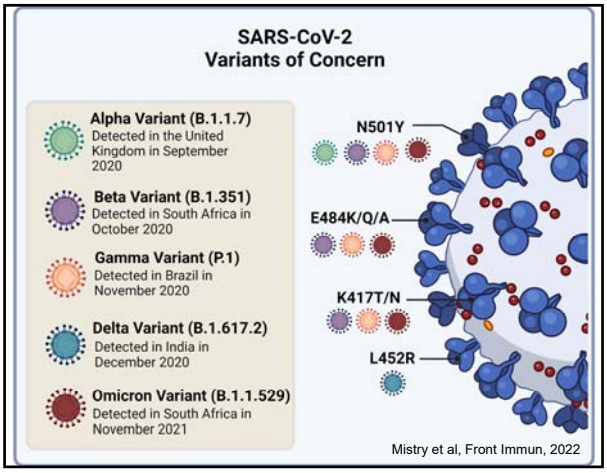
SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

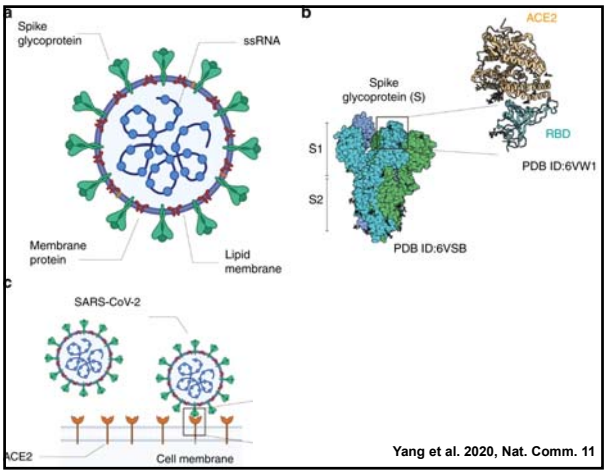
NEUROSCIENCE INSTITUTE

SIU SCHOOL of MEDICINE
FORWARD. FOR YOU.

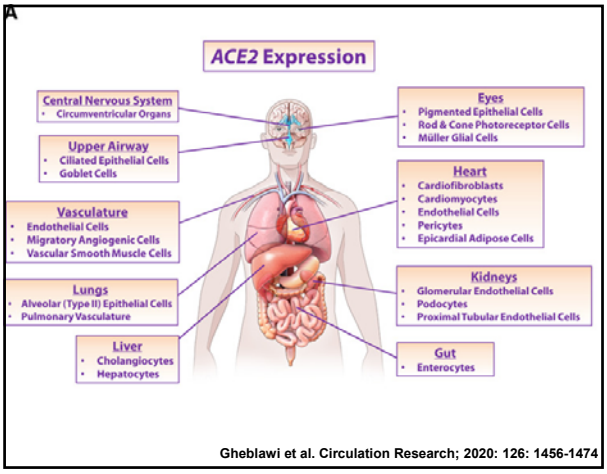
Learning Objectives

- Know the mechanisms associated with SARS-CoV-2 neuroinfection.
- Understand the resulting biological and anatomical CNS changes associated with neuroinfection.
- Recognize that mental impairments persist months after infection recovery and may accelerate cognitive decline.

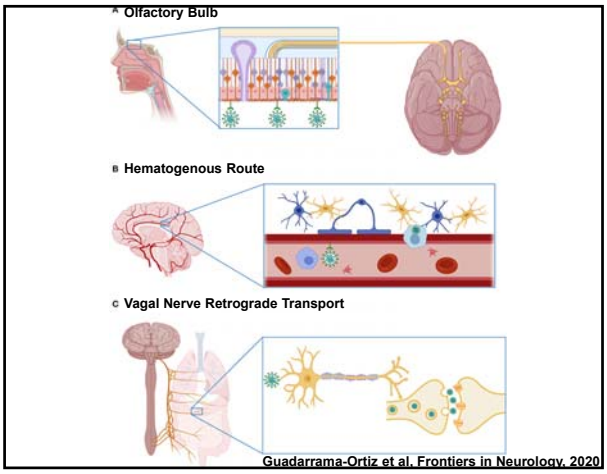




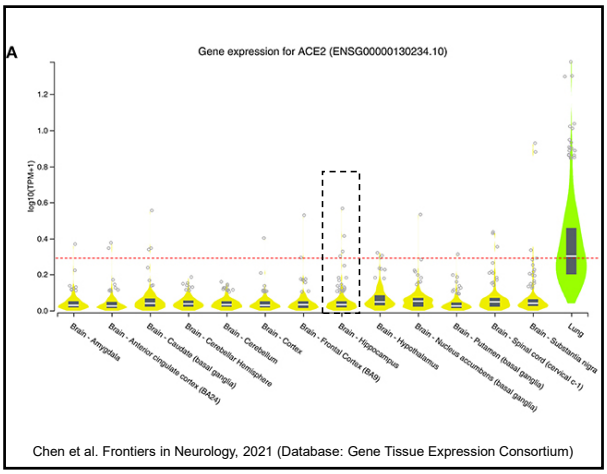
Yang et al. 2020, Nat. Comm. 11



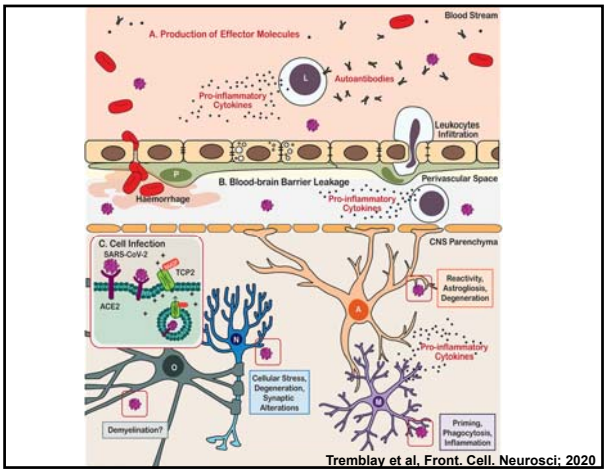
Gheblawi et al. Circulation Research; 2020: 126: 1456-1474



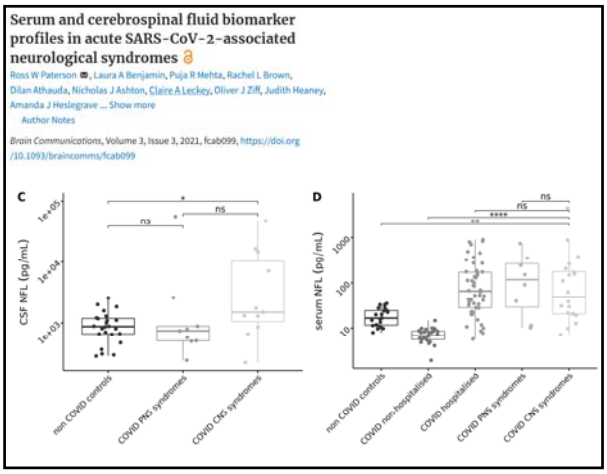
Guadarrama-Ortiz et al. Frontiers in Neurology, 2020

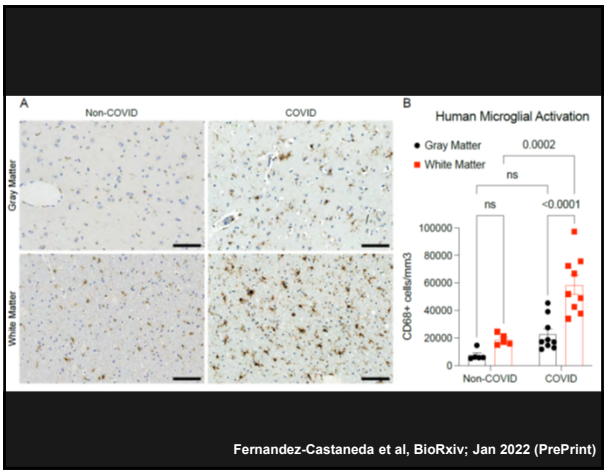


Chen et al. Frontiers in Neurology, 2021 (Database: Gene Tissue Expression Consortium)

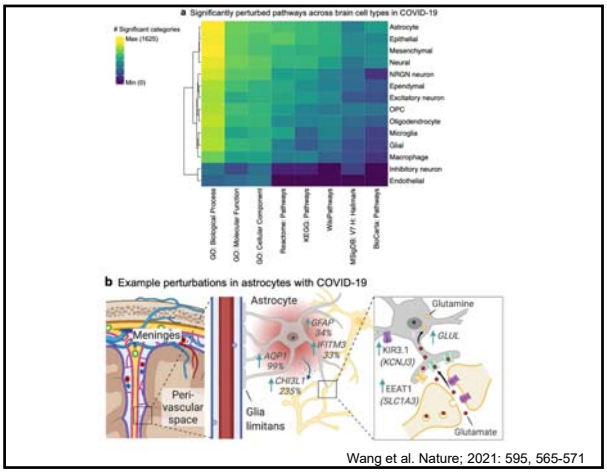


Tremblay et al. Front. Cell. Neurosci; 2020





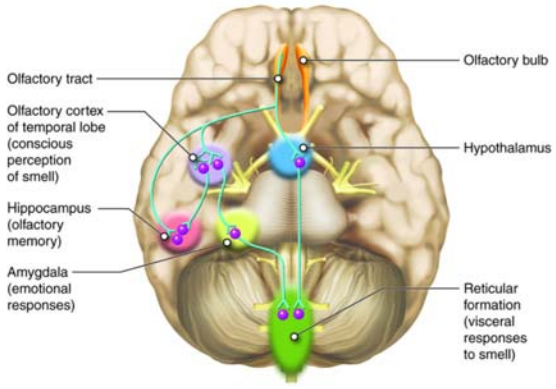
Fernandez-Castaneda et al, BioRxiv; Jan 2022 (PrePrint)



Wang et al. Nature; 2021: 595, 565-571

Neurological symptom	Affected region (reference)	Percentage (reference)
Acute cerebrovascular disease	Cerebral vessels[59,60]	2.8%[34]
Meningitis/encephalitis	CSF[33,84]	Case report[287]
Acute hemorrhagic necrotizing encephalopathy	Temporal lobe[288]	Case report[288,289]
Posterior reversible encephalopathy syndrome	Cortex[87,290,291]	Case report[87,290,291]
Demyelinating lesion	Spinal cord[292]	Case report[292]
Seizure	Left temporoparietal lobe[293,294,295]	0.5%[34]
Ischemic stroke	Cortex[34]	2.8%[34]
Dizziness	Whole brain[296]	9.4%[297] 16.8%[34]
Headache	Whole brain[34,298,299]	3.4%[300] 6.5%[297] 13.1%[34]
Ataxia	Whole brain[34]	0.5%[34]
Impaired consciousness	Whole brain[34]	7.5%[34]
Brain edema	Brainstem[301]	Case report[301]
Anosmia	Olfactory neurons[126]	5.1%[34]
Ageusia	Tongue nerves[106,107,302,303]	5.6%[34]
Dysopia	Optic nerves[34]	1.4%[34]
Guillain-Barré syndrome	Peripheral nerve demyelination[304,305,306,307,308,309,310]	Case report[310,311]
Miller Fisher syndrome	Whole brain[312,313]	Casa report[312,313]
Myalgia-muscle pain	Neuromuscular junction[214,215]	Case report[214,215]
Rhabdomyolysis	Muscle[216]	Case report[216]

Wan et al, Signal Transduction and Targeted Therapy; 2021: 6



https://courses.lumenlearning.com/austincc-ap1/chapter/special-senses-smell-olfaction/

Article | Published: 07 March 2022

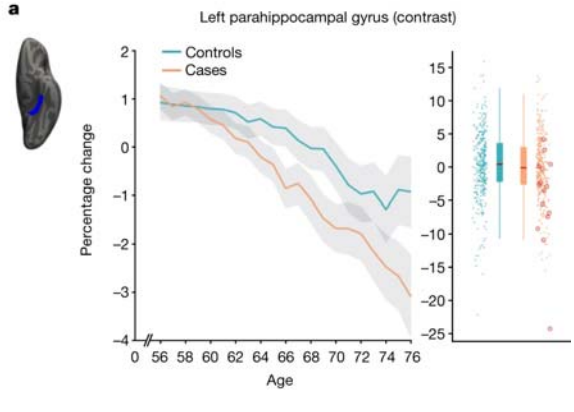
SARS-CoV-2 is associated with changes in brain structure in UK Biobank

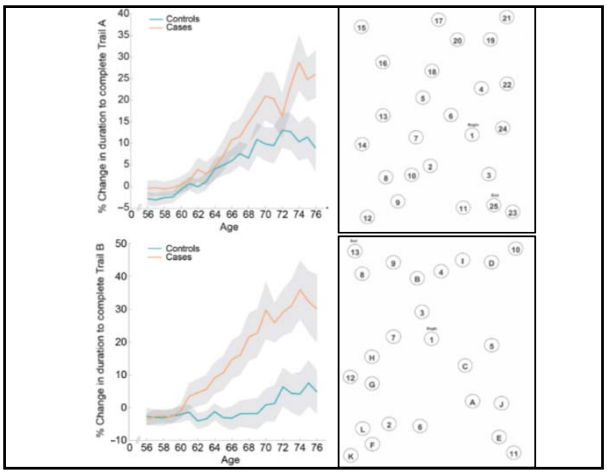
Gwenaëlle Douaud, Soojin Lee, Fidel Alfaro-Almagro, Christoph Arthofer, Chaoyue Wang, Paul McCarthy, Frederik Lange, Jesper L. R. Andersson, Ludovica Griffanti, Eugene Duff, Saad Jbabdi, Bernd Taschler, Peter Keating, Anderson M. Winkler, Rory Collins, Paul M. Matthews, Naomi Allen, Karla L. Miller, Thomas E. Nichols & Stephen M. Smith

Nature (2022) | Cite this article

	SARS-CoV-2	Control	P_{uncorr}
Number of participants	401	384	–
Age at scan 1 (mean ± s.d. (range))	58.9 ± 7.0 (46.9–80.2)	60.2 ± 7.4 (47.1–79.8)	0.15
Age at scan 2 (mean ± s.d. (range))	62.1 ± 6.7 (51.3–81.4)	63.3 ± 7.1 (51.3–81.3)	0.08
Sex (male/female)	172 (42.9%)/229 (57.1%)	164 (42.7%)/220 (57.3%)	0.96
Ethnicity (white/non-white*)	388 (96.8%)/13 (3.2%)	373 (97.1%)/11 (2.9%)	0.76
Years between scans 1 and 2 (mean ± s.d. (range))	3.2 ± 1.6 (1.0–7.0)	3.2 ± 1.6 (1.0–6.9)	0.98
Systolic blood pressure (mmHg)	130.3 ± 17.3	132.1 ± 17.6	0.16
Diastolic blood pressure (mmHg)	78.7 ± 10.6	79.0 ± 10.2	0.63
Diagnosed diabetes	18 (4.5%)	16 (4.2%)	0.82
Weight (kg)	76.4 ± 15.8	75.2 ± 14.4	0.65
Waist/hip ratio	0.87 ± 0.09	0.86 ± 0.09	0.37
BMI (kg m^{-2})	26.7 ± 4.4	26.6 ± 4.3	0.61
Alcohol-intake frequency (a.u.)	3.1 ± 1.3	3.0 ± 1.4	1.00
Tobacco smoking	0.61 ± 0.92	0.65 ± 0.89	0.87
Townsend deprivation index	−1.5 ± 2.9	−1.6 ± 2.9	0.65

Note: To date, this article has not completed peer review.





March 8, 2022

One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China

A Longitudinal Cohort Study

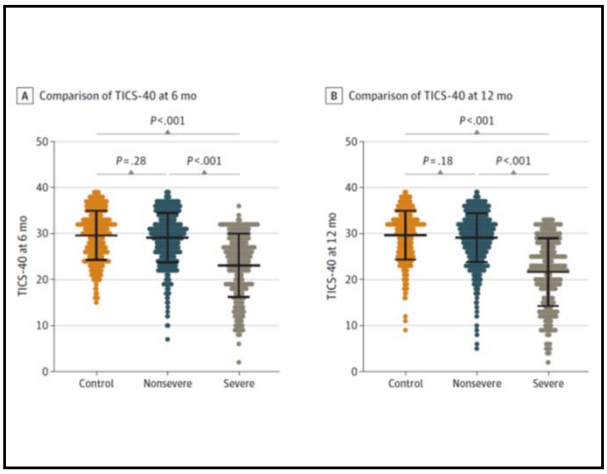
Yu-Hui Liu, MD, PhD[1]; Yang Chen, MD[1]; Qing-Hua Wang, MD, PhD[1]; et al

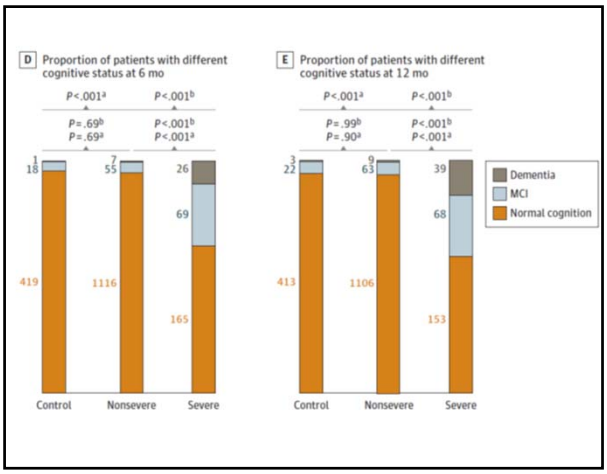
Author Affiliations | Article Information

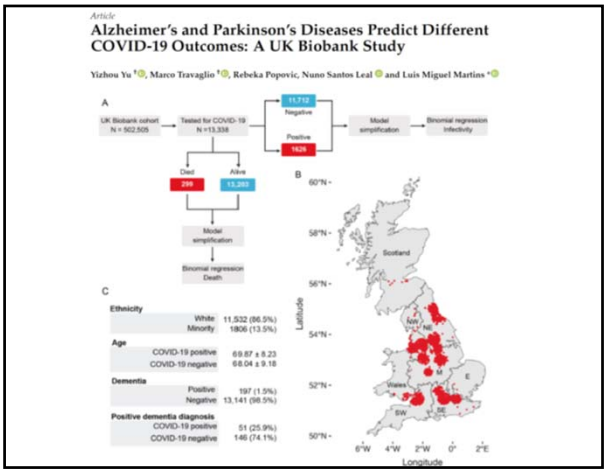
JAMA Neurol. Published online March 8, 2022. doi:10.1001/jamaneurol.2022.0461

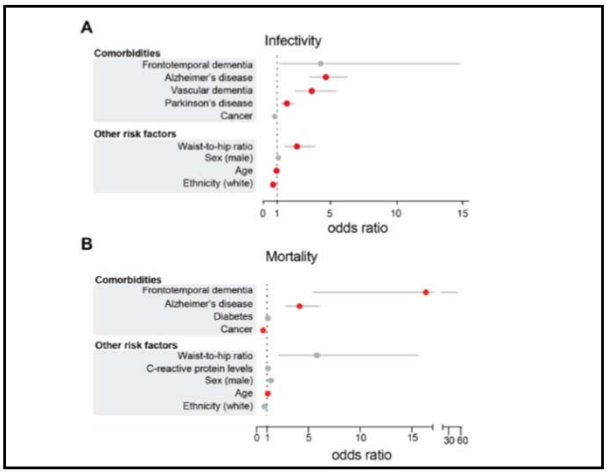
Table 1. Demographic and Baseline Information of Participants

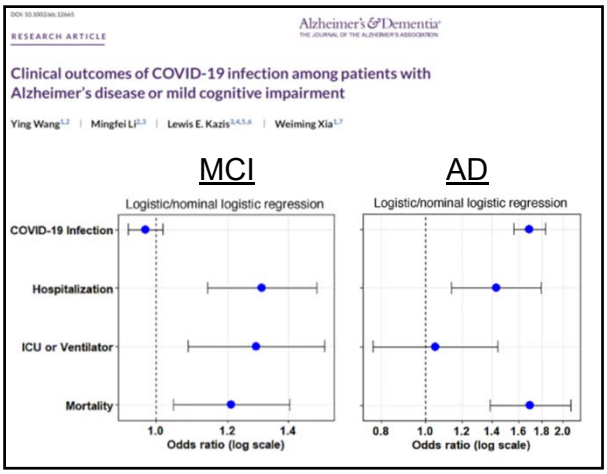
Variable	COVID-19 survivors			Uninfected control individuals (n = 438)	P value survivors vs control individuals	P value severe vs nonsevere cases
	Total group (n = 1438)	Severe cases (n = 260)	Nonsevere cases (n = 1178)			
Age, median (IQR), y	69 (66-74)	71 (67-79)	68 (66-73)	67 (66-74)	.30[a]	<.001[a]
Female, No. (%)	747 (51.95)	127 (48.85)	621 (52.72)	216 (49.32)	.35[b]	.27[b]
Male, No. (%)	691 (48.05)	133 (51.15)	557 (47.28)	222 (50.68)	.35[b]	.27[b]
Education, median (IQR), y	12 (9-12)	12 (6-12)	12 (9-12)	12 (9-12)	>.99[a]	.05[a]
BMI, median (IQR)	23.99 (22.54-25.38)	24.38 (22.90-25.64)	23.93 (22.44-25.33)	24.19 (22.51-25.69)	>.99[a]	.009[a]
Comorbidities, No. (%)						
Hypertension	561 (39.01)	133 (51.15)	426 (36.16)	151 (34.47)	.09[b]	<.001[b]
Diabetes	274 (19.05)	65 (25.00)	208 (17.66)	81 (18.49)	.84[b]	.01[b]
Hyperlipidemia	142 (9.87)	31 (11.92)	111 (9.42)	39 (8.90)	.58[b]	.25[b]
Stroke history	79 (5.49)	42 (16.15)	37 (3.14)	30 (6.85)	.29[b]	<.001[b]
Coronary heart disease	193 (13.42)	71 (27.31)	121 (10.27)	61 (13.93)	.81[b]	<.001[b]
COPD	142 (9.87)	43 (16.38)	99 (8.40)	41 (9.36)	.78[b]	<.001[b]
ICU admission, No. (%)	72 (5.01)	72 (27.69)	0	NA	NA	<.001[b]




D Proportion of patients with different cognitive status at 6 mo
E Proportion of patients with different cognitive status at 12 mo
P<.001a
P<.001b
P=.69b
P=.69a
P<.001b
P<.001a
P=.99b
P=.90a
Dementia
MCI
Normal cognition
Control
Nonsevere
Severe


Article
Alzheimer's and Parkinson's Diseases Predict Different COVID-19 Outcomes: A UK Biobank Study
Yizhou Yu, Marco Travaglio, Rebeka Popovic, Nuno Santos Leal and Luis Miguel Martins
Ethnicity
Age
Dementia
Positive dementia diagnosis
Latitude
Longitude
Scotland


A
Infectivity
Comorbidities
Frontotemporal dementia
Alzheimer's disease
Vascular dementia
Parkinson's disease
Cancer
Other risk factors
Waist-to-hip ratio
Sex (male)
Age
Ethnicity (white)
odds ratio
B
Mortality
Diabetes
C-reactive protein levels



SARS-CoV-2 infection causes

- macroscopic, microscopic, and transcriptomic changes to CNS tissue.
- cognitive impairments that scale to disease severity
- worse outcome in MCI and AD patients.

Emotional effects of the COVID-19 Pandemic on Persons with Memory Loss and their Caregivers

Andrea Perkins, APRN, FNP-BC
siumed.edu/alz

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Learning Objectives

- Identify COVID-19 factors which have contributed to emotional effects on persons with memory loss and their caregivers.
- State COVID-19 related emotional effects experienced by persons with memory loss and their caregivers.
- Identify interventions that are supported by the literature.

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It started when...

- She got sick with COVID.
- We couldn't go anywhere.
- We couldn't see anyone.
- His brother died of COVID.
- We couldn't have a funeral.

"I was the first one. They thought I had the virus and put me in a room by myself. I couldn't visit with anyone. It was the worst two weeks of my life. Then they found out the test was wrong. I was negative."…patient in nursing home.

"I've lost 19 of my friends over the past year to COVID."…patient in nursing home.

"We've really lost a year from our lives, and we don't know how many more years we have!"…wife/caregiver of patient living in a private residence.

"I am taking my mom for a drive after this appointment. When she goes back, she has to stay in her room for two weeks."…daughter/caregiver of patient living at Assisted Living facility.

"I can't hear you with my mask on!"…patient living in private residence.

"I am afraid. They are so short- staffed and my husband can't get his medicine on time. I don't know what to do. Please help me."…wife/caregiver living in an Assisted Living facility.

The mental health of caregivers and their patients with dementia during the COVID-19 pandemic: A systematic review

Carbone et al., 2021

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- Studies completed in ten countries during 2020 COVID-19 lockdowns.
- 17 studies included in the systematic review
  - Social isolation triggered behavioral symptoms in persons with memory loss and higher levels of anxiety and depression in caregivers.
  - Disruptions in healthcare delivery and changes in social support availability was associated with higher levels of anxiety in persons with dementia and worsening of caregivers' mental health.

Carbone et al., 2021

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

The psychological impact of COVID-19 pandemic and lockdown on caregivers of people with dementia

Altieri & Santangelo, 2021

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- Online survey of 84 caregivers of persons with dementia during the COVID-19 lockdown in Italy from April 21 – May 3, 2020.
- 79.8% of the persons with dementia were not aware of the COVID-19 situation.
- A rise in depressive symptoms in caregivers was associated with restriction and isolation of the lock-down.

Altieri & Santangelo, 2021

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- Caregivers who had *higher* levels of resilience experienced *higher* levels of anxiety.
- Caregivers with low levels of resilience paired with greater functional dependence by the person with dementia, led to higher levels of overall caregiver burden.

Altieri & Santangelo, 2021

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Impact of COVID-19 restrictions on behavioural and psychological symptoms in home-dwelling people with dementia: A prospective cohort study

Gedde et al., 2022

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- Participants included 104 dyads, living at home in Norway with assessment completed immediately before and 6-9 weeks after initiation of COVID-19 restrictions.
- Neuropsychiatric Inventory (NPI-12) scores got worse for 55% of the participants.
- There were higher scores to support psychosis subsyndrome and depression.

Gedde et al., 2022

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- Authors associated the increase in psychosis subsyndrome with insight into the COVID-19 pandemic and less contact with caregiver.
- Overall worsening of the NPI-12 was associated with reduced or delayed visits to the health care provider and due to greater impairment of cognition (as demonstrated on Mini Mental State Exam scores).

Gedde et al., 2022

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Impact of COVID-19 on the health and well-being of informal caregivers of people with dementia: A rapid systematic review

Hughes et al., 2021

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- 10 studies included in the systematic review all of which used telephone or online data collection methods. Participant numbers ranged from 31 to 4,913.
- Caregivers experienced an increase in anxiety that was associated to COVID-19 changes in life routines vs. level of cognitive impairment of their care receiver.
- Caregiver burden, however, was associated with advanced stages of dementia.

Hughes et al., 2021

SIU MEDICINE
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Results

- 4,913 caregivers reported an increase in anxiety, depression, irritability and distress related to the quarantines associated with the pandemic.
- Loss of control, the "new normal", and uncertainty were expressed by additional caregivers.

Hughes et al., 2021

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Minimal impact of COVID-19 pandemic on the mental health and wellbeing of people living with dementia: Analysis of matched longitudinal data from the IDEAL study

Sabatini et al., 2022

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- 2 groups (Pandemic group, n=115, tested before and during the pandemic AND Pre-Pandemic group, n=230, assessed before the pandemic) were assessed for mood, sense of self, wellbeing, optimism, quality of life and life satisfaction.
- No significant difference between the groups in terms of sense of self, quality of life, and wellbeing.

Sabatini et al., 2022

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- Depression/anxiety reduced in the *pandemic* group comparing before-pandemic numbers to during-pandemic numbers.
- Pandemic group had a decrease of satisfaction of life from 91.3% to 85.8%. Pre-pandemic group expressed a slight improvement.

Sabatini et al., 2022

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Neuropsychiatric symptoms in elderly with dementia during COVID-19 pandemic: definition, treatment, and future directions

Simonetti et al., 2020

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- 20 studies completed between March – June 2020.
- Isolation/restricted family contact led to depression, hopelessness, and increased suicidal ideations in persons with dementia.
- Social isolation in nursing homes led to increase in apathy which increased over time.

Simonetti et al., 2020

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- Restricted social interaction increased anxiety.
- Increase in fear and agitation were associated with confinement.
- No increase in hallucination/delusions but noted increase in paranoia related to switch from in-person contact to virtual contact.

Simonetti et al., 2020

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Recommendations

- Simplify daily routines; maintain consistency.
- Utilize technology for increased social interaction.
- Utilize Telehealth services, phone or audio/visual.
- Be cautious related to prescribing increased antipsychotics if unable to see the patient routinely.

Simonetti et al., 2020

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

A systematic review of home-setting psychoeducation interventions for behavioral changes in dementia: Some lessons for the COVID-19 pandemic and post-pandemic assistance

Alves et al., 2020

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- 43 studies included in this systematic review.
- Rural caregivers are more likely to experience burden due to lack of care accessibility. Thus, home-based interventions determining and addressing their needs is recommended.
- Home-based interventions providing cognitive and physical exercise are recommended.

Alves et al., 2020

SIU MEDICINE
DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

Results

- Home-based programs which assist caregivers in adapting to their roles and provide individual and family counseling, encourage support group participation, and offer ad hoc phone counseling supports caregivers and reduces long-term placement. (NYU Caregiver Intervention)
- Telephone-based support with trained staff can reduce caregiver burden and is associated with fewer hospital stays for persons with dementia. (FITT-C)

Alves et al., 2020

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"You don't understand. I have friends that are dying. The other ones have moved in with their kids. I have no one and no where to go."… patient living at Assisted Living facility.

References

Altieri, M., & Santangelo, G. (2021). The psychological impact of COVID-19 pandemic and lockdown on caregivers of people with dementia. *The American Journal of Geriatric Psychiatry*, *29*(1), 27–34. https://doi.org/10.1016/j.jagp.2020.10.009

Alves, G. S., Casali, M. E., Veras, A. B., Carrilho, C. G., Bruno Costa, E., Rodrigues, V. M., & Dourado, M. (2020). A systematic review of home-setting psychoeducation interventions for behavioral changes in dementia: Some lessons for the COVID-19 pandemic and post-pandemic assistance. *Frontiers in Psychiatry*, *11*, 577871. https://doi.org/10.3389/fpsyt.2020.577871

Carbone, E. A., de Filippis, R., Roberti, R., Rania, M., Destefano, L., Russo, E., De Sarro, G., Segura-Garcia, C., & De Fazio, P. (2021). The mental health of caregivers and their patients with dementia during the COVID-19 pandemic: A systematic review. *Frontiers in Psychology*, *12*, 782833. https://doi.org/10.3389/fpsyg.2021.782833

Gedde, M. H., Husebo, B. S., Vahia, I. V., Mannseth, J., Vislapuu, M., Naik, M., & Berge, L. I. (2022). Impact of COVID-19 restrictions on behavioural and psychological symptoms in home-dwelling people with dementia: a prospective cohort study (PAN.DEM). *BMJ open*, *12*(1), e050628. https://doi.org/10.1136/bmjopen-2021-050628

References

Hughes, M. C., Liu, Y., & Baumbach, A. (2021). Impact of COVID-19 on the health and well-being of informal caregivers of people with dementia: A rapid systematic review. *Gerontology & geriatric medicine*, *7*, 23337214211020164. https://doi.org/10.1177/23337214211020164

Sabatini, S., Bennett, H. Q., Martyr, A., Collins, R., Gamble, L. D., Matthews, F. E., Pentecost, C., Dawson, E., Hunt, A., Parker, S., Allan, L., Burns, A., Litherland, R., Quinn, C., & Clare, L. (2022). Minimal impact of COVID-19 pandemic on the mental health and wellbeing of people living with dementia: Analysis of matched longitudinal data from the IDEAL study. *Frontiers in Psychiatry*, *13*, 849808. https://doi.org/10.3389/fpsyt.2022.849808

Simonetti, A., Pais, C., Jones, M., Cipriani, M. C., Janiri, D., Monti, L., Landi, F., Bernabei, R., Liperoti, R., & Sani, G. (2020). Neuropsychiatric symptoms in elderly with dementia during COVID-19 pandemic: Definition, treatment, and future directions. *Frontiers in Psychiatry*, *11*, 579842. https://doi.org/10.3389/fpsyt.2020.579842

Current Alzheimer's Disease Clinical Research at SIU Medicine

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SIU MEDICINE
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WHAT IS A CLINICAL TRIAL?

- A clinical trial is a research study that tests a medicine or therapy in people.
- Clinical trials can also be called clinical studies or clinical research.
- Clinical research helps us answer questions about the medicine being studied, like does the medicine work and is it safe.
- The medicines inside your medicine cabinet have one big thing in common; before reaching you, they went through years of research studies to ensure that they were safe for you to take.

THINGS YOU NEED TO KNOW ABOUT CLINICAL TRIALS

People participate for different reasons. Some common reasons for study volunteers to join a clinical trial include:

- to advance science and treatments
- to help others with the same condition or disease as them
- to potentially obtain better treatment

THINGS YOU NEED TO KNOW ABOUT CLINICAL TRIALS

- Everyone conducting a clinical trial has strict regulatory and ethical duties.
- Institutional Review Board (IRB) or Central IRB, operate independently from the day-to-day conduct of research.
- The purpose of IRB is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in research.

THINGS YOU NEED TO KNOW ABOUT CLINICAL TRIALS

- Clinical trials are experiments, so the exact risks and benefits can be difficult to predict.
- Researchers only move forward with clinical trials when they are optimistic about the potential benefits and believe any risks for participants are acceptable.
- The risks and benefits are different for everyone.

THINGS YOU NEED TO KNOW ABOUT CLINICAL TRIALS

- For each trial, this set of criteria is needed to prove whether a medicine works or not in a specific patient population.
- Trial criteria are based on things like age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.

THINGS YOU NEED TO KNOW ABOUT CLINICAL TRIALS

- For most clinical trials, the study medicine is provided and visits are conducted at no cost to the participant.
- Some clinical trials pay or reimburse participants.
- Payment for participation is not meant to entice subjects to participate.

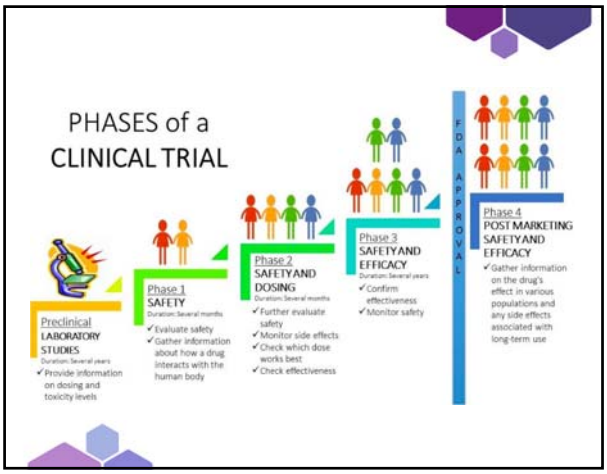
THE MOST IMPORTANT THING YOU NEED TO KNOW ABOUT CLINICAL TRIALS

- Participants can withdraw from a clinical trial at any time, for any reason.
- No matter the stage of the trial, participants have the right to change their mind.
- If a study volunteer decides to leave the study, the Principal Investigator will remove them from the trial in a safe manner.

CURRENTLY ENROLLING – LIFT-AD

- Athira Pharma, Inc., Bothell, WA
- ATH-1017-AD-0201

- A Randomized, Placebo-Controlled, Double-Blind Study of ATH-1017 Treatment in Subjects with Mild to Moderate Alzheimer's Disease
- Phase 2
- 55 Centers in USA (might open in Australia)
- 300 participants (we currently have four enrolled) – currently at 75% of target



CURRENTLY ENROLLING –
LIFT AD

The main purpose of this study is to investigate the effectiveness of ATH-1017 at different doses compared to a placebo, for the treatment of Alzheimer's disease (AD) and to determine the safety and tolerability (whether side effects of a medicine can be handled by study subjects) of ATH-1017 compared to a placebo, when administered once a day for up to 26 weeks.

CURRENTLY ENROLLING –
LIFT AD

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study comparing ATH-1017 40 mg/day and ATH-1017 70 mg/day with placebo in subjects with a clinical diagnosis of mild to moderate Alzheimer's disease (AD), diagnosed on a 'probable' level according to McKhann, 2011.

CURRENTLY ENROLLING –

LIFT AD

- Subjects and their trial partners will be required to sign an informed consent document and will be evaluated against the inclusion/exclusion criteria during a screening period.
- Those who meet all inclusion/exclusion criteria will be randomized in a ratio of 1:1:1 to three parallel arms, either to active treatment (ATH-1017 40 mg/day or ATH-1017 70 mg/day) or placebo.

CURRENTLY ENROLLING –

LIFT AD

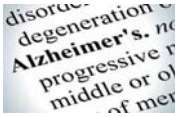
- During the study, patients will undergo cognitive assessments, collection of laboratory samples, ECG monitoring, and brain MRIs.

- The Screening Period (to confirm that you are suitable for the study) can last up to 28 days.
- The Treatment Period (where you will receive your assigned study medication) will last up to 26 weeks (approximately 6 months).
- The Post-treatment Follow-up Period (to check your overall health) may last up to 4 weeks or you may choose to go into the OPEN-LABEL EXTENSION period (more on that later).

CURRENTLY ENROLLING –

LIFT AD

- Study drugs will be administered by subcutaneous injection once-daily preferably during the daytime.
- The study partner will need to document all injections in a dosing diary.
- Subjects may experience risks and/or possible side effects while in the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all the side effects that may happen.



CURRENTLY ENROLLING –

LIFT AD

- There is no cost to the subject to participate – all study related visits, tests, etc. are covered by Athira.
- Subjects do receive $78 for each visit that is completed. This is distributed via a check mailed to their home. Bad news, this is income according to the IRS.
- Sara Boarman, BS, in the Leader Coordinator for this study – you can reach her at sboarman93@siumed.edu or 217.545.6829.

CURRENTLY ENROLLING –

LIFT AD

- Open-Label Extension (OLE) – only subjects who complete the 26 week blinded portion of study may *roll-over* in the OLE.
- The OLE is not blinded – Open-Label means everyone gets the real drug – no more possibility of placebo.
- This is also 26 weeks – it is run very similar to the blinded period.
- You do not have to enroll in the OLE – it is optional.

CURRENTLY ENROLLING –

NEW IDEAS

- American College of Radiology
- New IDEAS: Imaging Dementia—Evidence for Amyloid Scanning Study
- A Study to Improve Precision in Amyloid PET Coverage and Patient Care
- Mild Cognitive Impairment or Dementia
- 7,000 persons may be enrolled – United States
- Will having the results of an amyloid PET scan change your doctors treatment plan?
- Radioactive tracer injected via IV – wait 45 minutes, then PET scan of brain completed.
- **Currently only enrolling minorities of color** – this is expected to change in September 2022.
- Must be a Medicare recipient – Medicare is paying for scan.
- $75 check comes to subject's home directly from ACR.
- NOT A TREATMENT STUDY.
- Contact Stephanie Kohlrus, BA, CCRP, at 217.545.3013 or skohlrus@siumed.edu for more information.

NEW iDEAS
Brain Imaging Study for Alzheimer's

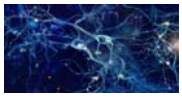
CURRENTLY ENROLLING –
CAREGIVER STUDY

- Caregiver Characteristics that may be associated with the optimal care of patients with Alzheimer's disease.
- Investigating various characteristics and features that may predict changes in caregiving over the course of three years. Couples will have a one-time visit at the clinic. During the one-time visit, the couple will be administered questionnaires, assessments, and physical measurements. After this visit, the caregiver will have a phone-call interview every two months, spanning three years. The caregiver will also complete two mail-in questionnaires every six months and a telephone depression screening.
- We hope to enroll 217 couples.
- Tom Ala, MD, is principal investigator.
- Each enrolled couple that completes the one-time visit and mail-in questionnaires will be paid $150. An additional payment of $100 will be given each succeeding 12 months for the phone-call interviews and for completing and returning the two questionnaires. A total payment of $450 will be paid to couples who complete the full three years. Payment will be given as a check mailed to your home address.
- Contact Stephanie Kohlrus, BA, CCRP, at 217.545.3013 or skohlrus@siumed.edu for more information.

ONGOING – NOT ENROLLING
TRAILBLAZER-2

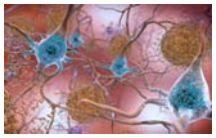
Lilly I5T-MC-AACI

- Assessment of safety, tolerability, and efficacy of donanemab in early symptomatic Alzheimer's disease.
- Phase 3
- Infusion every four weeks at SCI
- 1800 subjects world-wide
- Six subjects enrolled locally
- 78 weeks blinded
- 78 week OLE – all subjects are in OLE



ONGOING – NOT ENROLLING
TRAILBLAZER-2

During the study, patients will undergo cognitive assessments, collection of laboratory samples, ECG monitoring, brain magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, and you will receive either the study drug or placebo by intravenous (IV) infusion once every 4 weeks. An IV infusion is when the drug or placebo is given through a needle into your vein.



ONGOING – NOT ENROLLING

TRAILBLAZER-2

- 24 Jun 2021 - Lilly's donanemab receives U.S. FDA's Breakthrough Therapy designation for treatment of Alzheimer's disease.
- The Breakthrough Therapy designation aims to expedite the development and review of drugs that are intended to treat a serious condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over already available therapies that have received full FDA approval.

ONGOING – NOT ENROLLING

POST GRAD

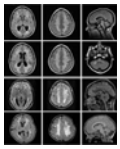
Hoffman-LaRoche WN42171

- An open-label, multicenter, rollover study to evaluate the safety, tolerability and efficacy of long-term gantenerumab administration in participants with Alzheimer's disease.
- Phase 3
- Injection every two weeks – in clinic.
- 2032 people enrolled world-wide.
- Four subjects enrolled locally (one still in GRADUATE).
- 18 month study

ONGOING – NOT ENROLLING

POST GRAD

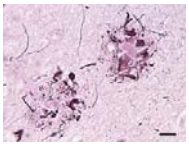
- Includes biosample repository plus tau and amyloid PET scan substudies.
- During the duration of the study, participants will undergo cognitive assessments, collection of laboratory samples, optional cerebral spinal fluid sampling, ECG monitoring, amyloid and tau PET assessments, and brain MRIs.



ONGOING – NOT ENROLLING

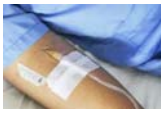
POST GRAD

- In **October 2021**, the FDA designated subcutaneous gantenerumab a Breakthrough Therapy, offering an accelerated review and approval process.
- The decision is based on promising results from the ongoing open-label extension trials, showing a significant reduction in brain amyloid plaque in Alzheimer's patients.



ONGOING – NOT ENROLLING

LAURIET

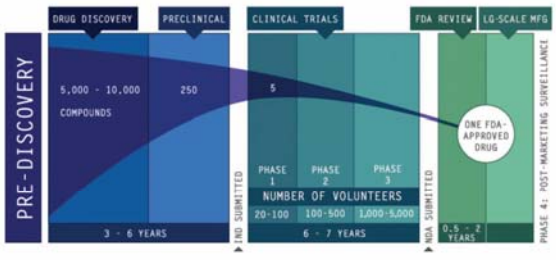


Genentech GN40040

- A Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy, and safety study of MTAU9937A in patients with moderate Alzheimer's disease.
- 260 subjects – 50 study centers
- One subject enrolled locally – currently in the OLE portion of the study
- 3.5 year study
- Infusion administered every four weeks – at SMH (aka MMC)
- If it works, MTAU9937A may slow down how fast the disease progresses.

Pathway to Your Medicine Cabinet

Drug Discovery and Development: A LONG, RISKY ROAD



PhRMA 2012 Annual Report
26

alzheimer's association

OUR CLINICAL RESEARCH TEAM

Tom Ala, MD – Principal Investigator
Jennifer Arnold, MD, PhD – Co-Investigator
Cindy Womack, DNP – Sub-Investigator
Charlene Young, FNP-BC – Sub-Investigator
Barbara Lokaitis, BA, CCRP – Senior Clinical Research Coordinator
Stephanie Kohlrus, BA, CCRP – Clinical Research Coordinator
Ann Jirmasek, MS, LPC – Rater
Amy Richey, LPN - Rater

OUR CLINICAL RESEARCH TEAM

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Rylee Manka, BA – Clinical Research Specialist
April Murrey – Data Manager
Stephanie Rasmussen, BSN, RN – Research Nurse
Karin Newhall, BSN, RN – Research Nurse
Missy Cartwright, BSN, RN – Research Nurse
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Normal Cognitive Aging in the SIU Longitudinal Cognitive Aging Study

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04.May.2022

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No Financial Disclosures

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- Steve Scaife
- Tom Ala, MD
- Angela Ardoin, MA
- Amber Fifer, PharmD
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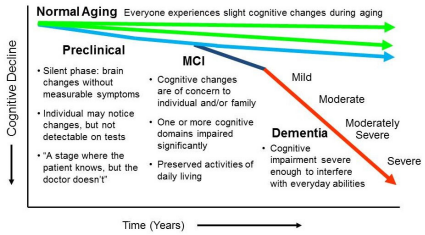
- Margi Bhatt

- Countless other students and research staff at the SIU Alzheimer's Center over the years.
- And anyone else who I forgot to include on this list!

LEARNING OBJECTIVES

- Provide information about the neurobiological and neurocognitive effects of normal cognitive aging.
- Provide a description of the demographic characteristics and study methods of the SIU Longitudinal Cognitive Aging Study.
- Provide information about the importance of neuropsychological testing for the diagnosis of neurocognitive disorders versus normal cognitive aging.

A Continuum of Normal Aging to Dementia



http://www.mind.uci.edu/alzheimers-disease/what-is-alzheimers/mild-cognitive-impairment

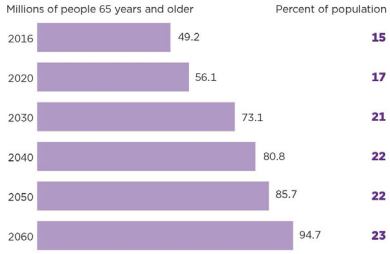
DEMOGRAPHICS OF AGING IN THE UNITED STATES

- In 2016, there were approximately 49.2 million people age 65 or greater.
- By 2060, that number is expected to double to 94.7 million.
- This increase, largely reflects the aging baby boomer population along with improvements in health care.
  - Those individuals born between 1946 and 1964.

DEMOGRAPHICS OF AGING IN THE UNITED STATES

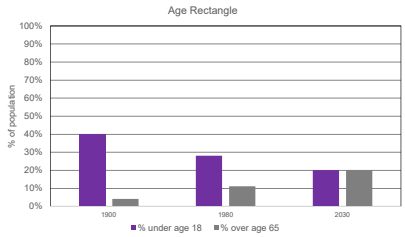
Projections of the Older Adult Population: 2020 to 2060

By 2060, nearly one in four Americans is projected to be an older adult.



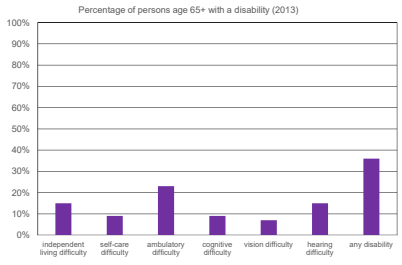
Source: U.S. Census Bureau, 2017 National Population Projections.

DEMOGRAPHICS OF AGING IN THE UNITED STATES



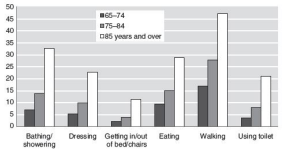
By 2030, there will be an equal percentage of the population under the age of 18 and over the age of 65.

DISABILITY IN OLDER ADULTS



Source: U.S. Census Bureau, American Community Survey. (2014). *Older Americans with a disability: 2008–2012.* U.S. Department of Commerce.

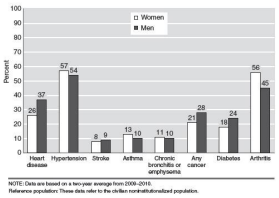
Percentage of persons with limitations in ADL by age group: 2009.



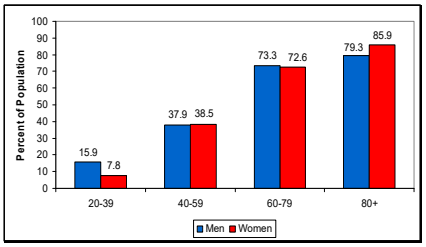
Source: Administration on Aging (AoA). (2011). *A profile of older Americans: 2011*. Retrieved from www.aoa.gov/aoaroot/aging_statistics/Profile/index.aspx

PERCENTAGE OF PEOPLE AGE 65 AND OVER WHO REPORTED HAVING SELECTED CHRONIC HEALTH CONDITIONS, BY GENDER, 2009–2010.

Many of these are risk factors for dementia and are modifiable!



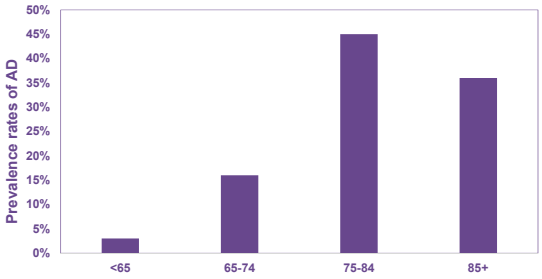
Source: Data from U.S. Census Bureau. Compiled by the Federal Interagency Forum on Aging-Related Statistics—Older Americans 2012: Key Indicators of Well-Being. Retrieved from www.agingstats.gov



Prevalence of CVD in adults age 20 and older by age and sex (NHANES: 2005-2006). Source: NCHS and NHLBI.

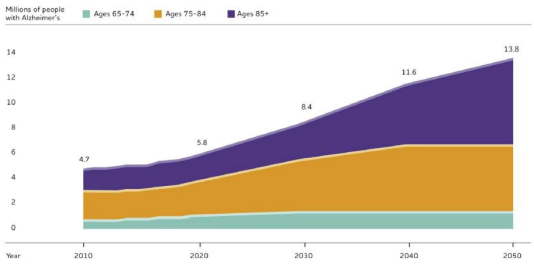
These data include coronary heart disease, heart failure, stroke, and hypertension.

INCREASING AGE IS ALSO THE #1 RISK FACTOR FOR LATE-ONSET ALZHEIMER'S DISEASE



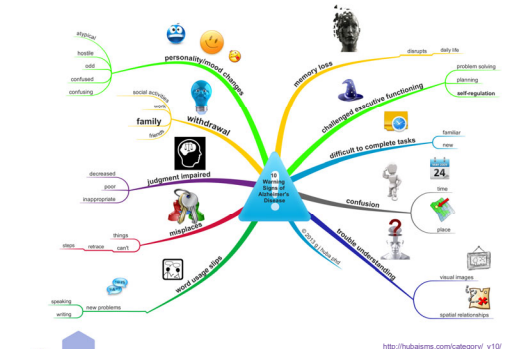
adapted Alzheimer's Association Facts and Figures 2019

THE PREVALENCE RATES OF ALZHEIMER'S DISEASE TRACK WITH THE INCREASING AGE OF THE UNITED STATES



- Declines over time in memory and other cognitive abilities, which are greater than expected for one's age are one of the first obvious symptoms of Alzheimer's disease.
- It is important to understand what normal cognitive aging looks like to be able to better understand what abnormal cognitive aging looks like.

WARNING SIGNS FOR ALZHEIMER'S DISEASE



SO "NORMAL" AGING IS ASSOCIATED WITH GREATER DISABILITY, MORE MEDICAL PROBLEMS, AND INCREASED RISK FOR ALZHEIMER'S DISEASE

- What does normal cognitive aging look like?
- What happens to brain structure and function in normal aging?

MANY DEFINITIONS OF WHAT IS NORMAL

- Typical
- Standard
- Average
- Not deviating from a norm
- Natural
- In accordance with scientific laws
- Lacking abnormalities
- Not abnormal
- Occurring naturally, not because of disease
- Free from mental disorder
- Balanced, well-integrated functioning

WHAT DOES NORMAL COGNITIVE AGING LOOK LIKE?

Vulnerable Processes	(Relatively) Preserved Processes
• Fluid IQ	• Crystallized IQ
• Reaction time	• Word reading
• Psychomotor speed	• Simple attention span
• Working memory	• Vocabulary
• Executive function	• Priming
• Episodic learning/memory	• Semantic memory
• Complex visual processing	• Procedural memory
	• Long-term autobiographical memory.

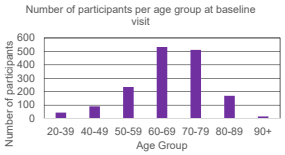
THE SIU LONGITUDINAL COGNITIVE AGING STUDY (LCAS)

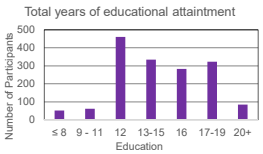
- LCAS is a community-based, longitudinal cohort study of the incidence of neurocognitive disorders such as AD in predominantly older adults who reside in Springfield and the surrounding communities.
- The study was started by Dr. Ronald Zec, PhD in 1984 with a focus on improving the sensitivity of neuropsychological testing to the diagnosis of mild cognitive impairment and dementia.
- The study was closed in 2016 and reopened in 2018.
- Over 1,600 (mostly older) adults (age range: 18-90+). Participants complete:
  - Serial cognitive testing (2.5 hours), every effort is made to see participants on a yearly basis.
  - 95% of participants in the cohort are white/Not-Hispanic and over 70% are female.
- Currently following over 150 participants, some of whom have been in the study for over 30 years!
- Over 100 sisters from Saint Francis, Sacred Heart, and Ursuline convents in the Springfield area have participated in the study.
- Participants are recruited from the community via newspaper advertisement, word-of-mouth, and community presentations.
- Sample is enriched for persons with a family history of AD (children, siblings, other relatives).
- 960 participants have passed away.

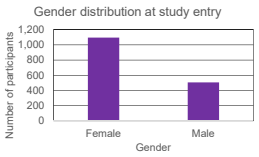
SIU LCAS INCLUSION AND EXCLUSION CRITERIA

- Individuals must be free of neurological, uncontrolled medical or psychiatric disease at their first visit.
- Preferably, 65+ years of age.
- Approximately 15% of participants met the diagnostic criteria for MCI or AD at baseline or developed these conditions on subsequent visits.
- Particularly interested in individuals with a family history of AD, minority groups, and individuals who reside in rural communities.

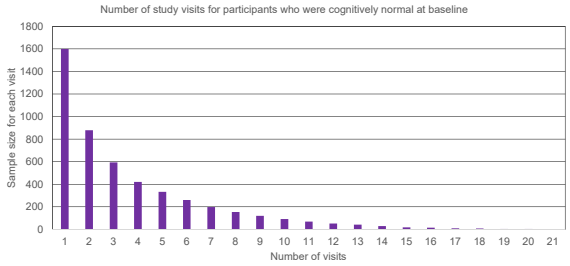
DEMOGRAPHIC DISTRIBUTION OF PARTICIPANTS AT STUDY ENTRY



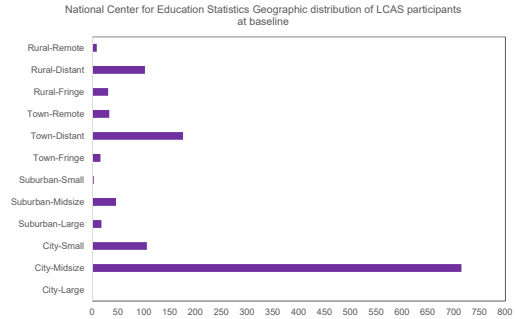




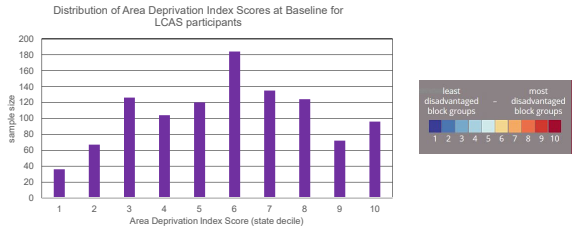
NUMBER OF PARTICIPANTS WITH ONE OR MORE STUDY VISITS



WHERE ARE LCAS PARTICIPANTS FROM?



WHAT KIND OF COMMUNITIES DO LCAS PARTICIPANTS LIVE IN?



- ADI is based on a measure created by the Health Resources and Service Administration over three decades ago using the American Community Survey.
- Updated every five years with last update being in 2019.
- Ranking of neighborhoods by socioeconomic disadvantage at the state or national level.
- Includes factors for the theoretical domains of income, education, employment, and housing quality.

CURRENT NEUROPSYCHOLOGICAL TEST BATTERY ASSESSES:

- Orientation and Mental Status
- Learning and Memory
- Language
- Visuospatial skills
- Processing Speed and Executive Function

CURRENT QUESTIONNAIRES

- Assess personality, subjective cognitive activities and complaints, mood, and anxiety.
- Assess lifestyle factors:
  - Independent living skills
  - Social activity
  - Diet
  - Physical Activity
- Detailed medical history inventory:
  - Information regarding personal medical and psychosocial histories,
  - family medical and psychosocial histories
  - Current medications.

OPTIONAL BRAIN DONATION PROGRAM

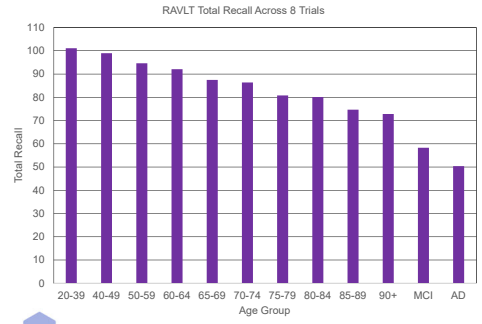
- 26 participants have died, donated their brain, and had an autopsy.
  - 17 were diagnosed with AD.
- 38 controls signed the intent to donate form and passed away without their brains being collected for unknown reasons.
- Of the participants we are currently following, around 60 have completed the intent to donate forms.
  - 2 participants who completed the intent-to-donate form after the study re-opened in 2018 passed away without their brains being collected.

So what does normal cognitive aging look like in this cohort?

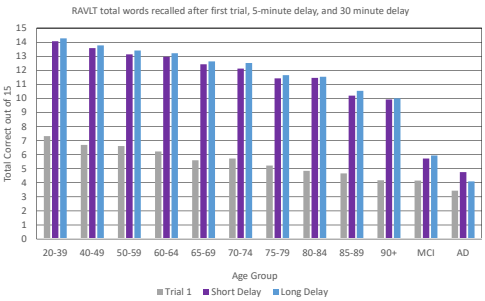
EPISODIC LEARNING/MEMORY

- Word list learning and memory:
  - Repeat the list several times and test free recall after each trial.
  - Test delayed recall for the list (5 and 30 minutes later).
  - Recognition memory.
    - Correctly identify words from the list intermixed with words that were not from the list.
- Story learning and memory:
  - Examinee is read a short story and asked to recall the story immediately after hearing it and then again 20 minutes later

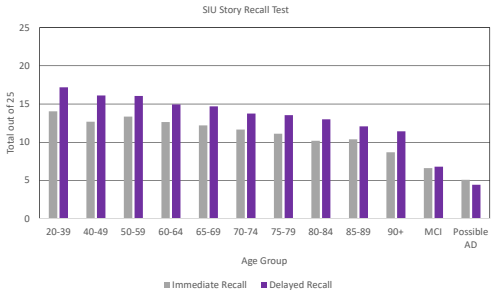
AGING EFFECTS ON A WORD LIST LEARNING/MEMORY TEST (RAVLT)



AGING EFFECTS ON A WORD LIST LEARNING/MEMORY TEST (RAVLT)

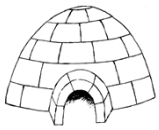


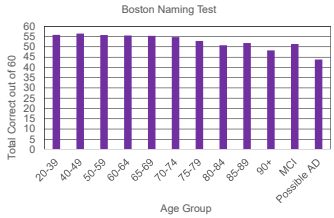
AGING EFFECTS ON THE SIU STORY RECALL TEST



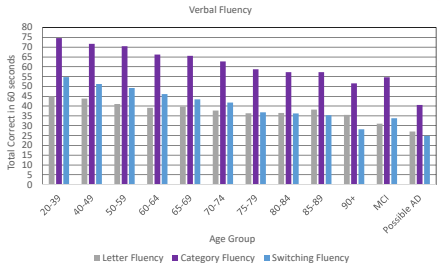
Aging effects on Language skills: Naming of Line drawings

What is this called?





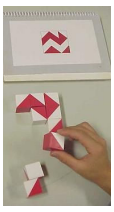
Aging effects on Language Skills: Verbal Fluency

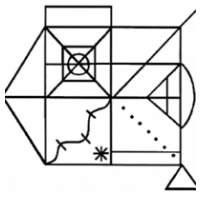


- Letter fluency: Tell me as many words as you can that begin with the letters 'F, A, S' but do not say any words that start with capital letters or numbers.
- Category fluency: Name as many unique animals, boys names, and states as you can.
- Switching fluency: Switch back and forth between saying occupations/colors, states of the United States and animals, and the letters C and P

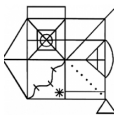
VISUOSPATIAL SKILLS

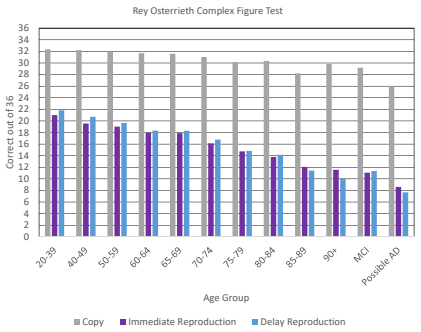
- Complex Figure Copy with immediate and delayed recall
- Spatial Reasoning



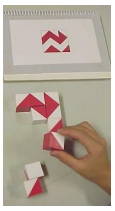


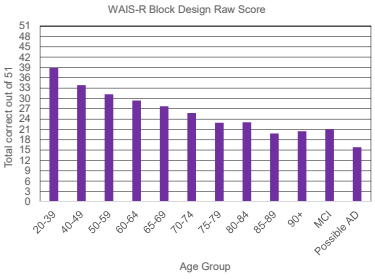
COPY, IMMEDIATE RECALL, AND DELAYED RECALL TRIALS



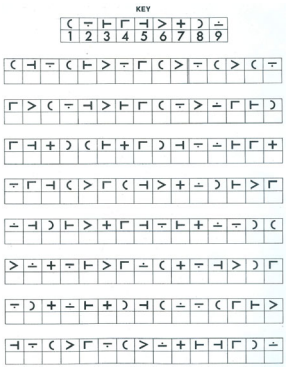


SPATIAL PROBLEM SOLVING





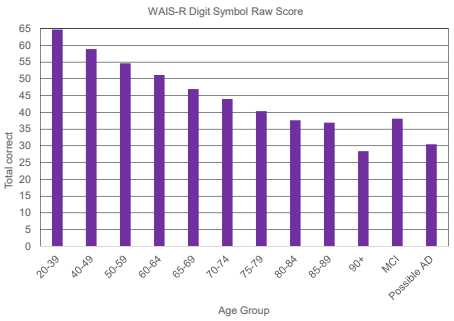
PROCESSING SPEED



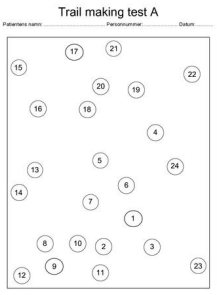
EXECUTIVE FUNCTIONS

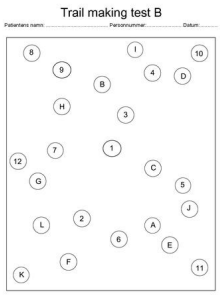
- "Frontal lobe functions"
- A set of cognitive processes that include:
  - Attentional control
  - Inhibitory control
  - Working memory
  - Cognitive flexibility
  - Multitasking
  - Reasoning
  - Problem solving
  - Planning/Organization
  - Set-Shifting

PROCESSING SPEED

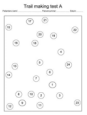


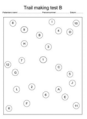
PROCESSING SPEED AND EXECUTIVE FUNCTION

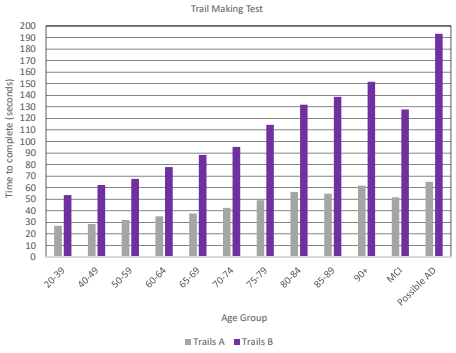




PROCESSING SPEED AND EXECUTIVE FUNCTION





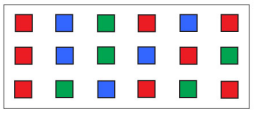


PROCESSING SPEED AND EXECUTIVE FUNCTION

Read the words as quickly as you can across each line until the end of the last line

RED BLUE GREEN RED BLUE RED
RED BLUE GREEN BLUE RED GREEN
RED GREEN BLUE RED GREEN RED

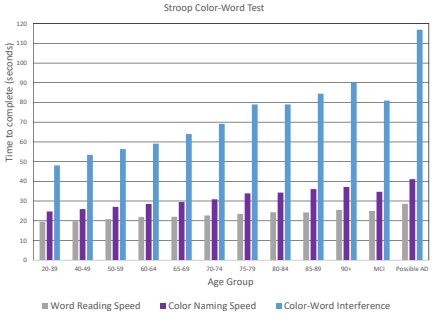
Name the colors as quickly as you can across each line until the end of the last line



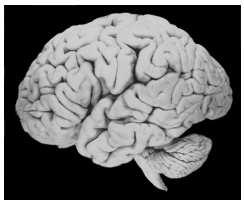
Name the color of the ink the words are printed in but do not read the words

RED BLUE GREEN RED BLUE RED
RED BLUE GREEN BLUE RED GREEN
RED GREEN BLUE RED GREEN RED

PROCESSING SPEED AND EXECUTIVE FUNCTION



WHAT BRAIN CHANGES ARE HAPPENING IN NORMAL AGING?



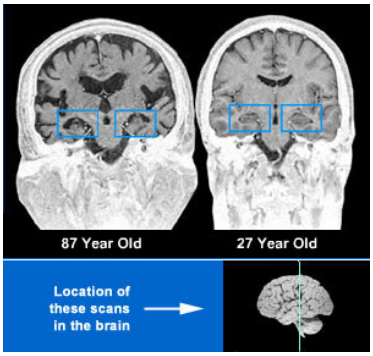
SHRINKAGE!

I was in the pool! I was in the pool!

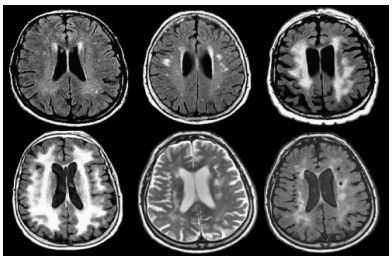
BRAIN VOLUME

- Brain volume ↓ with age at a rate of ~2% per decade beginning in early adulthood.
- CSF volume ↑ with age
- The percentage of brain volume loss correlates with declines in cognitive function in both normal aging and AD.
- Conflicting reports in the literature about which parts of the brain sustain greatest volume loss
  - Frontal vs. Temporal vs. Parietal vs. Occipital

THE AGING BRAIN



MICROVASCULAR CHANGES ON MRI



The spectrum of small vessel disease–related brain changes in MRI: white matter lesions ranging from punctate foci (*upper left*) to extensive confluent abnormalities (*lower left*) and lacunar infarcts (*lower right*).

MICROVASCULAR CHANGES IN NORMAL AGING

- More prominent white matter ischemia as age ↑.
- ↓ white matter integrity in normal aging.
- Speed of information processing along white matter tracts ↓ in normal aging
  - Critical for the processing and integration of complex information.
- Myelin breakdown in white matter contributes to the cognitive declines associated with normal aging.

AGING AND NEUROCHEMISTRY

- ↓ Dopamine
- ↓ Acetylcholine
- ↓ Norepinephrine
- ↓ Serotonin
- ↓ NMDA receptors
- ↓ Cholinergic receptors

THE AGING BRAIN: FUNCTIONAL CHANGES

- Single-unit recordings
  - Diminished neuronal firing rate/alteration in firing pattern
- Sensory evoked potentials
  - Diminished and delayed
- Blood flow (SPECT)
  - Diminished perfusion in select cortical regions
- Metabolic activity (PET)
  - Diminished uptake in select cortical regions
- fMRI
  - Changes in task-related activation

SUMMARY

- Aging is associated with increased prevalence of chronic medical conditions, disability, and dementia.
- The SIU LCAS study is but one of many large studies across the world that are examining neurobiological, neuropsychological, and psychosocial factors that are associated with both normal and abnormal aging.
- Normal Aging is associated with changes in brain structure/function, which correlates with age-related declines in cognitive function.
- Normal Aging is associated with declines in some (but not all) cognitive abilities.
  - These changes are less extensive than observed in individuals who go on to develop dementia.

Thank You for your attention!

Questions?

SIU MEDICINE

DALE & DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH & TREATMENT

"USE IT OR LOSE IT"

The Role of Brain Exercises

Cindy L. Womack, DNP, FNP-BC, CNRN
www.siumed.edu/alz

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DISCLOSURES

- Nothing to disclose
- Proprietary names used in this presentation are for the purpose of examples and are not intended to serve as a product or company endorsement

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LEARNING OBJECTIVES

1. Define neuroplasticity and cognitive reserve
2. Identify and describe three classes of cognitive interventions
3. Describe the benefits of cognitive stimulation
4. Delineate the types of activities for brain exercises

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COGNITION

Cognition – the mental activities and processes involved in receiving, comprehending, storing, retrieving, and using information.

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COGNITIVE DOMAINS

- memory
- attention
- executive functions
- language
- calculation

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COGNITIVE DOMAINS

reasoning
processing speed
visual-spatial skill

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CONCEPTUAL BASIS

Neuroplasticity

Cognitive resilience

Cognitive reserve

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NEUROPLASTICITY

- ability of the brain to modify, change, and adapt structure and function in response to experience across the life span
- essential for healthy brain function

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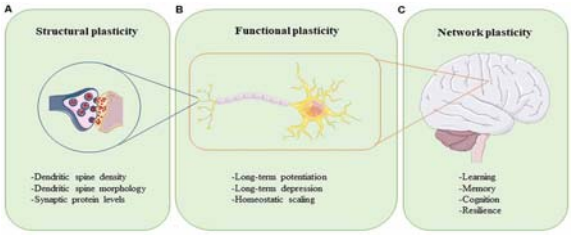
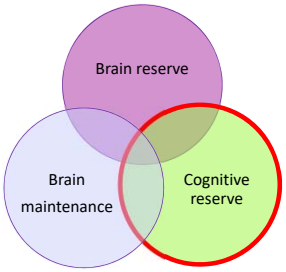
(Nelson, Jester, Petkus, & Andel, 2021; Arenaza-Urquiljo et al., 2020, Voss et al., 2017)

LEVELS OF NEUROPLASTICITY



(Koller & Chakrabarty, 2020)

COGNITIVE RESILIENCE



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(Stern, 2021; Arenaza-Urquiljo et al., 2020 ; Stern & Barulli, 2019)

COGNITIVE RESILIENCE

- Brain reserve – greater neurobiological capital (more neurons, more synapse)
- Cognitive reserve - neuronal network adaptability (efficiency, capacity, flexibility)
- Brain maintenance – reduced development of age-related brain changes & pathology (genetics and/or lifestyle)

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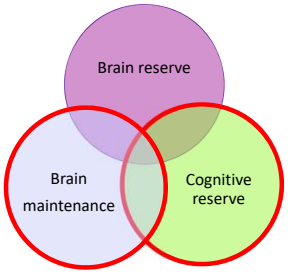
(Stern, 2021; Arenaza-Urquiljo et al., 2020; Stern & Barulli, 2019)

COGNITIVE RESILIENCE



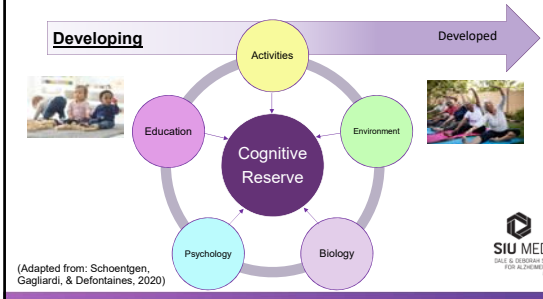
(Stern, 2021; Arenaza-Urquiljo et al., 2020 ; Stern & Barulli, 2019)

COGNITIVE RESERVE

- neuronal network adaptability (efficiency, capacity, flexibility)
- individual differences in cognitive or functional brain processes determine cognitive reserve

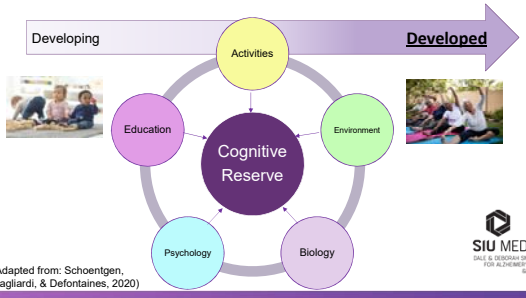
(Nelson, Jester, Petkus, & Andel, 2021; Arenaza-Urquiljo et al., 2020.; Stern & Barulli, 2019;Voss et al., 2017)

COGNITIVE RESERVE



(Adapted from: Schoentgen, Gagliardi, & Defontaines, 2020)

COGNITIVE RESERVE



(Adapted from: Schoentgen, Gagliardi, & Defontaines, 2020)

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COGNITIVE EXERCISE

COGNITIVE STIMULATION

COGNITIVE TRAINING

COGNITIVE REHABILITATION

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(Clare et al., 2018; Bahar-Fuchs, Clare, & Woods, 2013)

COGNITIVE EXERCISE

COGNITIVE STIMULATION

- non-specific engagement in a range of activities and discussions either individually or in a group setting i.e. reality orientation, reminiscence activities

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(Clare et al., 2018; Bahar-Fuchs, Clare, & Woods, 2013)

COGNITIVE EXERCISE

COGNITIVE TRAINING

- guided approach involving practice of standardized tasks targeting a particular cognitive function such as attention, memory, or problem solving
- computerized cognitive training (CCT)

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(Clare et al., 2018; Bahar-Fuchs, Clare, & Woods, 2013)

COGNITIVE EXERCISE

COGNITIVE REHABILITATION

- individualized approach with functional goals, creates compensatory strategies

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(Clare et al., 2018; Bahar-Fuchs, Clare, & Woods, 2013)

COGNITIVE EXERCISE

COGNITIVE STIMULATION (CS)

COGNITIVE TRAINING (CT, CCT)

COGNITIVE REHABILITATION (CR)

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(Clare et al., 2018; Bahar-Fuchs, Clare, & Woods, 2013)

ACTIVITIES – COGNITIVE STIMULATION

Discussion of past and/or present events

Word games

Puzzles – crossword, word search, sudoku, jigsaw

Music

Board games

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ACTIVITIES – COGNITIVE STIMULATION

Indoor gardening

Creative activities – baking, crafting, sewing

Socialization

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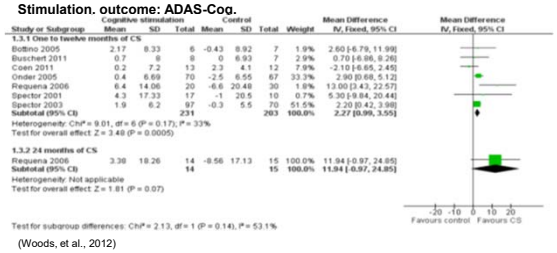
EVIDENCE FOR CS

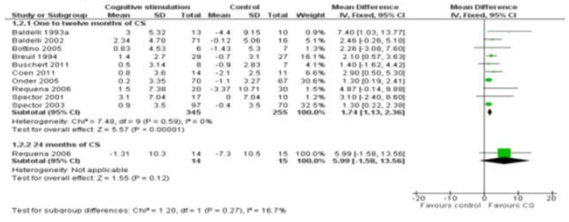
Figure 2. Forest plot of comparison: 1 Cognitive Stimulation vs No Cognitive Stimulation. outcome: ADAS-Cog.



(Woods, et al., 2012)

EVIDENCE FOR CS

Figure 3. Forest plot of comparison: 1 Cognitive Stimulation vs No Cognitive Stimulation, outcome: MMSE.



(Woods, et al., 2012)

ACTIVITIES – COGNITIVE TRAINING

Memory card games

Memorizing information/lists

Pattern detection games

Use of touch screens games to increase thinking speed

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ACTIVITIES – COGNITIVE TRAINING

Board games

Dance

Art

Music

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ACTIVITIES – COMPUTERIZED CT (CCT)

BrainHQ – Healthy older adults, ADHD, bipolar disease, depression, MCI, dementia, PD, MS, stroke, TBI

CogniFit – Healthy older adults, ADHD, depression, PD, stroke, PD, dyslexia, dyscalculia, insomnia, fibromyalgia

CogniPlus – Brain damage, ADHD, MCI

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(Irazoki et al., 2020; O'Shea et al., 2019)

ACTIVITIES – CCT

Cogmed – ADD, TBI, stroke, learning disorders, cognitive impairment

Luminosity – Healthy older adults

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(Irazoki et al., 2020; O'Shea et al., 2019)

EVIDENCE – CT MIDLIFE

Computerized Cognitive Training (CCT)

- Cognitive training group performed slightly better on reasoning (executive function)
- Control group performed slightly better on working memory
- No group difference on episodic memory

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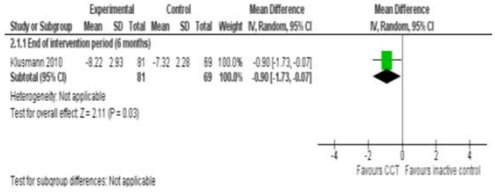
(Gates et al., 2019)

EVIDENCE – CT LATE LIFE

Figure 7. Forest plot of comparison: 2 Computerized cognition-based training versus inactive control, outcome: 2.1 Episodic Memory.



(Gates, et al., 2020)

EVIDENCE – CT MCI

CCT versus Active & Inactive Controls

1. None of the 8 trials examined development of dementia
2. No data to state that CT prevents dementia
3. Low quality evidence favoring CCT for improvement in global cognitive function, episodic memory, and working memory

(Gates et al., 2019)

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EVIDENCE – PREVENTION

CCT - MCI

1. No evidence that CCT prevents dementia
2. Improvement in visual and/or verbal episodic memory
3. Improvement in other cognitive domains

(O'Shea, De Wit, & Smith, 2019)

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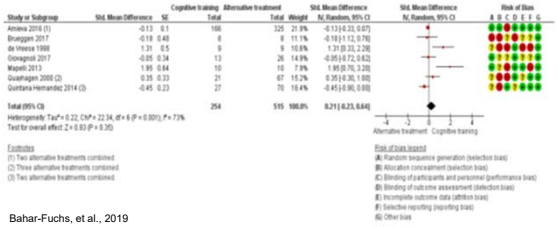
EVIDENCE – CT DEMENTIA

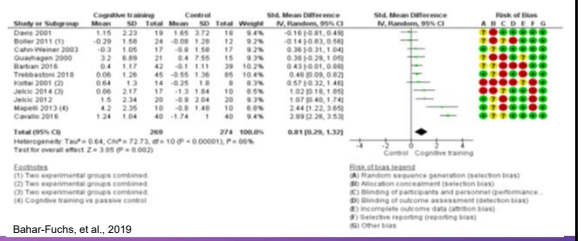
Figure 6. Forest plot of comparison: 3 Cognitive training vs alternative treatment immediately post intervention,



Bahar-Fuchs, et al., 2019

EVIDENCE – CT DEMENTIA

Figure 9. Forest plot of comparison: 1 Cognitive training vs control immediately post intervention, outcome: 1.6 Change in delayed memory.



Bahar-Fuchs, et al., 2019

EVIDENCE – CT EXERCISE

Simultaneous versus Sequential Exercise

1. Significant improvement in composite memory in SIM group
2. Executive function and reaction time improved in the SEQ group
3. Non-verbal abstract reasoning and complex attention in SIM group

(McEwen et al., 2018)

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EVIDENCE SUMMARY

1. CS, CT, or CCT does not prevent dementia
2. The evidence is mixed as to the effectiveness of CS, CT, or CCT in improving global and specific cognitive domains.
3. CS, CT, and CCT may offer some improvements in certain cognitive functions

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EVIDENCE SUMMARY

4. CS, CT, and CCT may offer some improvement in quality of life and ability to perform Activities of daily living for some individuals
5. Combining CS, CT, or CCT with aerobic exercise may offer a synergistic effect for improving certain cognitive functions

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EVIDENCE SUMMARY

6. There is no evidence to date for significant harm from CS, CT, CCT other than the cost of commercially available programs

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RECOMMENDATIONS

RESEARCH

1. There is a significant need for further research in this area:
    a. higher quality studies
    b. leveraging newer technologies i.e. virtual reality, artificial intelligence/machine learning

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RECOMMENDATIONS

CLINICAL

1. Healthy older people should be encouraged to participate in CS and CT activities despite the modest benefits
2. Those with subjective cognitive complaints and MCI should be encouraged to use CS and CT

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RECOMMENDATIONS

CLINICAL

3. Those with dementia should be encouraged to participate in CS programs
4. Brain health should be incorporated into the public health paradigm from a life span perspective beginning in childhood

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REFERENCES

Arenaza-Urquiljo, E. M., Bartres-Faz, D., Belleville, S., Cantillon, M., Chetelat, G., Clouston, S. A. P., ...Vuoksimaa, E. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's Dementia, 16,* 1305-1311. doi: 10.1016/j.jalz.2018.07.219

Bahar-Fuchs, A., Clare, L., & Woods, B. (2013). Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer's or vascular type: A review. *Alzheimer's Research & Therapy, 5,* 1-14. doi: 10.1186/alzrt189

Bahar-Fuchs, A., Martyr, A., GohAMY, Sabates, J., & Clare,L. (2019). Cognitive training for people with mild to moderate dementia. *Cochrane Database of Systematic Reviews*, *3*. 1-287/ doi:10.1002/14651858.CD013069.pub2.

Clare, L., Teale, J.C., Toms, G., Kudlicka, A., Evans, I., Abrahams, S., ...Thompson-Coon, J. (2018). Cognitive rehabilitation, self-management, psychotherapeutic and caregiver support interventions in progressive neurodegenerative conditions: A scoping review. *NeuroRehabilitation, 43,* 443-471. doi: 10:3233/NRE-172353

Irazoki, E., Contreras-Somoza, L. M., Toribio-Guzman, J. M., Jenaro-Rio, C., van der Roest, H., & Franco-Martin, M. A. (2020). Technologies for cognitive training and cognitive rehabilitation for people with mild cognitive impairment and dementia: A systematic review. *Frontiers in Psychology, 11,* 1-15. doi: 10.3389/fpsyg.2020.00648

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REFERENCES

Gates, N.J., Vernooij, R. W. M., Di Nisio, M., Karim, S., March, E., Martínez, G., & Rutjes, A. W. S. (2019). Computerized cognitive training for preventing dementia in people with mild cognitive impairment. *Cochrane Database of Systematic Reviews , 3,* 1-103. doi: 10.1002/14651858.CD012279.pub2.

Gates, N. J., Rutjes, A. W. S., Di Nisio, M., Karim, S., Chong, L. Y. , March, E., Martínez, G., & Vernooij, R.W.M. (2019) Computerized cognitive training for maintaining cognitive function in cognitively healthy people in midlife. *Cochrane Database of Systematic Reviews*, *3.* doi: 10.1002/14651858.CD012278.pub2.

Gates, N.J., Rutjes, A. W. S., Di Nisio, M., Karim, S., Chong, L. Y., March, E., Martínez, G., & Vernooij, R.W.M. (2020). Computerized cognitive training for 12 or more weeks for maintaining cognitive function in cognitively healthy people in late life. *Cochrane Database of Systematic Reviews*, *2,* 1-104. doi: 10.1002/14651858.CD012277.pub3.

Koller, E. & Chakrabarty, P. (2020). Tau-mediated dysregulation of neuroplasticity and glial plasticity. *Frontiers in Molecular Neuroscience, 13,* 1-23. doi:10.3389/fnmol.2020.00151

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REFERENCES

McEwen, S. C., Siddarth, P., Abedelsater, B., Kim, Y., Mui, W., Wu, P., ...Merrill, D. A. (2018). Simultaneous aerobic exercise and memory training program in older adults with subjective memory impairments. *Journal of Alzheimer's Disease, 62,* 795-806. doi: 10.3233/JAD-170846

Nelson, M. E., Jester, D. J., Petkus, A. J., & Andel, R. (2021). Cognitive reserve, Alzheimer's neuropathology, and risk of dementia: A systematic review and meta-analysis. *Neuropsychology Review, 31,* 233-250. doi: 10.1007/s11065-021-09478-4

Schoentgen, B., Gagliard, G., & Defontaines, B. (2020). Environmental and cognitive enrichment in childhood as protective factors in the adult and aging brain. *Frontiers in Psychology, 11,* 1-11. doi: 10.3389/fpsyg.2020.01814

O'Shea, D. M., De Wit, L., & Smith, G.. E. (2019). Doctor, should I use computer games to prevent dementia? *Clinical Gerontologist, 42,* 3-16. doi: 10:1080/07317115.2017.1370057

Stern, Y. (2021). How can cognitive reserve promote cognitive and neurobehavioral health? *Archives of Clinical Neuropsychology, 36,* 1291-1295. doi: 10.1093/arclin/acab049

Stern, Y., & Barulli, D., (2019). Cognitive reserve. In S. T. DeKosky & S. Asthana (Eds.), *Handbook of Clinical Neurology,* (pp. 181-190). doi: 10.1016/B978-0-12-804766-8.00011-X

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REFERENCES

Voss, P., Thomas, M. E., Cisneros-Franco, M., & de Villers-Sidani, E. (2017). Dynamic brains and the changing rules of neuroplasticity: Implications for learning and recovery. *Frontiers in Psychology, 8*, 1-11. doi: 10.3389/fpsyg.2017.01657

Woods, B., Aguirre, E., Spector, A.E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database of Systematic Reviews*, *2*, 1-72. doi:10.1002/14651858.CD005562.pub2.

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