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Alzheimer's & Dementia
Translational Research & Clinical Interventions

REPLY

Dense data enables 21th century clinical trials

Alzheimer's disease (AD) is one of the most significant challenges of our time. We need a diverse research portfolio. We cannot afford to shut down avenues of research. A century of domination by the amyloid hypothesis stifled AD research. We cannot again afford last century's opportunity cost. Health care delayed is health care denied. Trials take years. Trials should be done in parallel where possible. If we were to test all possible single-mode interventions before testing any other hypotheses, it would take decades—if not centuries. Given the high expected return on AD research investment, we do not advocate redistributing money among AD trials as a zero-sum game; rather, we should increase funding for all AD research. If there were a need to redistribute global AD funding, we note that pharmaceutical companies may spend billions of dollars bringing to market products that are less validated and less effective than multimodal therapy or its components. A recommendation to reallocate funding for multimodal trials that are several orders of magnitude less expensive than pharmaceutical trials seems mistargeted.

At the Institute for Systems Biology (ISB), we aim to change the epistemological nature of clinical studies.[1] Most 20th-century clinical trials were primarily built on two epistemological pillars: significance and effect size. There are limits to the knowledge that is reachable from standing only on these two pillars. Some knowledge—typically the most satisfying—can only be gained from mechanistic or causal insights. Integrated learning leveraging multiple diverse large datasets is increasingly important to many fields, including commerce, and is becoming a major driver of biomedical knowledge and breakthroughs. It is time for most clinical studies to generate the dense data necessary to power such learning. Contributing to global knowledge should now be a factor in clinical trial design. Commitment to generating globally useful datasets should be part of updated trial-design guidelines. Our recommendations are not restricted to AD research—they can be applied to all complex diseases. With sufficiently deep data, much can be learned by integrating data across multiple domains.

Multimodal AD therapies are in wide use; Americans are spending money and opportunity cost to pursue them. There is a demand from the members of our democracy to fund research for multimodal therapies. It is urgent to provide these citizens and their healthcare providers with science. Prospective randomized controlled trials (RCTs) provide the best form of evidence. We have an obligation to return research value to the people that support us.

Population-attributable risk models estimate 12 factors that may prevent 40% of dementia cases.[2] Most of the components of multimodal therapies have been validated individually and together.[3–5] Authorities have called for more RCTs.[6–8] Multimodal interventions may work best when combined—either because of synergy or from the combination of multiple small effects.[9] Such synergies might never be discovered if we insist that all of biology be constructed from linear models, with each coefficient identified before any combinations are tested.

If coaching is not scalable, then the path to democratization of therapies *requiring* coaching may be difficult. But multimodal therapies do not require coaching, and even without coaching, are likely to be better democratized than pharmaceuticals. Pharmaceuticals have a poor track record for democratization. On the other hand, lifestyle interventions are scalable and free of intellectual property. Plus, we think coaching *will be* scalable. In one envisionable future, many traditional jobs are replaced by artificial intelligence; workers are freed to provide personal contact. In the decades and centuries to come, personalized coaching may become a preferred therapy.

It is reasonable to see Precision Recommendations for Environmental Variables, Exercise, Nutrition, Training Intervention to Optimize Neurocognition (PREVENTION) through the lens of "merely testing coaching." It is also reasonable to see PREVENTION through many other lenses. PREVENTION is testing two separate doses of multimodal intervention: low dose and high dose. It is not possible to test zero dose—all people exercise or eat or use their brains to some extent. Many more trials are needed. PREVENTION and its sister trial COCOA (Coaching for Cognition in Alzheimer's)[10] will provide data to enable better design of such future trials.

We should be driving 21st-century electric cars, not 19th-century horse-drawn carts, and not quibbling about where the horse is placed. There is still plenty of room for horse-drawn research carts. But we must also trailblaze lest we end up stuck in a rut. We envision a world in which economical and individualized interventions are accessible to the millions of people with and at risk for AD and related dementias.

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CONFLICTS OF INTEREST

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