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Digital Twins and Alternative Clinical Trial Designs

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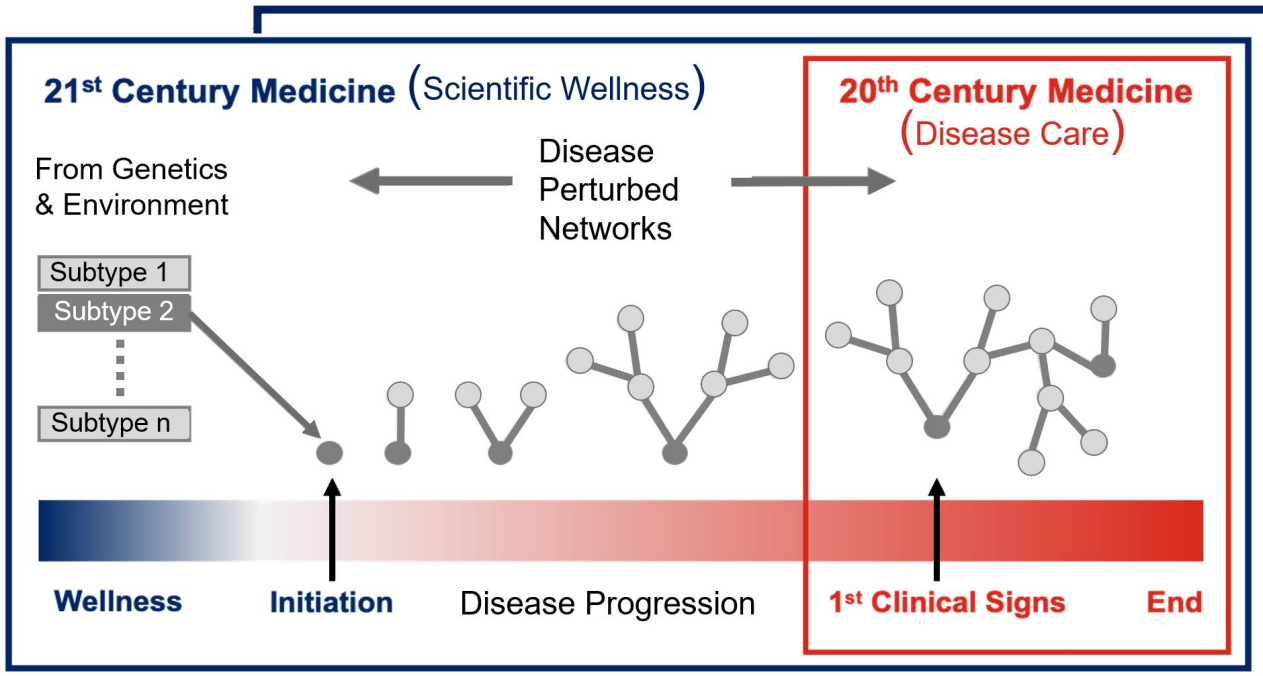
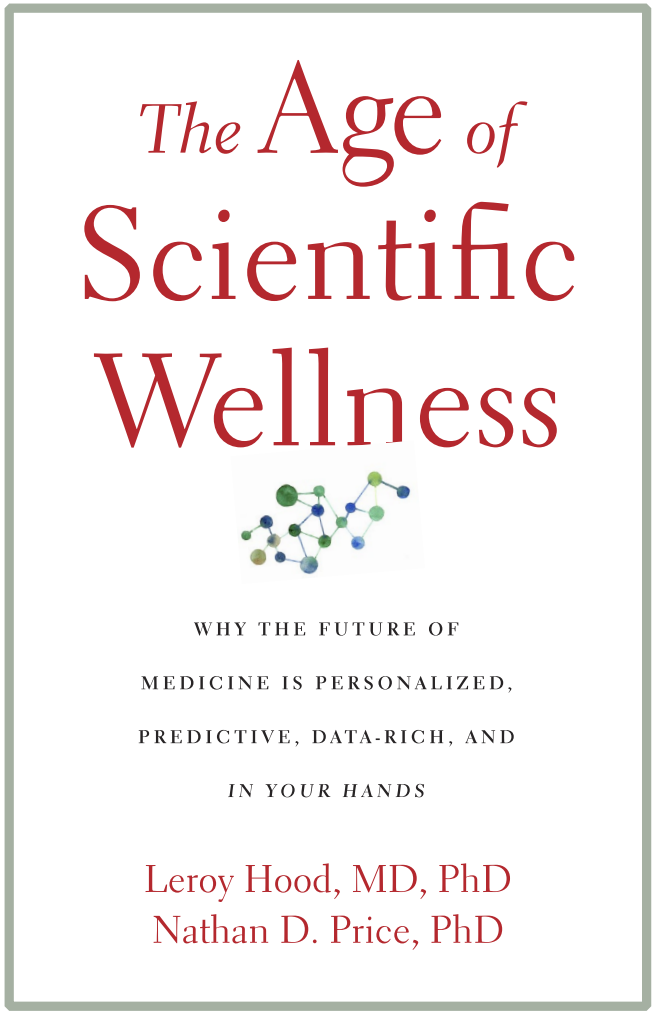
Studying the continuum of wellness to disease is critical for alternative approaches to prevention and therapy development



1. **Execute scientific and healthy aging**
2. **Identifies wellness to disease transition and reverse it**
3. **Manage disease–stratify patients**

We need to harness longitudinal multi-omic data during "wellness" -- and wellness to disease transitions -- to understand long term effects of both toxins and nutrients

Harvard University Press



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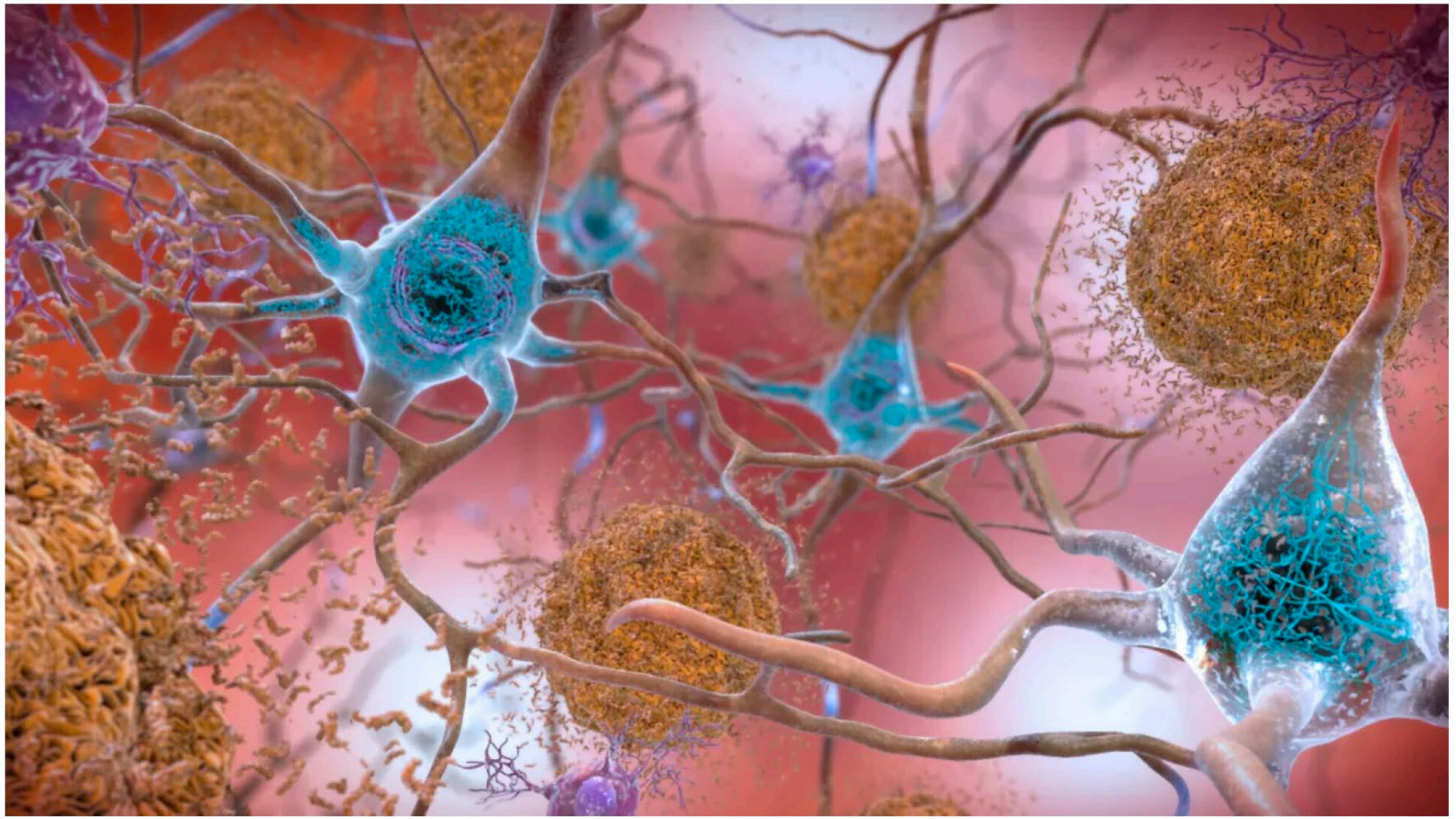
Opinion: New Alzheimer's drugs are costly and controversial. Are we going about this all wrong?



An illustration depicting neurons in a brain affected by Alzheimer's disease, with abnormal accumulations of beta-amyloid and tau proteins shown in brown and blue, respectively. (National Institute on Aging/National Institutes of Health via Associated Press)

BY NATHAN PRICE AND LEROY HOOD

JUNE 11, 2023 3:30 AM PT

Los Angeles Times

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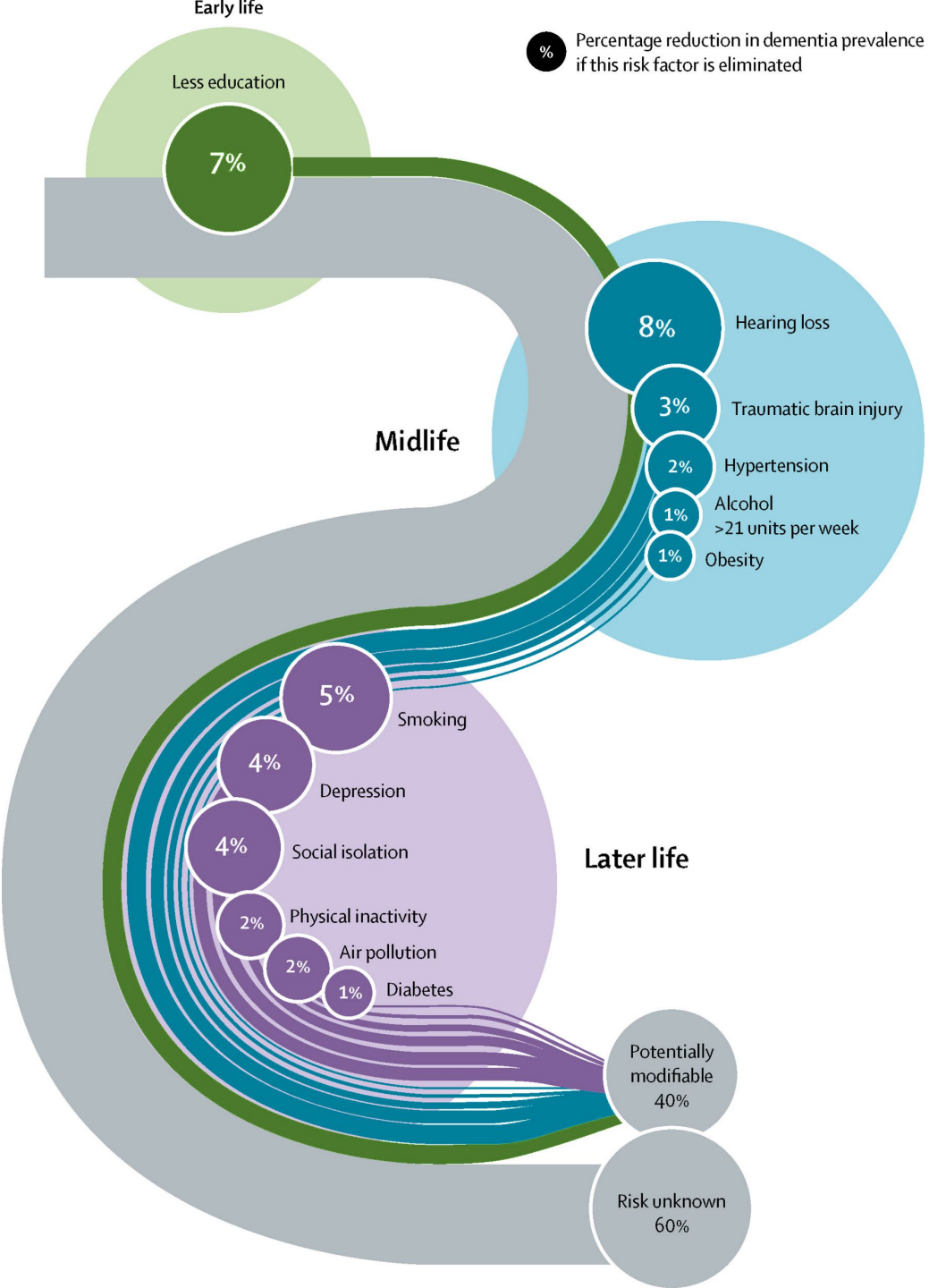
Modifiable Risk for Alzheimer's Disease



THE LANCET

THE LANCET COMMISSIONS | VOLUME 396, ISSUE 10248, P413-446, AUGUST 08, 2020 Download Full Issue

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

Prof Gill Livingston, MD • Jonathan Huntley, PhD • Andrew Sommerlad, PhD • Prof David Ames, MD • Prof Clive Ballard, MD • Prof Sube Banerjee, MD • et al. Show all authors

Published: July 30, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)30367-6 • Check for updates

- Diet/Obesity
- Diabetes
- Physical Inactivity
- Depression
- TBI
- Alcohol
- Hypertension

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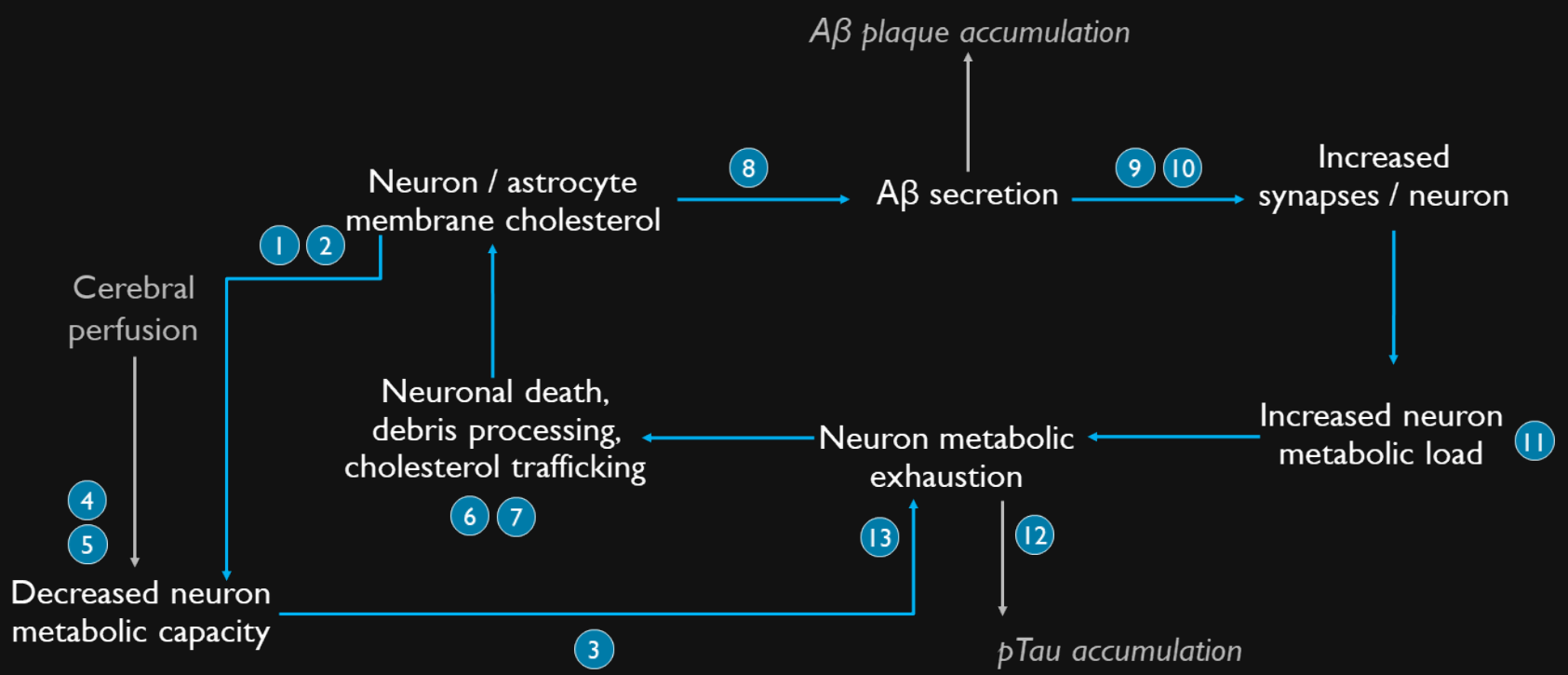
Digital Twin Model Represents A Complex, Quantitative, and Testable Hypothesis of How Brain Maintains Health (Wellness) and then How Alzheimer's Initiates, Progresses, and Kills:



'Digital twin' models dynamically simulate outcomes and interventions specific for individuals – highly personalized and predictive

Exclusive partnership with EmbodyBio in brain health, powering Thorne's Health Intelligence platform to deliver deep insights into prolonging brain health

Quantitative systems view of the causes and consequences in Alzheimer's disease – leading to highly personalized approaches to treatment and prevention

Leverages data and insight from >1000 scientific publications and compares against over 30 clinical trials and human research studies

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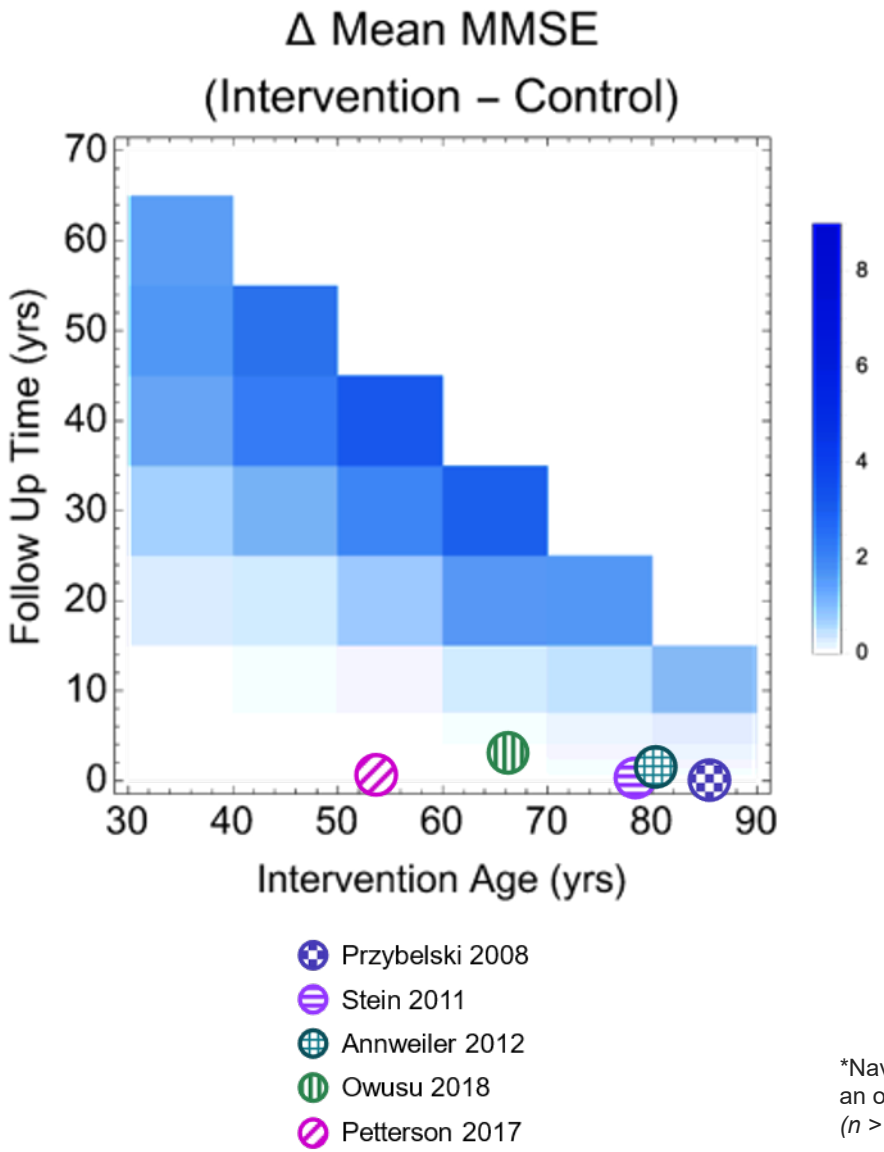
Personalized evidence-based medicine

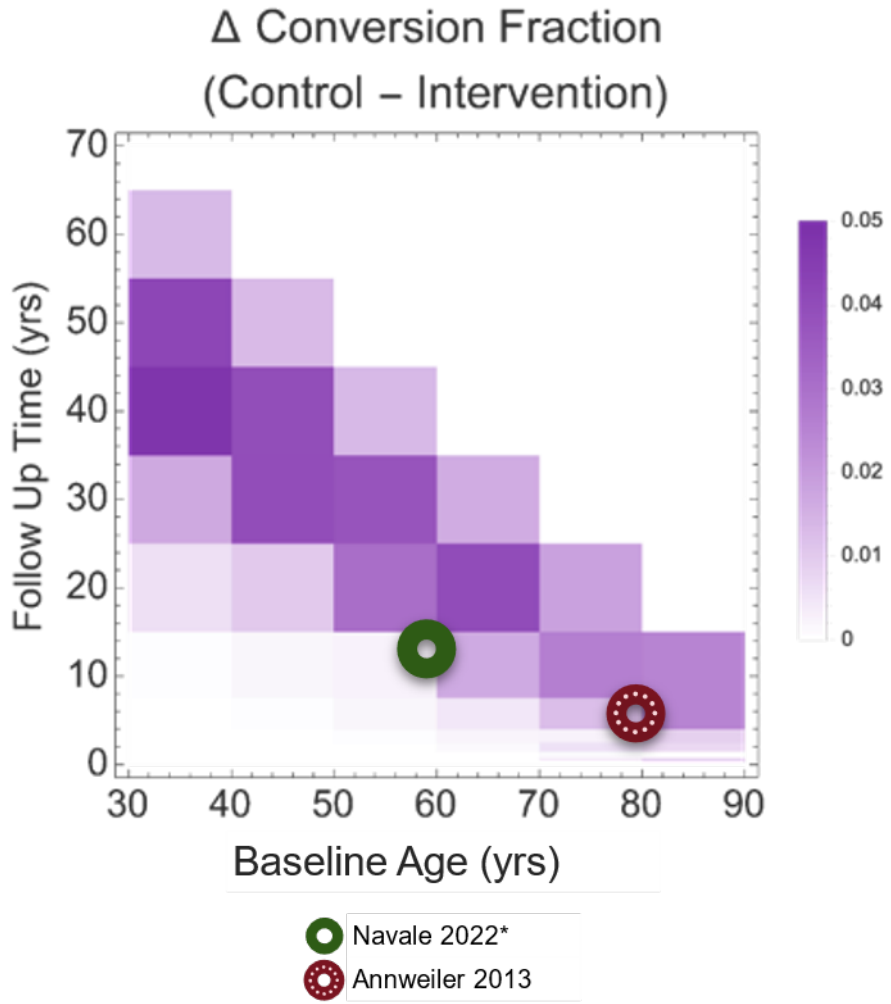
Digital-Twin Enabled Clinical Trial Design

Retrospective studies show that there is a reduced HR associated with high Vitamin D intake, but intervention studies have not shown a significant effect

Study	Study Type	Average Baseline Age	Average Follow Up (years)	Endpoint	Result
Annweiler, 2013	Retrospective	80.6	3-7	OR	0.23 (95% CI 0.08 - 0.69)
Owusu, 2018	Intervention	67.8	3	Δ MMSE cognitive score	No difference

Digital Twins Can Simulate Specific Trials and Evaluate if the Mechanism with the Measured Effect Size Would Show an Effect:





*Navale, S. S., Mulugeta, A., Zhou, A., Llewellyn, D. J. & Hyppönen, E. Vitamin D and brain health: an observational and Mendelian randomization study. Am J Clin Nutrition 116, nqac107- (2022).
(n > 400,000 UK Biobank study; primary study used for calibrating vitamin D effects in BHN3)

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Personalized clinical trials with digital twins

Current paradigm

- Run a blinded, randomized clinical trial
- Test one *compound*
- Lower effect size, so larger N needed
- Most participants are non-responders
- Many trials underpowered and not definitive
- End claim is that compound works (may not be proprietary)
- Causation vs correlation assessed for the compound based on outcome

Novel Alternative Method

- Run a blinded, randomized clinical trial
- Test the *digital twin model* (i.e. each person gets personalized, multi-factor treatment informed by DT)
- Higher effect size, so lower N needed
- Most participants are responders
- Economically viable for more preventives
- End claim is that recommendations from the DT work (proprietary)
- Causation vs. correlation for each compound is assessed based on mechanism in the DT being able to match molecular and outcome data

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What have we learned?

- Personalization — the best solutions vary person to person
- Combinations, especially when personalized, have MUCH larger effect sizes than a single intervention
- Plausible mechanisms explain observed effects but require long follow-up times – gave example for nutrients, but likely true in opposite direction for non-acute toxin exposures
- Human intervention trials for single products may often NOT be sufficient to observe prevention
- We may be devaluing many compounds that could be beneficial for preventive healthcare
- Provides a path for tying mechanisms into human-specific interventions without animals
- Best to test for predictive power initially on interventions that are safe

Thank You!

Questions?

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