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RESEARCH ARTICLE

The Coaching for Cognition in Alzheimer's (COCOA) trial: Study design

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Abstract

Comprehensive treatment of Alzheimer's disease (AD) requires not only pharmacologic treatment but also management of existing medical conditions and lifestyle modifications including diet, cognitive training, and exercise. We present the design and methodology for the Coaching for Cognition in Alzheimer's (COCOA) trial. AD and other dementias result from the interplay of multiple interacting dysfunctional biological systems. Monotherapies have had limited success. More interventional studies are needed to test the effectiveness of multimodal multi-domain therapies for dementia prevention and treatment. Multimodal therapies use multiple interventions to address multiple systemic causes and potentiators of cognitive decline and functional loss; they can be personalized, as different sets of etiologies and systems responsive to therapy may be present in different individuals. COCOA is designed to test the hypothesis that coached multimodal interventions beneficially alter the trajectory of cognitive decline for individuals on the spectrum of AD and related dementias (ADRD). COCOA is a two-arm prospective randomized controlled trial (RCT). COCOA collects psychometric, clinical, lifestyle, genomic, proteomic, metabolomic, and microbiome data at multiple timepoints across 2 years for each participant. These data enable systems biology analyses. One arm receives standard of care and generic healthy aging recommendations. The other arm receives standard of care and personalized data-driven remote coaching. The primary outcome measure is the Memory Performance Index (MPI), a measure of cognition. The MPI is a summary statistic of the MCI Screen (MCIS). Secondary outcome measures include the Functional Assessment Staging Test (FAST), a measure of function. COCOA began enrollment in January 2018. We hypothesize that multimodal interventions will ameliorate cognitive decline and that data-driven health coaching

will increase compliance, assist in personalizing multimodal interventions, and improve outcomes for patients, particularly for those in the early stages of the AD spectrum.

KEYWORDS
Alzheimer's disease, Alzheimer's disease and related disorders, cognitive decline, cognitive impairment, cognitive training, dementia, diet, exercise, hierarchical edge bundling, lifestyle, multimodal interventions, personalized coaching, remote coaching, systems biology

Highlights

- The Coaching for Cognition in Alzheimer's (COCOA) trial tests personalized multimodal lifestyle interventions for Alzheimer's disease and related dementias.
- Dense longitudinal molecular data will be useful for future studies.
- Increased use of Hill's criteria in analyses may advance knowledge generation.
- Remote coaching may be an effective intervention.
- Because lifestyle interventions are inexpensive, they may be particularly valuable in reducing global socioeconomic disparities in dementia care.

1 | INTRODUCTION

Complex diseases require complex therapies. Any unimodal approach to Alzheimer's disease (AD) and related disorders (ADRD) research, diagnosis, or treatment would be flawed, as it would miss opportunities to improve the health and wellness of patients. Most single-modality approaches have small effects at the individual level, and negligible effects on the public health burden. This is true for both pharmaceutical agents and lifestyle modalities. We hypothesize that multimodal interventions can slow progression, halt, or reverse the course of ADRD.

The Lancet Commission, through meta-analyses of population studies, identifies 12 modifiable risk factors that account for 40% of dementias: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution.[1] Some of these are likely to remain modifiable in some older individuals and be elements of treatment as well as prevention. Over the last decade, at least three lifestyle interventions have been shown through unimodal clinical trials to be effective for ameliorating cognitive decline: healthy diet, exercise, and cognitive training.[2–5] Several trials for combinations of these interventions for the prevention of cognitive decline have already been performed or are in progress, notably the FINGER trial.[6] These trials have generally shown protective effects of multimodal intervention.[7] An incremental and obvious next step is to test whether multimodal interventions work for individuals along the early stages of ADRD.[8]

We hypothesize that the effects of multiple lifestyle interventions together with state-of-the-art allopathic therapies will be synergistic, and not merely additive. However, it is not possible to test through traditional clinical trials all combinatorial possibilities for multimodal therapies. Such trials would take centuries, cost too much, and require more participants than are recruitable. Therefore, testing the hypothesis that multimodal interventions treat AD (or other complex disorders) benefits from a relatively new concept in trial design. This design both (1) tests a specific prespecified hypothesis, and (2) gathers dense longitudinal data to enable other categories of epistemological analysis, such as causal reasoning and application of Hill's criteria.[9] The Coaching for Cognition in Alzheimer's (COCOA) trial implements such a design. COCOA is designed both to be a prospective randomized controlled trial (RCT) to test the efficacy of coaching personalized multimodal interventions to improve cognitive trajectory in ADRD and also to gather dense data to enable systems analyses.

2 | TRIAL GOALS AND OBJECTIVES

One major COCOA objective is to evaluate the efficacy of data-driven personalized health coaching focused on multimodal lifestyle interventions for ADRD compared to standard of care without coaching. This choice of objective builds on observations and experience from studies of similar interventions in longitudinal cohorts (e.g., Isaacson et al.[10]). We anticipate that coaching will increase the amount, or "dose," of healthy behaviors. A second major objective is to analyze longitudinal multi-omic data from individuals on a trajectory through early-stage dementia. Analyses for this objective aim to discover correlations between measured variables and identify mechanisms and/or models of causation that can further advance knowledge and research in brain degeneration and healthy living. These multi-omic data can be analyzed both in aggregate cohort and stratification analyses as well as at the individual level. Given the complexity of the disease and the interventions, each individual may be sufficiently unique, and grouping them for aggregate analyses might blur available insights. That is, if different subsets of systems are dysregulated in each individual, and each

RESEARCH IN CONTEXT

- Systematic Review: Studies of randomized controlled trials (RCTs) and epidemiological research on lifestyle interventions targeting cognitive health were reviewed. These inform trial design and the coached multimodal intervention delivered in the Coaching for Cognition in Alzheimer's (COCOA) trial.
- Interpretation: Clinical trials should gather dense longitudinal molecular and clinical data to enable future studies to leverage past data for epistemological consistency and coherency; to perform trial analytics such as systems analyses that require previously collected dense data; and to create synthetic controls, digital twins, and similar constructs.
- Future Directions: Results from the COCOA study will enable testing the hypothesis that coached multimodal lifestyle interventions are an effective therapy for the spectrum of Alzheimer's disease and related dementias. Future studies should build on COCOA data to improve and focus trial design. Iterative short trials should steadily improve the design and personalization of multimodal interventions.

system responds to a different set of components of the therapy, then studying individual dense data sets may enable mechanistic insights not conveyed by data averaged across multiple individuals. Longitudinal (dynamic) data enable epistemology that exploits timing of changes in molecular subsystems in response to the timing of changes in molecular correlates of interventions. Therefore, we aim to perform frequent molecular assays, balancing increased frequency against increased trial budget and burden on participants. Dense molecular and clinical data also enable future studies to leverage COCOA data to create synthetic controls, digital twins, and other trial analytics that require previously collected dense data. Table 1 provides a Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.[11]

3 | METHODS

COCOA collects comprehensive assessments and biomarker collection at these six timepoints: baseline, 4, 8, 12, 18, and 24 months (Table 2). Much of the methodology of COCOA was previously tested in the 100-Person Wellness Project, in which we used the same approach to data generation for a longitudinal cohort of generally healthy individuals and were able to generate biological knowledge through analysis of the dense dynamic data acquired for each individual.[12] As our single primary outcome measure for COCOA, we preselected the Memory Performance Index (MPI) summary statistic of the MCI Screen (MCIS). The MPI accounts for age, race, education, sex, method of test administration, and word list used. In a study of 121,481 normal or cognitively impaired subjects, the proportion of variance explained by MPI was several-fold greater than by total scores.[13]

3.1 | Trial design

COCOA is a prospective, 24-month, and two-arm, RCT (ClinicalTrials.gov NCT03424200, registered January 2018) for adults across the spectrum of ADRD. Participants are randomly assigned to data-driven, personalized, multimodal lifestyle intervention either with or without remote health coaching. The objectives of COCOA are to (1) test the effectiveness of data-driven multimodal coaching for amelioration of cognitive decline, and (2) identify individual data trajectories that inform basic and translational knowledge of AD and dementia. Participants in COCOA are not blinded; the intervention precludes blinding. Administrators of assessments and evaluators of data are blinded. The logistics of coaching and dense data assays were contracted to Arivale (Seattle, Washington, USA) from the start of the trial through April 2019.[14] After Arivale ceased operations, these logistics were assumed in house.

3.2 | Participants

Subjects are recruited from a high-volume memory clinic in Orange County, California. The primary inclusion criterion is an MPI (EMBIC Corporation) of 65 or below. Eligibility criteria also included: age at least 50 years old, Functional Assessment Staging Test (FAST) stage 2–4, English fluency, possession of and ability to operate an internet-connected computer, and ability to converse with a coach telephonically. Exclusion criteria: diagnosis of non-AD neurodegenerative disorder (e.g., Lewy body dementia and frontotemporal dementia), diagnosis of cerebrovascular disease as the primary cause of cognitive impairment, participant or immediate family members with AD mutation in the *PSEN* or *APP* genes, or previous participation in a similar remote coaching intervention. Block randomization was used to achieve a 3:2 ratio of participants in the intervention arm to control arm. Biomarkers are not used as part of inclusion/exclusion criteria. However, a review of records of the first 39 participants enrolled in COCOA found 22 with previous cerebrospinal fluid or positron emission tomography studies to assay amyloid. All 22 of these were positive for amyloid, meeting the National Institute on Aging–Alzheimer's Association (NIA-AA) Research Framework's definition of biomarker positivity.[8]

3.3 | Personalized remote coaching and behavioral intervention

Participants in the control arm receive standard of care plus written guidelines for diet, exercise, and cognitive training. Data-driven remote health coaching is provided to participants in the intervention arm.

TABLE 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist for the COCOA trial[11]

Item	Domain	Implementation
1	Title	Coaching for Cognition in Alzheimer's (COCOA)
2	Trial registration	ClinicalTrials.gov NCT03424200
3	Protocol version	Version 1
4	Funding	Alzheimer's Translational Pillar of Providence St. Joseph Health
5	Roles and responsibilities	Clinical oversight: WRS; Analysis oversight: JCR; Research coordination: JH, DF, LH, RR, AS, SP; Data-driven recommendations: JCL, KJ; Coaching: MKR; Psychometrics: LD
6	Background and rationale	Multimodal interventions are in wide use. Other therapies are ineffective. Multimodal interventions need to be tested for efficacy. Data need to be generated to enable personalization, mechanistic insight, and causal reasoning. These pilot data will also aid in design of future trials.
7	Objectives	(1) Generate dense data on a diverse longitudinal cohort; (2) test the hypothesis that personalized data-driven coached lifestyle interventions ameliorate cognitive decline in a real-world setting.
8	Trial design	Prospective dense-data longitudinal randomized controlled trial (RCT) and cohort study
9	Study setting	High-volume memory clinic in Orange County, California
10	Eligibility criteria	Memory Performance Index (MPI) ≤ 65[a]
11	Interventions	Data-driven personalized remotely coached multimodal lifestyle interventions[a]
12	Outcomes	MPI, Functional Staging Assessment Test (FAST), descriptive and mechanistic molecular models[a]
13	Participant timeline	See Table 2
14	Sample size	Target enrollment is 200 participants
15	Recruitment	Flyers and provider outreach in Orange County, California
16	Assignment of interventions	Block randomization, min = 4 max = 8
17	Blinding	Participants not blinded; assessments blinded[a]
18	Data collection methods	As described in Zubair et al.[44]
19	Data management	As described in Zubair et al.[44]
20	Statistical methods	Linear mixed model[a]
21	Data monitoring	Lifestyle interventions are low risk; data monitoring is managed by the PI
22	Harms	Conceivable risks include data breaches and effects from blood draws
23	Auditing	Institutional and IRB auditing, at the discretion of these institutions
24	Research ethics approval	Western Institutional Review Board (WIRB) protocol # 20172152
25	Protocol amendments	None
26	Consent or assent	Informed consent is obtained from participants.
27	Confidentiality	Personal health information is maintained in confidentiality.
28	Declaration of interests	WS is an employee of EMBIC Corporation.
29	Access to data	Authorized research staff
30	Ancillary and post-trial care	None
31	Dissemination policy	Results will be published in peer-reviewed journals.

[a]Described in more detail in the main body of the text.
Abbreviations: IRB, institutional review board; PI, principal investigator.

Our expectation is that COCOA arms will not just enable testing the effectiveness of coaching, but also stratify participants by "dose" of recommended interventions. For example, we expect that individuals in the coached arm will exercise more and have a healthier diet than those in the control arm. A dataset of individuals with a range of intervention doses enriches systems biology analyses.

The coach facilitates interpretation and communication of participants' clinical, genomic, and other biological data and uses these data to develop personalized interventions. Coaches are registered dietitians or registered nurses. Coaching calls typically occur on a monthly basis, with e-mail and text communication occurring between the monthly calls. Clinical and genetic data are available for participants via a web

TABLE 2 COCOA trial timeline (months)

	Screen	Enroll	Baseline	4	8	12	18	24
Consent & screening	x							
Randomization		x						
Wellness coaching			x	X	X	x	X	x
Medical record release/collection	x					x		x
Standard neuro/physical evaluation			x					
Clinical chemistry data			x	X	X	x	x	x
Stool and saliva samples			x			x		x
Lifestyle data			x	X	X	x	x	x
Anthropometrics			x	X	X	x	x	x
Participant questionnaires			x	X	X	x	x	x
MCI Screen	x		x	X	X	x	x	x
Healthy brain checklist			x	X	X	x	x	x
The Delis-Kaplan Executive Functioning System			x			x		x
MoCA			x			x		x
Functional Staging Assessment Test (FAST)	x		x			x		x

Note: Wellness coaching and lifestyle data collection occurs at least once a month (extra columns for these are not displayed).
Abbreviations: COCOA, Coaching for Cognition in Alzheimer's; MoCA, Montreal Cognitive Assessment.

dashboard and mobile app, which they could also use to communicate with their coach and schedule calls or blood draws. Coaches provided specific recommendations to address out-of-range clinical lab results based on clinical practice guidelines, published scientific evidence, or professional society guidelines. Examples of the evidence behind the coaching recommendations include guidelines from the American Heart Association or American Diabetes Association,[15–17] comprehensive lifestyle interventions such as those developed for the Diabetes Prevention Program (DPP),[18] nutrition recommendations such as those based on the DASH (dietary approaches to stop hypertension) dietary pattern[19] or MIND (Mediterranean DASH Intervention for Neurogenerative Delay) diet,[20] and exercise recommendations from the American College of Sports Medicine.[21] Clinical recommendations were further personalized in the context of the participant's health goals and relevant genetic predispositions. Coaches did not make recommendations solely based on genetic risk, although they might take genetics into account when developing a behavioral plan for an out-of-range biomarker. The behavioral intervention was based on Bandura's Social Cognitive Theory (SCT)[22] model of behavior change. SCT takes into account personal, behavioral, and environmental factors that influence an individual's behavior. Specific strategies used by coaches to support behavior change included cognitive behavioral therapy approaches,[23] motivational interviewing,[24] appreciative inquiry,[25] and habit-based coaching. Coaches were trained in all these modalities and adapted their work with each individual to meet them where they were in terms of readiness for behavior change.

Using an individuals' biological, activity, and behavioral data the coach supports adoption and maintenance of healthy behaviors including nutrition, physical activity, stress management, weight management, and adherence to medical regimens. All diet, lifestyle, and other recommendations are based on standard, well-researched, and published interventions. Knowledge for genetics-based coaching is limited but growing. For example, increased salt vigilance is recommended for those with genetic underpinnings for salt sensitivity. In most individuals, the main foci of coaching are diet, exercise, lipids, blood pressure, and weight. The MIND diet is the basis for dietary coaching, modified as necessary by personal tolerance and circumstances.[26] Other examples of possible personalization include (1) if omega-3 blood markers are low, recommend supplementation; (2) if lipids are high, reduce saturated fats; (3) if blood sugar is elevated, reduce carbohydrates. These genres of personalized recommendations have been successful in increasing healthy lifestyle in previous studies (e.g., Nothwehr[27]). We include recommendations that might be considered directed toward overall health metrics such as heart health, blood sugar, and stress, as well as those that might be specifically linked to mechanisms postulated to cause or potentiate AD, such as inflammation.[28] We include all of these recommendations because we hypothesize that all of these interventions can target at least some systems that can contribute to progression on the clinical AD spectrum.

3.4 | Cognitive training

Brain training is primarily implemented with Posit Science's BrainHQ web-based training tools. The National Academies listed evaluation of cognitive training as a priority for future research.[29] The selection, duration, and frequency of training exercises for COCOA were chosen based on data and results from the ACTIVE trial as well as other trials testing subsets of BrainHQ exercises.[30] A set of validated

exercises focuses on aspects of perception and cognition, including processing speed, accuracy, cognitive control, sensory discrimination, and working memory.[31–38] Data from studies in cognitively impaired populations suggests that training is most effective if done daily.[39–43] Therefore, we prescribe 30 minutes of cognitive training daily to the intervention arm over the 24-month course of participation. Coaches encourage participants to complete the full training schedule, but allow for attenuation (e.g., fewer days per week) for those who find the schedule too intense. The difficulty and sequencing of the exercises are adaptive, so no participants should find the exercises too hard or too easy; however, in extreme cases we seek alternative cognitive training options. Training will be delivered in three sequential stages: (1) base plus additional low-level perceptual discrimination exercises, (2) base plus memory exercises, and (3) base plus high-level facial processing and social cognition exercises. These exercises will be provided over the 2-year course of participation. Data from BrainHQ is collected at each session, including the frequency, duration of training, and score for each exercise. COCOA will be the first study to intervene with BrainHQ for 24 months; most studies of cognitive training interventions are for 1 year or less (e.g., FINGER).[6] The BrainHQ training schedule is provided in Table S1 in supporting information.

3.5 | Assessments

3.5.1 | Cognition

Each patient will be assessed for cognitive and functional abilities using (1) MCIS administered at baseline and at 4, 8, 12, 18, and 24 months; (2) the Delis-Kaplan Executive Function System administered at baseline and 12 and 24 months; and (3) the Montreal Cognitive Assessment (MoCA) administered at baseline and at 12 and 24 months. MCIS administration is offset from the other tests by 2 weeks to avoid interference effects. The MCIS can be administered frequently because multiple distinct wordlists prevent learning effects.[13]

3.5.2 | Genetic data

At baseline, DNA is extracted from blood for genomic analysis.

3.5.3 | Blood analyses

Blood is collected at baseline and at 4, 8, 12, 18, and 24 months at a phlebotomy center run by an independent CLIA-certified laboratory (LabCorp, Inc.). Blood is analyzed for a wide range of clinical chemistries (aka, "clinical labs") and nutritional biomarkers as enumerated in Zubair et al.:[44] 443 proteins associated with neurobiology, cardiovascular disease, and inflammation performed by Olink Bioscience with targeted chip-based proteomics, and >1000 metabolites performed by Metabolon with mass spectrometry.

3.5.4 | Microbiome and cortisol

Stool samples for gut microbiome composition and saliva samples for stress hormone levels are collected at baseline and at 12 and 24 months by the participants at home. Each saliva collection for cortisol will include four samples over a single day.

3.5.5 | Lifestyle data

Physical activity, heart rate, and sleep data are collected by using a FitBit tracker.

3.5.6 | Anthropometrics

Body weight and waist circumference are collected at baseline and at 4, 8, 12, 18, and 24 months.

3.5.7 | Questionnaires

Questionnaire data will be collected from the participants at baseline, and at 4, 8, 12, 18, and 24 months. Questionnaires include: (1) the Big Five Personality Survey, a personality questionnaire assessing five dimensions of personality;[45] (2) Perceived Stress Scale 4 (PSS-4), a measure of perceived stress;[46–47] (3) Oxford Happiness Questionnaire,[48] a measure of an individual's degree of happiness and life satisfaction; (4) personal and family medical history and vitals including height, weight, medication and supplement usage, and coaching preferences; (5) Arivale digestion & lifestyle questionnaire, a questionnaire assessing digestive symptoms, diet, exercise, sleep, alcohol use, drug use, and environment;[49–50] and (6) the Patient Health Questionnaire (PHQ-9) for screening, diagnosing, monitoring, and measuring severity of depression.[51]

3.5.8 | Function

The FAST will be used at baseline and 12 and 24 months. The FAST is an internationally validated, semi-quantitative measure of the functional changes in AD from the entirely asymptomatic stage to severe dementia.[52–54]

3.6 | Primary analysis

To test our primary hypothesis, we will use a linear mixed model (LMM) to compare the differences in cognitive trajectories between the two arms. Power calculations for LMMs require estimation of several parameters.[55] One of the resources to be created by the COCOA trial will be pilot data to improve these estimates for future trials. In lieu of firm parameter estimates, we used two approaches to gain

confidence that COCOA will be adequately powered. First, we evaluated power over a range of possible values. Second, we surveyed the literature for comparable completed trials. For the COCOA trial design for an effect size of 3 (units = MPI points), random intercept variance of 40, random slope variance of 20, slope-intercept correlation of 0.8, and residual variance of 10, we would need 84 total number of participants (N) to achieve 80% power (alpha = 0.05). For an effect size of 2, N would need to be 190. These are conservative choices for parameters; we expect actual power to be higher. For example, for an effect size of 1, using variance estimates from Ng et al.[56] applied to the COCOA design, 80% power is achieved with N = 36.

3.7 | Systems analyses

One goal of systems biology is to use sufficient prior knowledge of physiology to enable mechanistic inferences from large-scale datasets acquired from a single individual. This approach permits one to quantitatively address plausibility and coherence elements of epistemology.[9] Mechanistic knowledge of physiology is increasing rapidly and is increasingly easy to access.[57] For example, we know that carbohydrate consumption increases serum glucose, insulin, and HgA1C; our prior knowledge includes knowing that such increases are time dependent and modifiable by factors such as medications and exercise. As the amount of prior knowledge increases, the set of data is increasingly a single measurement of the individual as a whole rather than a set of independent observations requiring disjoint statistical analyses and multiple test corrections.[58] One should not wait for complete knowledge of a system before embarking on dense data collection in a clinical trial; to do so would needlessly delay clinical research and prolong human suffering. The richness of knowledge produced from COCOA will grow with time, both as prior general knowledge of physiology increases, and as additional datasets from neurodegeneration clinical studies provide additional context and comparison.[59] It is also our hope and plan that future scientists will create and test hypotheses and perform analyses using our data that we and other contemporary scientists can neither conceive nor imagine. Our protocol is designed to provide data to enable such analyses. There should be value in COCOA data even if no significant difference in primary outcome measure is observed between arms. The majority of the value of COCOA data is expected to come from systems analyses.

For planned COCOA systems analyses, we will combine existing knowledge with new dense data to produce novel insights. Human molecular physiology is increasingly understood, providing increasingly rich context and coherence for these analyses. For example, in one such analysis we will create a hierarchy of concepts related to dementia causation as an instantiation of existing knowledge. We will then portray static and longitudinal correlations between variables in the context of this existing tree of knowledge (Figure 1). Dense molecular data also enable insights from the analysis of individual trajectories.[60] Composite or synthetic biomarkers formed from functions of individual biomarker values can be used to connect physiology such as biological aging or properties of the gut microbiome to particular outcomes.[61–62] Dose-response and time dependency can be considered.[9] Regulation of molecular subsystems can be assayed with tools such as differential rank conservation.[63]

4 | DISCUSSION

COCOA and its sister PREVENTION trial[64] are together designed as pilot studies to illuminate and guide future trial designs of multimodal therapies for individuals on the spectrum of ADRD. Although these studies are similarly designed, and test a similar hypothesis in different settings, they also provide complementary data: COCOA explores a broader, more diverse population of individuals with dementia; PREVENTION focuses on individuals within the AD spectrum as defined by the 2018 NIA-AA Research Framework.[8] In broad clinical practice, many individuals carry a diagnosis of AD without having been tested for an AD biomarker.[65] By analogy, if one were studying the physics of billiard balls, it would be of great use to have two sets of experiments: (1) limited diversity experiments with angle and force on the cue ball invariant, and (2) data acquired from breaks using a range of forces and break angles. One study establishes parameters of variation and focuses epistemology on a narrow slice of natural history, increasing statistical power at the loss of generalizability. The other study explores more dimensions and can reveal new phenomena.

Studies similar to COCOA and PREVENTION include FINGER and its successors.[66] These studies focus on at-risk asymptomatic states to early symptomatic stages of late-onset dementia, including AD. COCOA and PREVENTION intend to enroll early to moderate stages, so will augment and extend the range of the studied ADRD spectrum. There are few other systematic studies of multimodal intervention in AD. One proof-of-concept study has shown that metabolic factors, including fasting serum glucose, homeostatic model assessment for insulin resistance, vitamin D, and high-sensitivity C-reactive protein, improved significantly after multimodal intervention, and suggested that these may contribute to improvement in cognitive trajectory.[67] In a cohort studied by Isaacson et al.,[10] compliance with a multimodal intervention was associated with cognitive improvement, lending support to the hypothesis that coaching will also lead to improved cognition through increased compliance.

Scientific wellness, a translational application of systems biology, seeks to use personal, dense, dynamic data (PD3) to enhance wellness, prevent disease, and reverse disease at its earliest stages of inception.[68] These PD3 data "clouds" contain a wide array of molecular data, including genomes, proteomes, metabolomes, clinical chemistries, microbiomes, and health data from wearable devices. PD3 clouds enable many analyses, including: (1) correlations and connections among genetic, molecular, clinical, and outcome data that can be used to help suggest candidate biomarkers and inform therapeutic strategies; (2) identification of wellness to disease transition states; (3) stratification of AD subtypes and clinical trajectories;[67–69] and (4) outlier analyses. PD3 clouds enable studies to leverage previously collected data and external datasets. In turn, future studies can leverage present and past PD3-cloud studies. For example, the use of synthetic

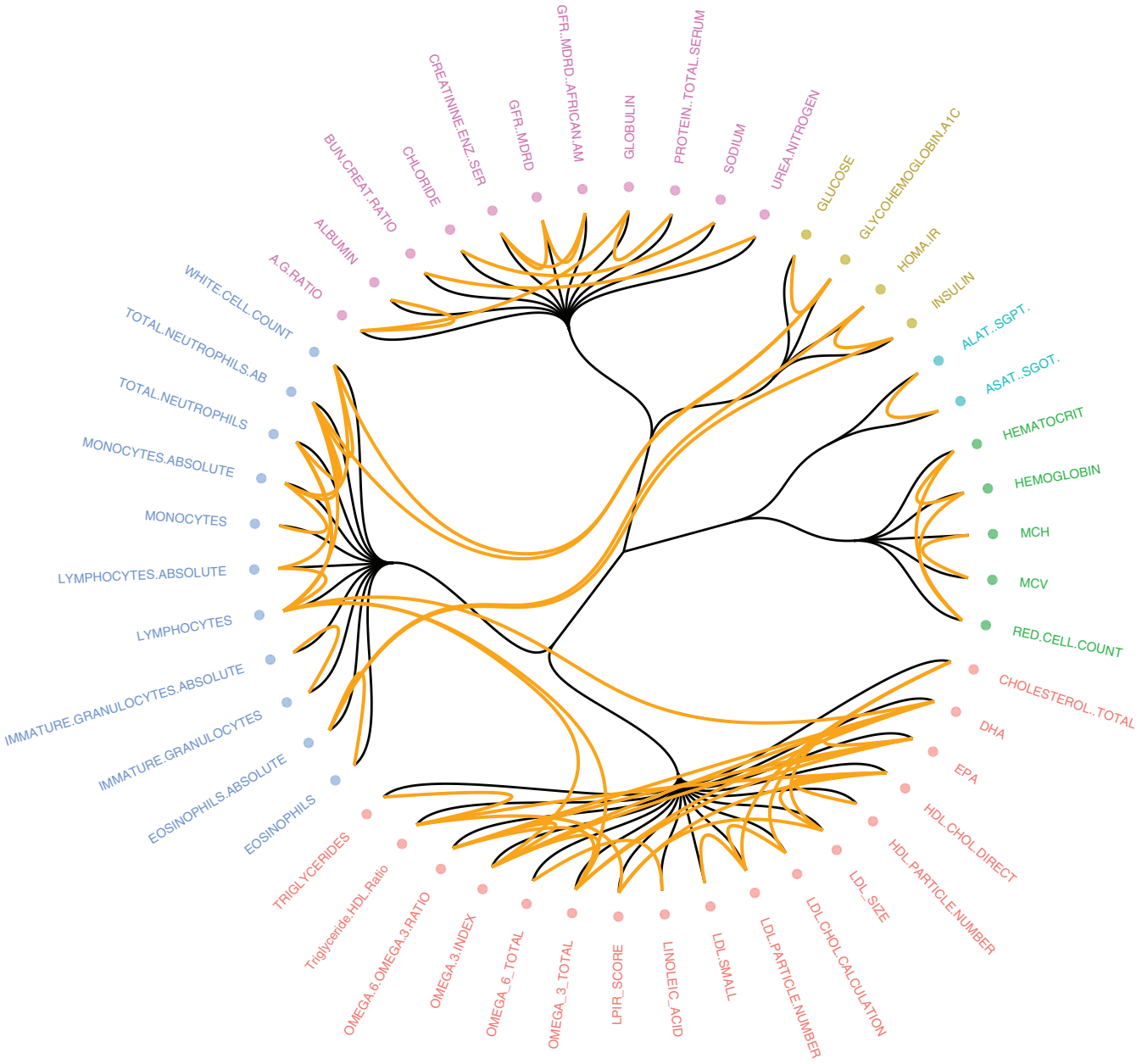

FIGURE 1 Hierarchical edge bundling. This diagram illustrates the basic concept of systems biology analyses: the marriage of pre-existing knowledge with new data. In this simple example, pre-existing knowledge is in the form of a hierarchical tree that clusters clinical chemistries by biological function (black). For example, new data in the form of correlations between clinical laboratory values can be superimposed on this tree in the form of chords connecting correlated values (orange). Of particular interest are chords that connect chemistries in different biological-function classes. Such insights are brought out by the combination of old knowledge with new data

controls requires high-quality dense data from previous trials. Encouraging current trials to provide data for synthetic controls for future trials should be a policy priority.[70]

A decade ago, incorporation of pharmacogenomic marker discovery into clinical trials was considered impractical due to the multiple testing problems that arose when data were analyzed in the absence of contextual knowledge.[71] Furthermore, budget constraints force a trade-off in trial design: more participants with less data acquired for each participant, or fewer participants with more data acquired for each participant. Increases in biomedical knowledge accumulation coupled to reductions in the cost of molecular data acquisition, particularly for the proteome and metabolome, have changed the balance of these considerations (e.g., Carvalho et al.[72] and Cuperlovic-Culf & Badhwar[73]). Part of the intention of the COCOA trial is to test the epistemological value of dense data gathered longitudinally for a trial with a relatively small number of participants.

The objection of futility is sometimes leveled at trials that test complex interventions. It might be argued that multiple interventions

must be tested in a combinatorial design to thoroughly test all interventions individually, and in all combinations which, for sufficiently complex interventions, would take more time and money than could exist in the universe. Or it could be argued that sufficiently complex diseases have such a diverse range of patients that no reasonable inclusion criteria could recruit a sufficiently homogenous cohort except by recruiting thousands of individuals; world economics and limited patient pools permit very few such large trials. If such arguments prevailed, innovative and/or non-patentable hypotheses would never be tested. We put forward the claim, which must be tested repeatedly with trials such as COCOA, that these criticisms are relative but not absolute criticisms, and do not constitute deal breakers. No single trial need test all combinations, nor is it absolutely necessary to disentangle a set of interventions that are together beneficial. Not all of these problems will be completely solved by the COCOA trial. COCOA is a start.

There are trade-offs when including multiple goals in a trial design. Multiobjective optimization will generally result in a Pareto-optimal front with solutions that are suboptimal for any particular goal. If one goal requires as many participants (N_p) as possible, then the cost per participant must be driven down to pack as many participants as possible into a trial budget. This may increase power to test a particular hypothesis, but at a sacrifice in overall knowledge generated and in the future value of the data. Thus, failure to gather dense data during a trial, and then to share these data, may result in possible ethical failure to maximize the value of the volunteerism of trial participants. For COCOA, we have a chosen a relatively small N_p, reducing the power of the study to test our primary hypothesis, in exchange for these extra molecular and clinical data. Dense molecular and clinical data trials are designed to be of increasing value in the future. They may allow exploration of hypotheses not conceived prior to or during the trial. Much understanding of mechanism relies on elucidation of systems, and much of this elucidation will happen in the future. For example, the identification of xenobiotics from mass spectra is still imperfect. In the future we will have more identification of these xenobiotics. Because we already have the spectra, no further clinical study necessarily needs to be done to accrue this future benefit. Furthermore, the relationship of diet and other factors such as microbiome to these xenobiotics will be better understood. This steady accumulation of future knowledge will enable better placement of these xenobiotics into causal relationships, with knowledge gained from COCOA accruing long after the trial itself has closed.

There has been a growing awareness of the need for systems-biology–based clinical trials.[74–75] Novel clinical trial designs have leveraged dense data for patient stratification, arm assignment, and other innovations.[76] One goal of systems biology is to use prior knowledge to enable mechanistic inferences from newly generated data. The more prior knowledge, the better are new inferences. Mechanistic understanding ultimately allows knowledge to be generated even from single individuals, much as an auto mechanic can use causality inferences to diagnosis a single car. It is important to gather data in anticipation of future analyses that will leverage as-yet-unlearned knowledge to test hypotheses that have yet to be conceived.[59] Trials must broadly share their data to best enable epistemological synergy between datasets.

Recruitment and retention of diverse participants is particularly important for personalized data-driven trials of conditions that have multiple causes and multiple treatments. Dementia is one such disease. Part of personalizing therapies for these conditions includes consideration of genetics/race and culture/ethnicity. Several barriers to inclusion are modifiable.[77,78] Our dense-data trial design specifically addresses the modifiable barrier created by strict inclusion/exclusion criteria. The justification for this barrier is usually to ensure statistical homogeneity. Because dense-data analyses thrive on diversity, dense-data trials can be designed with less strict enrollment criteria. Although heterogeneity might decrease power of some classic statistics, it is likely to enrich systems analyses by illuminating more topography of the state-of-the-system landscape. Due to pilot-study constraints, a number of barriers to diversity remain for COCOA. Of these, the largest is the resource-dictated limitation of our recruitment site to Orange County, California; our studied population will reflect this area of Southern California. Future studies could abrogate this restriction by either going completely remote or having resources to fund recruitment and testing sites in multiple locations.

AD in conjunction with other dementias is on its way to becoming the most common cause of death and suffering in the United States and the world. Drugs that have been approved for clinical use such as donepezil and memantine have small effects on symptoms, but cannot reverse disease, or even slow down underlying pathological progression. Molecular understanding of AD and dementia will be critical to design therapies that directly affect the pathology of disease progression. This pathology is almost certainly sufficiently complex that the best therapies will be multimodal. This is true for other diseases such as hypertension. For example, in severe hypertension lifestyle interventions and multiple drugs are used as a multimodal intervention. Deep insight into the molecular and physiological mechanisms of hypertension pathology enable the design and personalization of such therapies. We anticipate that similar progress can be made for AD by other trials building on the backs of trials such as COCOA.[64]

Transformative new technologies enable exploration of new dimensions of patient data space. A decade ago, affordable personalized whole-genome sequencing revolutionized diagnosis of rare diseases.[79] Now, other inexpensive molecular technologies are revolutionizing clinical trials, diagnostics, and therapy for AD. Dense molecular and clinical data trial design can also be applied to many other clinical conditions, ranging from COVID-19[80] to Parkinson's disease.[81] We expect this trial design can enable not just paradigm shifts in the conduct of clinical trials, but also innovations in therapy, including a focus on multimodal therapies that are delivered through coaching interventions.

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CONFLICTS OF INTEREST

Drs. Shankle and Hara are employees of EMBIC Corporation. There are no other conflicts of interest for any of the authors. Author disclosures are available in the supporting information.

REFERENCES

1. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. https://doi.org/10.1016/S0140-6736(20)30367-6
2. Buckinx F, Aubertin-Leheudre M. Nutrition to prevent or treat cognitive impairment in older adults: a GRADE recommendation. *J Prev Alzheimers Dis*. 2021;8(1):110-116. 10.14283/jpad.2020.40
3. Zhu L, Li L, Wang L, Jin X, Zhang H. Physical activity for executive function and activities of daily living in AD patients: a systematic review and meta-analysis. *Front Psychol*. 2020;11:560461. Published 2020 Dec 3. https://doi.org/10.3389/fpsyg.2020.560461
4. Demurtas J, Schoene D, Torbahn G, et al. Physical activity and exercise in mild cognitive impairment and dementia: an umbrella review of intervention and observational studies. *J Am Med Dir Assoc*. 2020;21(10):1415-1422.e6. https://doi.org/10.1016/j.jamda.2020.08.031
5. Shah TM, Weinborn M, Verdile G, Sohrabi HR, Martins RN. Enhancing cognitive functioning in healthly older adults: a systematic review of the clinical significance of commercially available computerized cognitive training in preventing cognitive decline. *Neuropsychol Rev*. 2017;27(1):62-80. https://doi.org/10.1007/s11065-016-9338-9
6. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255-2263. https://doi.org/10.1016/S0140-6736(15)60461-5
7. Toman J, Klímová B, Vališ M. Multidomain lifestyle intervention strategies for the delay of cognitive impairment in healthy aging. *Nutrients*. 2018;10(10):1560. Published 2018 Oct 21. https://doi.org/10.3390/nu10101560
8. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. https://doi.org/10.1016/j.jalz.2018.02.018
9. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol*. 2015;12:14. Published 2015 Sep 30. https://doi.org/10.1186/s12982-015-0037-4
10. Isaacson RS, Ganzer CA, Hristov H, et al. The clinical practice of risk reduction for Alzheimer's disease: a precision medicine approach. *Alzheimers Dement*. 2018;14(12):1663-1673. https://doi.org/10.1016/j.jalz.2018.08.004
11. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207. https://doi.org/10.7326/0003-4819-158-3-201302050-00583
12. Price ND, Magis AT, Earls JC, et al. A wellness study of 108 individuals using personal, dense, dynamic data clouds. *Nat Biotechnol*. 2017;35(8):747-756. https://doi.org/10.1038/nbt.3870
13. Shankle WR, Mangrola T, Chan T, Hara J. Development and validation of the Memory Performance Index: reducing measurement error in recall tests. *Alzheimers Dement*. 2009;5(4):295-306. https://doi.org/10.1016/j.jalz.2008.11.001
14. Wainberg M, Magis AT, Earls JC, et al. Multiomic blood correlates of genetic risk identify presymptomatic disease alterations. *Proc Natl Acad Sci U S A*. 2020;117(35):21813-21820. https://doi.org/10.1073/pnas.2001429117
15. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e563-e595. https://doi.org/10.1161/CIR.0000000000000677
16. Nierenberg JL, Li C, He J, et al. Blood pressure genetic risk score predicts blood pressure responses to dietary sodium and potassium: the GenSalt Study (Genetic Epidemiology Network of Salt Sensitivity). *Hypertension*. 2017;70(6):1106-1112. https://doi.org/10.1161/HYPERTENSIONAHA.117.10108
17. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127-e248. https://doi.org/10.1016/j.jacc.2017.11.006
18. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care*. 2002;25(12):2165-2171. https://doi.org/10.2337/diacare.25.12.2165
19. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336(16):1117-1124. https://doi.org/10.1056/NEJM199704173361601
20. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. *Alzheimers Dement*. 2015;11(9):1015-1022. https://doi.org/10.1016/j.jalz.2015.04.011
21. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1081-1093. https://doi.org/10.1161/CIRCULATIONAHA.107.185649
22. Bandura A. Health promotion from the perspective of social cognitive theory. *Psychol Health*. 2007;13:623-649.
23. Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev*. 2006;26(1):17-31. https://doi.org/10.1016/j.cpr.2005.07.003
24. Lundahl B, Moleni T, Burke BL, et al. Motivational interviewing in medical care settings: a systematic review and meta-analysis of randomized controlled trials. *Patient Educ Couns*. 2013;93(2):157-168. https://doi.org/10.1016/j.pec.2013.07.012
25. Whitney DD, Trosten-Bloom A. *The Power of Appreciative Inquiry*. San Francisco, CA: Berrett-Koehler Publishers; 2010.
26. Kheirouri S, Alizadeh M. MIND diet and cognitive performance in older adults: a systematic review. *Crit Rev Food Sci Nutr*. 2021;1-19. https://doi.org/10.1080/10408398.2021.1925220
27. Nothwehr F. People with unhealthy lifestyle behaviours benefit from remote coaching via mobile technology. *Evid Based Nurs*. 2013;16(1):22-23. https://doi.org/10.1136/eb-2012-100953
28. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement (N Y)*. 2018;4:575-590. Published 2018 Sep 6. https://doi.org/10.1016/j.trci.2018.06.014
29. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Downey A, Stroud C, Landis S, et al., eds. *Preventing Cognitive Decline and Dementia: A Way Forward*. Washington (DC): National Academies Press (US); 2017.
30. Mahncke HW, Connor BB, Appelman J, et al. Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci*

U S A. 2006;103(33):12523-12528. https://doi.org/10.1073/pnas.0605194103
31. Edwards JD, Xu H, Clark DO, Guey LT, Ross LA, Unverzagt FW. Speed of processing training results in lower risk of dementia. *Alzheimers Dement (N Y)*. 2017;3(4):603-611. Published 2017 Nov 7. https://doi.org/10.1016/j.trci.2017.09.002
32. Unverzagt FW, Guey LT, Jones RN, et al. ACTIVE cognitive training and rates of incident dementia. *J Int Neuropsychol Soc*. 2012;18(4):669-677. https://doi.org/10.1017/S1355617711001470
33. Van Vleet TM, Chen A, Vernon A, Novakovic-Agopian T, D'Esposito MT. Tonic and phasic alertness training: a novel treatment for executive control dysfunction following mild traumatic brain injury. *Neurocase*. 2015;21(4):489-498. https://doi.org/10.1080/13554794.2014.928329
34. Van Vleet TM, DeGutis JM, Merzenich MM, Simpson GV, Zomet A, Dabit S. Targeting alertness to improve cognition in older adults: a preliminary report of benefits in executive function and skill acquisition. *Cortex*. 2016;82:100-118. https://doi.org/10.1016/j.cortex.2016.05.015
35. Mahncke HW, Bronstone A, Merzenich MM. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. *Prog Brain Res*. 2006;157:81-109. https://doi.org/10.1016/S0079-6123(06)57006-2
36. Gooding AL, Choi J, Fiszdon JM, et al. Comparing three methods of computerised cognitive training for older adults with subclinical cognitive decline. *Neuropsychol Rehabil*. 2016;26(5-6):810-821. https://doi.org/10.1080/09602011.2015.1118389
37. Edwards JD, Valdés EG, Peronto C, et al. The efficacy of insight cognitive training to improve useful field of view performance: a brief report. *J Gerontol B Psychol Sci Soc Sci*. 2015;70(3):417-422. https://doi.org/10.1093/geronb/gbt113
38. Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. *J Am Geriatr Soc*. 2009;57(4):594-603. https://doi.org/10.1111/j.1532-5415.2008.02167.x
39. Adcock RA, Dale C, Fisher M, et al. When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia. *Schizophr Bull*. 2009;35(6):1132-1141. https://doi.org/10.1093/schbul/sbp068
40. Bamidis PD, Fissler P, Papageorgiou SG, et al. Gains in cognition through combined cognitive and physical training: the role of training dosage and severity of neurocognitive disorder. *Front Aging Neurosci*. 2015;7:152. Published 2015 Aug 7. https://doi.org/10.3389/fnagi.2015.00152
41. Charvet LE, Yang J, Shaw MT, et al. Cognitive function in multiple sclerosis improves with telerehabilitation: results from a randomized controlled trial. *PLoS One*. 2017;12(5):e0177177. Published 2017 May 11. https://doi.org/10.1371/journal.pone.0177177
42. Lewandowski KE, Sperry SH, Ongur D, Cohen BM, Norris LA, Keshavan MS. Cognitive remediation versus active computer control in bipolar disorder with psychosis: study protocol for a randomized controlled trial. *Trials*. 2016;17(1):136. Published 2016 Mar 12. https://doi.org/10.1186/s13063-016-1275-7
43. Fisher M, Holland C, Merzenich MM, Vinogradov S. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *Am J Psychiatry*. 2009;166(7):805-811. https://doi.org/10.1176/appi.ajp.2009.08050757
44. Zubair N, Conomos MP, Hood L, et al. Genetic predisposition impacts clinical changes in a lifestyle coaching program. *Sci Rep*. 2019;9(1):6805. Published 2019 May 2. https://doi.org/10.1038/s41598-019-43058-0
45. John OP, Naumann LP, Soto CJ. Paradigm shift to the integrative Big-Five trait taxonomy: history, measurement, and conceptual issues. In: John OP, Robins RW, Pervin LA, eds. *Handbook of personality: Theory and research*. New York, NY: Guilford Press; 2008:114-158.
46. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983;24(4):385-396.
47. Warttig SL, Forshaw MJ, South J, White AK. New, normative, English-sample data for the Short Form Perceived Stress Scale (PSS-4). *J Health Psychol*. 2013;18(12):1617-1628. https://doi.org/10.1177/1359105313508346
48. Hills P, Argyle M. The Oxford Happiness Questionnaire: a compact scale for the measurement of psychological well-being. *Pers Individ Differ*. 2002;33(7):1073-1082.
49. Zimmer A, Korem Y, Rappaport N, et al. The geometry of clinical labs and wellness states from deeply phenotyped humans. *Nat Commun*. 2021;12(1):3578. Published 2021 Jun 11. https://doi.org/10.1038/s41467-021-23849-8
50. Lean ME, Anderson AS, Morrison C, Currall J. Evaluation of a dietary targets monitor. *Eur J Clin Nutr*. 2003;57(5):667-673. https://doi.org/10.1038/sj.ejcn.1601596
51. Costantini L, Pasquarella C, Odone A, et al. Screening for depression in primary care with Patient Health Questionnaire-9 (PHQ-9): a systematic review. *J Affect Disord*. 2021;279:473-483. https://doi.org/10.1016/j.jad.2020.09.131
52. Reisberg B. Dementia: a systematic approach to identifying reversible causes. *Geriatrics*. 1986;41(4):30-46
53. Reisberg B. Functional assessment staging (FAST). *Psychopharmacol Bull*. 1988;24(4):653-659
54. Reisberg B, Jamil IA, Khan S, et al. Staging dementia. In: Abou-Saleh MT, Katona C, Kumar A, eds. *Principles and Practice of Geriatric Psychiatry*, 3rd ed. Hoboken, NJ: John Wiley & Sons, Ltd.; 2010:162-169
55. Donohue MC, Edland SD, Gamst AC. Power for linear models of longitudinal data with applications to Alzheimer's Disease Phase II study design. https://mran.microsoft.com/snapshot/2015-07-10/web/packages/longpower/vignettes/longpower.pdf. Published January 5, 2015. Accessed February 22, 2022
56. Ng KP, Ng A, Assam P, Heng E, Kandiah N. Role of cognitive enhancer therapy in Alzheimer's disease with concomitant cerebral white matter disease: findings from a long-term naturalistic study. *Drugs R D*. 2014;14(3):195-203. https://doi.org/10.1007/s40268-014-0057-5
57. Biomedical Data Translator Consortium. Toward a universal biomedical data translator. *Clin Transl Sci*. 2019;12(2):86-90. https://doi.org/10.1111/cts.12591
58. van der Greef J, Hankemeier T, McBurney RN. Metabolomics-based systems biology and personalized medicine: moving towards n = 1 clinical trials? *Pharmacogenomics*. 2006;7(7):1087-1094. https://doi.org/10.2217/14622416.7.7.1087
59. Bielekova B, Vodovotz Y, An G, Hallenbeck J. How implementation of systems biology into clinical trials accelerates understanding of diseases. *Front Neurol*. 2014;5:102. Published 2014 Jun 27. https://doi.org/10.3389/fneur.2014.00102
60. Magis AT, Rappaport N, Conomos MP, et al. Untargeted longitudinal analysis of a wellness cohort identifies markers of metastatic cancer years prior to diagnosis. *Sci Rep*. 2020;10(1):16275. Published 2020 Oct 1. https://doi.org/10.1038/s41598-020-73451-z
61. Earls JC, Rappaport N, Heath L, et al. Multi-Omic biological age estimation and its correlation with wellness and disease phenotypes: a Longitudinal Study of 3,558 Individuals. *J Gerontol A Biol Sci Med Sci*. 2019;74(Suppl_1):S52-S60. https://doi.org/10.1093/gerona/glz220
62. Wilmanski T, Rappaport N, Earls JC, et al. Blood metabolome predicts gut microbiome α-diversity in humans. *Nat Biotechnol*. 2019;37(10):1217-1228. https://doi.org/10.1038/s41587-019-0233-9
63. Eddy JA, Hood L, Price ND, Geman D. Identifying tightly regulated and variably expressed networks by Differential Rank Conservation (DIRAC). *PLoS Comput Biol*. 2010;6(5):e1000792. Published 2010 May 27. https://doi.org/10.1371/journal.pcbi.1000792
64. McEwen SC, Merrill DA, Bramen J, et al. A systems-biology clinical trial of a personalized multimodal lifestyle intervention for early

Alzheimer's disease. *Alzheimers Dement (N Y)*. 2021;7(1):e12191. Published 2021 Jul 20. https://doi.org/10.1002/trc2.12191
65. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol*. 2010;9(11):1118-1127. https://doi.org/10.1016/S1474-4422(10)70223-4
66. Kivipelto M, Mangialasche F, Snyder HM, et al. World-Wide FINGERS Network: a global approach to risk reduction and prevention of dementia. *Alzheimers Dement*. 2020;16(7):1078-1094. https://doi.org/10.1002/alz.12123
67. Rao RV, Kumar S, Gregory J, et al. ReCODE: a personalized, targeted, multi-factorial therapeutic program for reversal of cognitive decline. *Biomedicines*. 2021;9(10):1348. Published 2021 Sep 29. https://doi.org/10.3390/biomedicines9101348
68. Huang S, Hood L. Personalized, precision, and n-of-one medicine: a clarification of terminology and concepts. *Perspect Biol Med*. 2019;62(4):617-639. https://doi.org/10.1353/pbm.2019.0036
69. Geifman N, Kennedy RE, Schneider LS, Buchan I, Brinton RD. Data-driven identification of endophenotypes of Alzheimer's disease progression: implications for clinical trials and therapeutic interventions. *Alzheimers Res Ther*. 2018;10(1):4. Published 2018 Jan 15. https://doi.org/10.1186/s13195-017-0332-0
70. Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and external controls in clinical trials - A primer for researchers. *Clin Epidemiol*. 2020;12:457-467. Published 2020 May 8. https://doi.org/10.2147/CLEP.S242097
71. Pusztai L. Limitations of pharmacogenomic predictor discovery in Phase II clinical trials. *Pharmacogenomics*. 2007;8(10):1443-1448. https://doi.org/10.2217/14622416.8.10.1443
72. Carvalho AF, Solmi M, Sanches M, et al. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. *Transl Psychiatry*. 2020;10(1):152. Published 2020 May 18. https://doi.org/10.1038/s41398-020-0835-5
73. Cuperlovic-Culf M, Badhwar A. Recent advances from metabolomics and lipidomics application in Alzheimer's disease inspiring drug discovery. *Expert Opin Drug Discov*. 2020;15(3):319-331. https://doi.org/10.1080/17460441.2020.1674808
74. Escudier B, Heng DY, Smyth-Medina A, Porta C. Considerations for the design of future clinical trials in metastatic renal cell carcinoma. *Clin Genitourin Cancer*. 2014;12(1):1-12. https://doi.org/10.1016/j.clgc.2013.07.004. Epub 2013 Nov 9
75. Manem VSK, Salgado R, Aftimos P, Sotiriou C, Haibe-Kains B. Network science in clinical trials: a patient-centered approach. *Semin Cancer Biol*. 2018;52(Pt 2):135-150. https://doi.org/10.1016/j.semcancer.2017.12.006. Epub 2017 Dec 24
76. Pitzalis C, Choy EHS, Buch MH. Transforming clinical trials in rheumatology: towards patient-centric precision medicine. *Nat Rev Rheumatol*. 2020;16(10):590-599. https://doi.org/10.1038/s41584-020-0491-4. Epub 2020 Sep 4.
77. Indorewalla KK, O'Connor MK, Budson AE, Guess DiTerlizzi C, Jackson J. Modifiable barriers for recruitment and retention of older adults participants from underrepresented minorities in Alzheimer's disease research. *J Alzheimers Dis*. 2021;80(3):927-940. https://doi.org/10.3233/JAD-201081
78. Wong R, Amano T, Lin SY, Zhou Y, Morrow-Howell N. Strategies for the recruitment and retention of racial/ethnic minorities in Alzheimer disease and dementia clinical research. *Curr Alzheimer Res*. 2019;16(5):458-471. https://doi.org/10.2174/1567205016666190321161901
79. Roach JC, Glusman G, Smit AF, et al. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. *Science*. 2010;328(5978):636-639. https://doi.org/10.1126/science.1186802
80. Su Y, Chen D, Yuan D, et al. Multi-omics resolves a sharp disease-state shift between mild and moderate COVID-19. *Cell*. 2020;183(6):1479-1495.e20. https://doi.org/10.1016/j.cell.2020.10.037
81. Espay AJ, Schwarzschild MA, Tanner CM, et al. Biomarker-driven phenotyping in Parkinson's disease: a translational missing link in disease-modifying clinical trials. *Mov Disord*. 2017;32(3):319-324. https://doi.org/10.1002/mds.26913

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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