



Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE): Protocol



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ABSTRACT

Despite the ubiquity of normal age-related cognitive decline there is an absence of effective approaches for improving neurocognitive health. Fortunately, moderate intensity exercise is a promising method for improving brain and cognitive health in late life, but its effectiveness remains a matter of skepticism and debate because of the absence of large, comprehensive, Phase III clinical trials. Here we describe the protocol for such a randomized clinical trial called IGNITE (*Investigating Gains in Neurocognition in an Intervention Trial of Exercise*), a study capable of more definitively addressing whether exercise influences cognitive and brain health in cognitively normal older adults. We are conducting a 12-month, multi-site, randomized dose-response exercise trial in 639 cognitively normal adults between 65 and 80 years of age. Participants are randomized to (1) a moderate intensity aerobic exercise condition of 150 min/week ($N = 213$), (2) a moderate intensity aerobic exercise condition at 225 min/week ($N = 213$), or (3) a light intensity stretching-and-toning control condition for 150 min/week ($N = 213$). Participants are engaging in 3 days/week of supervised exercise and two more days per week of unsupervised exercise for 12 months. A comprehensive cognitive battery, blood biomarkers and battery of psychosocial questionnaires is assessed at baseline, 6 and 12-months. In addition, brain magnetic resonance imaging, physiological biomarkers, cardiorespiratory fitness, physical function, and positron emission tomography of amyloid deposition are assessed at baseline and at the 12-month follow-up. The results from this trial could transform scientific-based policy and health care recommendations for approaches to improve cognitive function in cognitively normal older adults.

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1. Introduction

The proportion of older adults in the population is expected to dramatically increase over the next 40 years, fueling fears of escalating healthcare costs due to a greater prevalence of age-related diseases and impairments, including cognitive decline. Most adults > 65 years old experience normal age-related losses in cognitive function and do not have dementia or mild cognitive impairment (MCI) [1]. Yet, despite the ubiquity of normal age-related cognitive decline, there is an absence of effective approaches for improving neurocognitive health. Despite the absence of well-established and effective approaches, there are several lifestyles and behaviors that have shown significant promise for influencing the trajectory of cognitive losses [2–6]. Moderate intensity exercise is one of these promising methods for improving brain and cognitive health in late life [7–10], but its effectiveness remains a matter of continued skepticism and debate [11]. Although many studies have reported that exercise improves cognitive and brain health in older adults, there are other studies that report null effects or indicate very small effect sizes [12–14]. The lack of scientific consensus about the benefits of exercise on cognitive and brain health is likely one key factor prohibiting its widespread prescription and adoption as a method for improving brain health [15]. Another critical limitation of the existing literature is the lack of consensus about how much exercise is needed to improve cognitive and brain outcomes [10]. Most studies examining dose of exercise have had small sample sizes or a limited scope of outcomes [16]. Yet, many other physiological and health-related outcomes (e.g., risk for cardiovascular disease and mortality, weight management) do vary by the dose of exercise such that engagement in greater amounts is predictive of better health outcomes [17–20]. However, there are also diminishing returns as the levels and volume of activity reach certain levels. Thus, in this study we sought to address the gap in knowledge about the dose-response nature of exercise on brain and cognitive outcomes. Here we describe a protocol for a Phase III multi-site randomized dose-response clinical trial called IGNITE (NCT02875301, R01AG053952). Given its unprecedented size and scope, the IGNITE trial is positioned to more definitively address whether exercise influences cognitive and brain health in cognitively normal older adults.

We focus here on cognitively normal older adults instead of individuals with mild cognitive impairment (MCI) or Alzheimer's disease (AD). It is estimated that ~30% of individuals > 65 years meet criteria for dementia or MCI, indicating that “normal” cognitive decline is far more prevalent than impairment [21]. Normal age-related cognitive changes are preceded by changes in the biochemistry, structure and function of brain regions including those supporting memory (hippocampus) and executive functions (prefrontal cortex; PFC) [22–27]. For example, it is estimated that 20–40% of cognitively normal adults have evidence of β -amyloid ($A\beta$) in their brain depending on age [21], and the presence of this peptide precedes cognitive decline as well as structural and functional brain changes in cognitively normal adults [28,29].

The IGNITE trial was designed to address several important unanswered questions: (1) Are the recommended public health guidelines of 150 min/week [30] of moderate intensity exercise sufficient for improving cognitive performance? (2) Does exercise influence brain structure and/or function? (3) Is there a dose-response effect of exercise on cognitive performance or brain structure/function, such that exercise that exceeds the recommended levels of 150 min/week results in even greater benefits in cognitive and brain health? (4) Can we identify possible mechanisms (e.g., cardiometabolic, inflammatory, neurotrophic, or psychosocial changes) by which exercise influences cognitive and brain health? (5) Are there factors (e.g., demographic characteristics, presence of brain $A\beta$, genotype) that attenuate or magnify the effects of exercise on brain, cognitive, and psychosocial health and contribute to the individual variability in intervention outcomes? And, (6) could changes in amyloid accumulation as a function of

participation in exercise explain any cognitive, brain, or psychosocial improvements? The absence of answers to these questions reflect significant gaps in our understanding and are several key factors limiting widespread adoption and prescription of exercise to ameliorate cognitive problems in late life; and these are the questions we aim to answer in this study.

2. Materials/methods

2.1. Summary of aims

The objective of the IGNITE study is to test several aims: (1) Examine whether a 12-month moderate intensity exercise intervention improves cognitive performance in older adults and whether these improvements occur in a dose-dependent manner; (2) Examine whether a 12-month exercise intervention augments MRI markers of brain health and whether these changes happen in a dose-dependent manner; (3) Examine whether cardiometabolic, inflammatory, neurotrophic, or psychosocial changes mediate improvements in brain and cognition; (4) Examine subgroup and individual differences (e.g., presence of brain $A\beta$, baseline fitness levels, genotype) that attenuate or magnify the effect of the exercise intervention on cognitive, brain, and psychosocial outcomes to better understand the factors that predict ‘responders’ versus ‘non-responders’ to the intervention; (5) Examine whether a 12-month exercise intervention influences the accumulation of amyloid in cognitively normal older adults and to determine whether changes in amyloid levels could be mediating improvements in cognitive, brain, or psychosocial outcomes. IGNITE is a multi-center, randomized, trial with three conditions: 150 min/week of moderate intensity exercise; 225 min/week of moderate intensity exercise; or 150 min of light intensity stretching and toning. The stretching and toning group will serve as an active control for the two experimental groups involving aerobic exercise. As a result of this design, changes observed in the aerobic groups can be attributed to the aerobic component of the intervention rather than to other, potentially confounding factors, such as social contact or expectancy effects. The study will enroll and randomize 639 cognitively normal, low active older adults. We hypothesize that the exercise intervention will enhance cognitive and brain health in a dose-dependent manner. We also hypothesize that exercise participation will decrease pro-inflammatory cytokines, central adiposity, arterial stiffness and insulin resistance and increase brain-derived neurotrophic factor (BDNF) levels. The favorable effects of exercise on cognition and brain health will be greatest for older adults with $A\beta$ burden and those with a genetic susceptibility for accelerated cognitive decline [31–33]. Finally, we predict that exercise will modify the rate of amyloid accumulation.

2.2. Primary outcome

The primary endpoint will be a composite score of executive function. More specifically, we are predicting that there will be a significant exercise-related improvement in executive function over the course of the 12-month period (i.e., Time x Group interaction term for executive function). Changes in composite scores of other cognitive domains including episodic memory and processing speed will be considered secondary outcomes. Our analysis plan focusing on a composite of executive function indicates that our primary outcome is not a measured outcome (e.g., Stroop task performance) but rather a latent factor composed of performance on several tasks, which is considered to more accurately represent the cognitive domain (as performance on any one task is not a reliable representation of any cognitive domain). The latent factors and loadings for executive function and other cognitive constructs will be determined based on a confirmatory factor analysis using baseline data.

2.3. Recruitment

Recruitment for IGNITE began in September of 2017, and the goal is to randomize 639 participants across three sites by December 2020 with an equal number at each site. Participants are 65–80 years of age, low active and cognitively normal according to a clinical adjudication process described below. Recruitment of racial and ethnic minorities is in proportion to the demographic representation at each of the three study sites: Boston, Massachusetts (25% black; 14% Hispanic; 7.3% Asian); Kansas City (11% black; 2.8% Hispanic; 1.5% Asian); Pittsburgh (26% black; 2.3% Hispanic; 4.4% Asian). We anticipate approximately 60% of the sample to be female. Recruitment strategies target community samples through newspapers, health system research registries, direct mailings, senior centers and churches, and online media (e.g., Facebook). Recruitment, enrollment, and randomization occurs on a rolling basis.

2.4. Eligibility

The eligibility criteria were crafted to recruit individuals who are relatively inactive, cognitively normal within broad limits, but who can safely engage in regular moderate intensity exercise (see Table 1). The goal was to create eligibility criteria that would maintain safety while maximizing generalization of the results to a broad population of older adults.

2.5. Study assessments

See Table 2 for a complete schedule of all study assessments.

2.6. Screening

Questions about engagement in structured exercise, medical history, safety to exercise (e.g., history of falls), and MRI safety are asked in an initial phone screen. The Telephone Interview of Cognitive Status [34] (TICS) is administered and only those that score > 25 (i.e., 26 or above) remain eligible. Participants are required to have a primary care physician (PCP) and be medically cleared to exercise and be safe for an

MRI scan before enrolling.

2.7. Cognitive testing and adjudication of MCI and dementia

The first baseline assessment session includes the collection of demographic, general health history, and medication use information, along with a battery of neuropsychological tests relevant for adjudication of cognitive status. The initial baseline session lasts approximately 2.5 h. All tests are double scored and double entered into a database by staff at the coordinating center (Pittsburgh) and any discrepancies resolved. The standardized scores and percentiles are then sent to a panel of clinical neuropsychologists that adjudicate each participant using 2011 National Institute on Aging-Alzheimer's Association (NIA-AA) criteria to determine if the person meets criteria for dementia, mild cognitive impairment (MCI), or are cognitively normal [36,37]. Only participants who meet criteria for being cognitively normal and/or without any significant subjective memory complaints (as recorded by a score of < 1.3 on the Everyday Cognition Questionnaire; detailed in psychosocial assessments) are considered eligible to continue in the study. Any participant who is considered to have dementia or amnesic MCI is excluded and referred to their PCP for further testing and follow-up.

A second assessment visit includes an additional battery of cognitive and neuropsychological tests which are not used for adjudication (see Table 3 for a description of the tests and time points of collection). The second cognitive session lasts approximately 2.5 h.

2.8. Cardiorespiratory fitness (CRF) testing

CRF testing is conducted at both baseline and 12-months to examine whether the intervention was successful at changing fitness levels and to determine whether changes in fitness mediate changes in cognitive or brain function. For this assessment, participants complete a maximal graded exercise test to assess aerobic capacity following a modified Balke protocol [55]. After a brief warm-up session, including a resting blood-pressure reading and resting echocardiogram (ECG) review, the participant walks on a motor-driven treadmill at a constant speed (1.5 to 3.5 mph – determined based on ability of the participant in

Table 1
IGNITE inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ● Men and women 65–80 yrs. ● Ambulatory without pain or the use of assisted walking devices ● Able to speak and read English ● Medical clearance by primary care physician (PCP) ● Living in community for duration of the study ● Reliable means of transportation ● No diagnosis of a neurological disease ● Eligible to undergo MRI ● Telephone Interview of Cognitive Status [9] score > 25 ● Cognitive adjudication decision of cognitively normal 	<ul style="list-style-type: none"> ● Current diagnosis of an Axis I or II disorder including Major Depression ● History of major psychiatric illness including schizophrenia (not including general anxiety disorder or depression (Geriatric Depression Scale [GDS] ≥ 9) [10] ● Current treatment for cancer – except non-melanoma skin cancer ● Neurological condition (MS, Parkinson's, Dementia) or brain injury (Stroke) ● Type I Diabetes, Insulin-dependent Type II Diabetes, uncontrolled Type II diabetes (defined as an HbA1c level > 10) ● Current alcohol or substance abuse or treatment for abuse in the past 5 years ● Current treatment for congestive heart failure, angina, uncontrolled arrhythmia, deep vein thrombosis (DVT) or another cardiovascular event ● Myocardial infarction, coronary artery bypass grafting, angioplasty or other cardiac condition in the past year ● Regular use of an assisted walking device ● Presence of metal implants (pacemaker, stents) that are MR ineligible ● Inability to complete the MRI scan ● Claustrophobia ● Color Blindness ● Not fluent in English ● Not medically cleared by PCP ● Engaging in > 20 min of moderate intensity physical activity per day for 3 days or more per week ● Not local or able to travel 3 times per week to the exercise facility ● Travelling consecutively for 3 weeks or more during the study ● Telephone Interview of Cognitive Status [9] score < 25 ● Cognitive adjudication decision of memory impairment ● Unwillingness to be randomized to one of the three groups ● Current participation in an ongoing trial likely to influence exercise ability or cognitive function (e.g., mindfulness training).

Table 2
Assessment schedule.

	Phone screening	In person screening	Baseline	Randomization	2 months	4 months	6 months (mid-point)	8 months	10 months	12 months (follow-up)
Prescreening questionnaire	✓									
Demographics	✓	✓								
Family History	✓									
TICS [34]	✓									
GDS [35]		✓					✓			✓
Informed Consent		✓								
Health History		✓								
Medications		✓					✓			✓
Cognitive Session 1		✓					✓			✓
Adjudication for cognitive impairment			✓							
Cognitive Session 2			✓				✓			✓
Cardiorespiratory Fitness			✓							✓
Physical Activity Monitoring			✓		✓	✓	✓	✓	✓	✓
Physical Function			✓							✓
DXA			✓							✓
PWV			✓							✓
Hair Sample			✓							✓
Fasting Blood Draw			✓				✓			✓
Psychosocial Assessments and questionnaires			✓				✓			✓
MRI			✓							✓
PET			✓							✓

TICS (Telephone Interview of Cognitive Status); GDS (Geriatric Depression Scale); DXA (dual-energy X-ray absorptiometry); PWV (pulse wave velocity); PET (positron emission tomography).

consultation with the exercise physiologist) and increments of an incline. The intensity is increased in two-minute stages with a 2% increase in incline at each stage. Heart rate is continuously monitored via a 12 lead ECG along with blood pressure readings and Rating of Perceived Exertion [56] (RPE) every two minutes. When the participant reaches the endpoint of the exercise test (symptom limitation and/or volitional exhaustion), they undergo a four-minute active cool-down followed by a four-minute seated cooldown period. During the exercise test, exhaled air is collected and analyzed for various metabolic factors. Each maximal exercise test is administered by a trained exercise physiologist and assistant technicians. We followed ACSM criteria for

determining whether a test was maximal [57]. A maximal exercise test is determined when three of the four following criteria are met: (1) Plateau in VO₂ between two or more workloads (increase < 0.15 L / min or 2.0 mL/kg/min during the last minute of corresponding workloads). (2) Respiratory Exchange Ratio (RER) equal to or > 1.10. (3) Heart Rate within 10 beats of age predicted maximal heart rate (220-age). (4) Rating of Perceived Exertion (RPE) > or equal to 17.

2.9. Physical activity monitoring

Physical activity monitoring is being conducted for measuring

Table 3
Cognitive tests.

Task	Format	Session	Expected domain(s)	Baseline	6-months	12-months
Synonym and Antonym – VCAP battery ^a [38]	Computerized	1	Language	✓	✓	✓
Montreal Cognitive Assessment [39] (MOCA)	Verbal; paper/pencil	1	General cognition	✓		✓
Trail Making A [40]	Paper-pencil	1	Processing Speed	✓	✓	✓
Trail Making B [40]	Paper-pencil	1	Executive Function	✓	✓	✓
Hopkins Verbal Learning Test [34] (HVLIT)	Verbal	1	Verbal memory	✓	✓	✓
Letter Fluency [41]	Verbal	1	Executive Function/Language	✓	✓	✓
Category Fluency [42]	Verbal	1	Executive Function/Language	✓	✓	✓
Brief Visuospatial Memory Test-Revised [43] (BVMRT)	Paper-pencil	1	Visuospatial Memory	✓	✓	✓
Wechsler Test of Adult Reading [44]	Verbal	1	Crystallized Intelligence	✓		
Digit Symbol Substitution Test [44]	Paper-pencil	1	Processing speed	✓	✓	✓
Boston Naming [45]	Verbal	1	Language	✓		
Logical Memory – VCAP battery [46]	Computerized	2	Episodic Memory	✓	✓	✓
Spatial Relations – VCAP battery [47]	Computerized	2	Visual-spatial	✓	✓	✓
Paired Associates – VCAP battery [48]	Computerized	2	Episodic Memory	✓	✓	✓
Matrix Reasoning – VCAP battery [49]	Computerized	2	Fluid Reasoning	✓	✓	✓
Dimensional Card Sort Task – NIH Toolbox [50]	Computerized	2	Executive Function	✓	✓	✓
List Sort Working Memory – NIH Toolbox [50]	Computerized	2	Working Memory	✓	✓	✓
Picture Sequence – NIH Toolbox [50]	Computerized	2	Working Memory	✓	✓	✓
Flanker – NIH Toolbox [50]	Computerized	2	Executive Function	✓	✓	✓
Spatial Working Memory [51]	Computerized	2	Working Memory	✓	✓	✓
Cohen's Relational Memory [52]	Computerized	2	Relational/episodic Memory	✓	✓	✓
Stroop Task	Computerized	2	Executive Function	✓	✓	✓
Task-switching	Computerized	2	Executive Function	✓	✓	✓
Iowa Gambling Task [53]	Computerized	2	Reward/Learning	✓	✓	✓
Letter Comparison (VCAP) [54]	Paper-pencil	2	Processing speed	✓	✓	✓

^a VCAP Synonym/Antonym is not used for adjudication but is administered at cognitive session 1.

Table 4
Selected details of the MRI protocol.

Sequence	Parameters
T1-weighted MPRAGE structural	Sagittal, 0.8 mm isotropic resolution, TE/TI/TR = 2.31/1060/2400 ms, Field of View (FOV) 256 mm, 224 slices
High resolution Hippocampus	Resolution: $0.4 \times 0.4 \times 2$ mm, TE/TR = 78/8830 ms, aligned perpendicular to hippocampus
Resting state EPI	Resolution: $2.5 \times 2.5 \times 2.5$ mm, TE/TR = 40/1000 ms, Multiband factor = 8 (CMRR EPI sequence [60–63]), 64 slices, 480 measurements
fMRI RISE task	Resolution: $2.5 \times 2.5 \times 2.5$ mm, TE/TR = 40/1000 ms, Multiband factor = 8, 64 slices, 413 measurements
fMRI n-back task	Resolution: $2.5 \times 2.5 \times 2.5$ mm, TE/TR = 40/2000 ms, Multiband factor = 4, 64 slices, 183 measurements
fMRI RISE Recognition task	Resolution: $2.5 \times 2.5 \times 2.5$ mm, TE/TR = 40/1000 ms, Multiband factor = 8, 64 slices, 923 measurements
Diffusion weighted acquisition	Resolution: $2.5 \times 2.5 \times 2.5$ mm, TE/TR = 95.6/2800 ms, Multiband factor = 4, b-values of 1500, 3000 s/mm ² , 64 gradient directions
3D T2 TSE FLAIR	Sagittal, 1 mm isotropic resolution, Turbo spin echo, TE/TI/TR = 388, 2200, 6000 ms, non-selective inversion recovery
pCASL TGSE	3D GRASE pCASL sequence [64,65], Resolution: $3.1 \times 3.1 \times 2.5$ mm, TE/TR = 22.08/4300 ms, 48 slices, Post-label delay 2 s, Background Suppression, 10 measurements for labeling and control, 4 segment readout

activity patterns throughout the trial, confirming engagement of exercise intensity during unsupervised sessions, and to determine contamination of systematic increases in activity for the stretching-and-toning group or reductions in activity for the exercise groups. Participants are fitted with a physical activity monitoring device (ActigraphG Link) around the non-dominant wrist. These devices are worn at baseline, 2, 4, 6, 8, 10, and 12-months. At each point, the device is worn for a minimum of 7 continuous days including periods of sleep. The device measures raw acceleration, energy expenditure, Metabolic Equivalent of Task rates, steps, physical activity intensity, activity bouts, sedentary bouts, body position, sleep latency, total sleep time, and sleep efficiency. All participants also complete a diary of activities and sleep patterns during each wearing of the device.

2.10. Brain magnetic resonance imaging (MRI)

One of the principal aims of the IGNITE study is to examine the impact of aerobic exercise on brain morphology (e.g., volume), function, connectivity, white matter microstructure, and cerebral blood flow. Accordingly, an MRI scan is completed at baseline and following the 12-month intervention (Table 4). The University of Pittsburgh and Northeastern University are using a Siemens Prisma 3 T scanner with a 64-channel head coil and the University of Kansas Medical Center is using a Siemens Skyra 3 T scanner with a 32-channel head coil. Imaging protocols were designed to be exact matches across the two scanner types. Before enrolling participants in the study, the image sequences and image quality was standardized across sites. Phantom scans are run at each site on a regular basis to ensure stability of the data quality and geometric accuracy of the MRI scanners. A human phantom (GAG) is also scanned annually at each site. Sequences collected include high-resolution three-dimensional (3D) magnetization-prepared rapid acquisition with gradient echo (MPRAGE) T1-weighted anatomical scan, a hippocampal focal T2-weighted sequence, a resting state echo planar imaging (EPI) scan, n-back working memory task-evoked EPI scan, Relational and Item Specific Encoding (RISE) and Recognition task-evoked EPI scans [58], a multi-shell diffusion weighted white matter sequence, a 3D fluid-attenuated inversion recovery (FLAIR) sequence for assessing white matter hyperintensities, and a Pseudo-Continuous Arterial Spin Labeling (pCASL) sequence for cerebral blood flow. Associated field map scans were obtained for all EPI acquisitions (functional MRI and Diffusion) by acquiring a short spin echo EPI acquisition and flipping the phase encode axis between 2 repeats.

All MRI data are transferred to the XNAT server at the coordinating center for quality control assessment within 24 h of collection. The MRI data then go through a rigorous 4-stage quality control process to assess incoming data for (1) sequence accuracy (e.g., naming standards) and completeness (e.g., correct number of volumes per sequence) and conversion to nifti format and organization into brain imaging data structure (BIDS) format on a secure server, 2) ensuring that the correct sequence parameters were collected by comparing header information from each sequence to expected values, 3) visual inspection of each

image to assess accuracy of brain coverage and image orientation; and 4) quantitative quality control via MRIQC software [59] and internally generated scripts to calculate measurements (e.g., signal-to-noise) for each sequence. All the above steps are completed by the coordinating center within 48 h of data upload to the XNAT server and any anomalies or significant variation (of 2 standard deviations) are flagged for follow-up. All baseline MRI scans are also sent to a neuroradiologist (JM), who provides a clinical reading of incidental findings.

2.11. Dual-energy x-ray absorptiometry (DXA), pulse wave velocity (PWV), and hair samples

Exercise-induced changes to body composition, arterial function, and stress hormones have been proposed as pathways by which cognitive and brain changes are realized. As such, we are collecting these measures to determine whether they act as significant mediators. Body composition is assessed via dual-energy x-ray absorptiometry (DXA) using a GE Lunar iDXA dual-energy x-ray absorptiometer (Lunar, Inc., Madison, WI) at each site. Full-body DXA scans provide data for fat mass, fat-free mass, % body fat, and bone mineral density. PWV measures the velocity at which pressure waves travel through a vessel, and this is associated with degree of arterial stiffness. PWV is assessed using ultrasound. Each site uses the SphygmoCor XCEL with the AtCor Medical Tonometer, which is a non-invasive diagnostic tool for central arterial pressure and arterial stiffness. Hair samples are collected to measure the amount of the stress hormone, cortisol, that is secreted over the prior 3 months. DXA, PWV, and hair samples are collected at baseline and the 12-month assessment for each participant. A human phantom (GAG) is scanned at each site to ensure stability and standardization of the DXA and PWV procedures.

2.12. Blood assays, epigenetics, genotyping, and gene expression

Fasting blood is collected at baseline, 6-, and 12-months. At each blood draw we collect approximately 47 cc of blood for a total of 141 cc for each subject during the duration of the study. Blood sampling is postponed for subjects experiencing an acute infection (e.g., respiratory or flu-like symptoms) along with those participants having recent vaccination or tattoo. Blood is processed and stored at -80 °C as plasma, buffy coats, serum, whole blood, RNA and isolated mononuclear cell samples. The main blood analytes to be assessed in this trial include brain derived neurotrophic factor, C-reactive protein, Interleukin-6, TNF-alpha, Cathepsin-B, vascular cell adhesion molecule 1, telomere length, vascular endothelial growth factor, irisin, chemokine ligand 13, immunoglobulin-1, interleukin 17, adiponectin, cholesterol, insulin-like growth factor 1, insulin, glucose, HbA1c, splicing factor 1, and Klotho.

Planned genotyping includes an array-based genome wide association study (GWAS) analysis as well as a targeted approach for common single nucleotide polymorphisms that have been found to be related to cognitive function and are not present on genotyping array (e.g., APOE) or are on proposed pathways by which exercise influences brain and

Table 5
Psychosocial assessments.

Name	Description
Barriers Self-Efficacy Scale (BARSE) [69]	A 13-item questionnaire that assesses the degree of confidence that one could exercise despite a variety of limitations such as bad weather, while on vacation, etc.
Big Five Trait Taxonomy II Questionnaire (BFI) [70]	A 44-item questionnaire that measures the Big Five personality dimensions including Openness-to-experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism.
Cognitive Function Index (CFI) [71]	A 15-item questionnaire that asks about daily cognitive and memory ability on a Yes, No, Maybe scale
Cohen's Social Network Index [72]	A 12-items questionnaire that assesses participation in 12 types of social relationships including spouse, parents, friends, family members, etc.
Composite Scale of Morningness (CSM) [73]	A 13-item measure examining participants' optimum times of day and quality of sleep.
Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [74]	A 14-items questionnaire on the severity of various ailments, including those of a cardiac, vascular, muscular, respiratory or gastro-intestinal nature.
Demographics and Health History (baseline only)	A 37-item questionnaire detailing symptoms, injuries, consumption of alcohol and tobacco use, and demographics
Dietary History (NCI) [75]	A 153-item questionnaire on the types and quantities of specific foods eaten over the past month.
Everyday Cognition Questionnaire (ECOG) [76]	A 12-item questionnaire for the degree to which participants perceive any changes (compared to their perceived abilities 10 years ago) across various cognitive tasks such as remembering where objects are located, planning and multi-tasking activities, and understanding instructions.
EQ-5D-5 L [77]	A 5-item questionnaire assessing participants' functioning across 5 dimensions of health (mobility, self-care, anxiety/depression, pain/discomfort, usual activities).
Exercise Self-Efficacy (EXSE) [78]	An 8-item measure to assess degree of confidence in the ability to continue exercising at a moderate intensity 3 times per week for at least 40 min per session.
Exercise Social Provisions Scale [79]	A 24-item questionnaire about current relationships within the exercise program, such as I do not think other people in the exercise group respect my skills and abilities. Adapted from its original form to be specific to exercise.
Expectancy Questionnaire (12-month assessment only) [80]	A 19-item questionnaire assessing expectations about the benefits of regular exercise.
Fatigue Symptom Inventory (FSI) [81]	A 14-item measure designed to assess the severity, frequency, and daily pattern of fatigue as well as its perceived interference with quality of life.
Female Reproductive Health and History (Menopause)	Only given to female study participants. This 10-item questionnaire asks a variety of questions about menopause and reproductive history (e.g., hormone use, pregnancies)
Florida Cognitive Activity Scale [82]	A 25-item questionnaire on the frequency of cognitively stimulating activities such as playing games like chess or board games, puzzles, listening to music, gardening, reading, cooking, home repair, discussions, etc.
Geriatric Depression Scale (GDS) – Short form [35]	A 15-item measure to assess depressive symptoms in older adults.
Godin Leisure Time Exercise Questionnaire [83]	A brief 3 item assessment of leisure-time and structured exercise habits during a typical week.
Health Care Resource Utilization (HRU) [84]	A 10-item questionnaire that asks participants to detail health care visits, services, and ability to do chores for the calculation of economic burden.
Hospital Anxiety and Depression Scale (HADS) [85]	A 14-item questionnaire with items asking about feelings of depression, anxiety and emotional distress in the past week.
Instrumental Activities of Daily Living (IADL) [86]	A 26-item questionnaire assessing daily cognitive and self-care activities in terms of routine and ability.
Lifestyle Self-Efficacy Scale (LSE) [87]	A 6-item measure to assess beliefs in the ability to accumulate 30 min of physical activity on 5 or more days of the week in the future.
MacArthur Socioeconomic Status Index [88]	An 11-item questionnaire regarding participants perception of their socioeconomic status relative to their community and country, their living situation, level and degree of education obtained, job status, income, and debt.
McGill Pain Questionnaire – Short form [89]	A 16-item brief pain index to assess qualitative experiences of pain using descriptors for sensory, affective, and intensity of the perception of pain.
Current medication list	3 sections, information about prescription and over-the-counter medications and vision impairment
Mindful Attention Awareness Scale (MAAS) [90]	A 12-item questionnaire that assesses mindfulness during daily activities such as conversation, commuting, and eating. Assesses open or receptive awareness of, and attention to, what is taking place in the present.
Perceived Stress Scale (PSS) [91]	A 10-items questionnaire measuring the degree of perceived stress regarding certain life events during the past month.
Physical Activity Self-regulation scale (PASR) [92]	A 12-item scale assessing goal setting and self-monitoring in relation to the engagement of physical activity.
Physical Self-Perception Profile (PSPP) [93]	A 24-item questionnaire assessing physical self-esteem.
Pittsburgh Sleep Quality Index (PSQI) [94]	A 9-item questionnaire assessing sleep quality.
PROMIS Applied Cognition: Abilities [95]	An 8-item questionnaire assessing perceived functional abilities in terms of cognitive performance including the perception that one's cognitive ability (e.g., concentration, memory) has changed in the last 7 days.
PROMIS Applied Cognition: General Concerns [95]	An 8-item questionnaire assessing perceived cognitive deficits including mental acuity, concentration, verbal and non-verbal memory, verbal fluency, and perceived changes in these functions. These questions also gather information on whether the deficits interfere with daily functioning whether other people observe the deficits, and the impact of the deficits on quality of life.
Rosenberg self-esteem scale (RSE) [96]	A 10-item scale that measures global self-worth by assessing both positive and negative feelings about the self.
Satisfaction with Life Scale (SWLS) [97]	A 5-item questionnaire in which participants respond to how satisfied they are with the conditions of their life on a 1–7 scale. Measures global life satisfaction.
SF-36 Health Survey [98]	A 36-item self-report quality of life measure that assesses eight health-related dimensions: physical functioning, physical limitations, pain, behavior disturbances due to emotional problems, mental capacity, perceptions of health, social functioning, and feelings of energy/fatigue.
Sitting Time Questionnaire [99]	A 5-item questionnaire that assesses how much time participants spend sitting at work, at home, while watching TV or leisure time, and driving on an average day. The amounts are broken down by weekday and weekends.
Social Goal Importance [100]	A 2-item questionnaire that assesses the importance of social support available to achieving certain goals.
UCLA Loneliness Scale [101]	A 20-item scale to assess feelings of loneliness as well as social isolation.
Visual Analog Scale of health (VAS) [102]	A 1 question item indicating level of health on 100-point scale.
Work Design Questionnaire (WDQ) [103]	A 78-item questionnaire in which participants answer questions about the nature and responsibilities of their current or previous job such as job autonomy and complexity, task variety and significance, and cooperative components such as social interactions inside and outside of the organization.

cognition (e.g., *BDNF*). Gene expression is being assessed by use of RNAseq. Genome-wide DNA methylation and gene expression will be assessed at baseline, 6, and the 12-month assessment. Remaining samples are stored for future analyses.

2.13. Physical function

Several measures of physical function will be collected including the Senior Fitness Test [66], the Short Physical Performance Battery [67],

and measures of gait speed and variability [68]. Physical function data will be collected during the baseline and 12-month assessment sessions. These tests will be used to measure changes in mobility, strength, flexibility, endurance and balance after completing a 12 month exercise intervention. These tasks are conducted separately from, or prior to, the VO_{2max} test.

2.14. Psychosocial assessments

A battery of questionnaires is administered at baseline, 6, and 12-months including social, mood, and quality of life scales and instruments (see Table 5). Exercise self-efficacy, social provisions and groups, mood and anxiety, personality traits, social networks, pain, fatigue, etc., have all been shown to either influence exercise adherence or cognitive function and might explain, mediate, or moderate some of the effects of exercise on cognition (e.g., someone engaging in both exercise and in intellectually stimulating activities might see larger effects than those engaging in less intellectually stimulating activities). As such, we carefully selected a battery of tests that would considerably add to our knowledge of how exercise influences cognitive and brain health. These questionnaires are relatively brief and take most participants approximately 1–2 h to complete.

2.15. Positron emission tomography (PET) for amyloid

PET imaging occurs at the baseline and 12-month follow-up session using the tracer, Neuroceq (Florbetaben F^{18}). Neuroceq is a sterile, non-pyrogenic radioactive diagnostic agent for intravenous injection and is radiolabeled with $[^{18}F]$ fluorine. Neuroceq is an FDA approved drug and is sensitive to levels of the protein $A\beta$. Participants have an IV with an intravenous catheter with an injection of 8.0 mCi $[^{18}F]$ Florbetaben, using a slow bolus of approximately 20 s. The participant then relaxes for 75 min and the scan begins at 90 min (+/– 5 min) after injection. The stop time of the scan is at 110 min. Standardized approaches are used for quantifying amyloid levels [104] including using the cerebellum as a reference with white matter and partial volume correction.

2.16. Blinding and randomization

Participants are randomized after baseline sessions are completed and data have been checked for quality assurance. The lead study biostatistician (CK) randomizes participants using a stratified permuted block randomization algorithm with equal allocation to one of the three groups. We also stratify the randomization by (1) study site, (2) age at study entry (≤ 72 , > 72), and (3) gender (male, female) to ensure equal allocation of participants to each group based on these criteria. Briefly, the randomization algorithm assigns the groups so that at each site there will be exactly 213 people in the trial with an equivalent distribution across the arms. The same randomization algorithm also splits by age and gender and simply weights someone's group assignment by their age and gender to ensure that at the end of the trial we have minimal differences in gender distribution or age across the different conditions. Participants are randomized to 1 of the 3 supervised exercise groups: (1) 150 min per week of moderate intensity exercise, (2) 225 min per week of moderate intensity exercise, and (3) 150 min per week of light intensity stretching and toning. All investigators and staff involved with assessments are blind to group assignment. Only staff involved in the exercise interventions, scheduling, data management, and coordination are unblinded. The PIs are only unblinded in the case of an adverse or serious adverse event.

2.17. Intervention

The group prescribed 150 min per week (approximately 5 days of 30 min each day) of aerobic exercise and the group prescribed 225 min per week (approximately 5 days of 45 min each day) of aerobic exercise

receive 3 days per week of moderate-intensity exercise (based on heart rate reserve calculated during the initial VO_{2max} test) under the supervision of an exercise trainer and two days per week of unsupervised moderate intensity exercise. Participants are allowed to do more activity on any given day (up to 60 min) to achieve their prescribed volume of supervised activity. Participants engage in this exercise regimen for 12 months and use weekly diaries to record all physical activities and to document compliance of the unsupervised exercise. All participants are trained to use the RPE scale and record all unsupervised RPE scores to ensure intensity. Walking is the encouraged form of exercise, but participants are allowed to use up to 2 modes of exercise in any session that could include bike, elliptical, rower, or stair climber. The selected mode of activity is recorded at all sessions.

During the supervised sessions, each participant wears a Polar A360 device around the wrist that measures heart rate. The exercise staff records average heart rate readings at 15-min epochs to ensure that the moderate-intensity zone is achieved. If the zone is not being achieved the participant is instructed to increase the speed, resistance, or incline. For the first 6 weeks of the intervention, participants engage in light intensity exercise (50–60% Heart Rate Reserve from VO_{2max} test and RPE of 11–12). For the remainder of the exercise sessions, the intensity is increased to 60–75% of the Heart Rate Reserve determined during the VO_{2max} test and RPE of 13–14. Participants begin the intervention completing 15 min of exercise per session and increase by 5 min per session each week until they reach the weekly volume goal. The supervised sessions are conducted in small groups and/or individually depending on the times the sessions are offered.

Participants randomized to the stretching and toning condition are prescribed a volume of 150 min per week of light intensity exercise. This volume is achieved through 3 days per week of light intensity exercise (based on heart rate) under the supervision of an exercise trainer and two days per week of unsupervised exercise. The supervised sessions follow 16 exercise routines (4 routines in each of the 4 categories: Yoga / Mobility, Total Body Fusion, Pilates / Balance, and Stretch / Tone), each routine is delivered for one week before switching to the next routine. Each of the routines is played in video format during class with the exercise staff monitoring heart rate and exercise form of the participants. This ensures that each site delivers the same routine in regard to both the intensity and timing of the stretching and toning activities. Activities consist of gentle movements of the major joints of the body. Like the aerobic exercise groups, all participants assigned to this group receive weekly diaries, heart rate is monitored during the supervised sessions at 15-min epochs, and RPE is obtained. The intensity of this group is maintained by keeping heart rate below 100 and an RPE of 9–10. The stretching and toning sessions are performed in small groups at each site in a separate space from the aerobic based supervised sessions.

2.18. Monitoring adverse events and Data Safety and Monitoring Board

All adverse events and serious adverse events are carefully monitored and managed throughout the trial and will be reported in future manuscripts according to NIA guidelines. A Data Safety and Monitoring Board (DSMB) meets every 6 months to discuss study progress and safety.

2.19. Data management and quality control

Before the start of the study and collection of any data, all staff involved in the project receive ethics training and appropriate certification of research training modules. In addition, to maintain consistency in data collection and intervention procedures over the course of the trial, all staff undergo annual on-site training certification. An external consultant annually observes the intervention and assessment session procedures at each site and relates the findings of the observation in a report to the Principal Investigators.

There is an 8-week window to complete all baseline measures. Once a participant enrolls, all non-electronic data are double entered into a REDCap database in which appropriate permissions are controlled by a Data Management team (Pittsburgh). Before randomization, all data are accounted for, checked for quality control purposes, and archived on a secure server.

At the 6-month assessment visit, participants complete questionnaires, the cognitive battery of tests, a blood draw, and a physical activity assessment (ActigraphG). These data are collected in a 4-week period with the window opening exactly two weeks before the 6-month time point and closing two weeks after the 6-month time point. Similar quality control and completeness checks are conducted as described above for baseline assessments.

At the 12-month time point (post-intervention), the participants repeat each of the above assessment sessions. These sessions are collected over a 6-week period with the window opening exactly two weeks before their 12-month anniversary and closing 4 weeks after the 12-month anniversary. The scheduling of sessions is flexible, but the cognitive, fitness, and blood draw assessments are prioritized in order to be scheduled as proximal as possible to the end of the intervention.

2.20. Power and analytic strategy

Calculations were performed to determine the statistical power for the target sample size of 639 ($N = 213/\text{condition}$). We estimated power based on the linear contrasts resulting from a repeated measures model with an effect size of 0.50 for our primary outcome, a composite score of executive function. Accordingly, $N = 91/\text{group}$ is necessary to reach 80% power at $p \leq 0.05/2 = 0.025$ to limit inflation of Type I error due to multiple testing of two-sided hypotheses using Bonferroni correction. As such, $N = 176$ per group is sufficient to detect differences in each cognitive outcome between groups with 80% power even with 20% attrition. Effect sizes from neuroimaging data (0.40–0.50) indicate that we will be sufficiently powered to test for differences in volume, functional connectivity, white matter, and task-evoked activity. In sum, our planned sample size of 639 ($N = 213$ per group) will be sufficient for allowing us to test our primary hypotheses with enough residual power to further examine statistical mediators and individual differences.

Prior to hypothesis testing, all data will be examined to determine: 1) frequency distributions for missing data and out-of-range values; 2) normality and internal consistency of subscales; and, 3) association between variables that may be highly correlated to guard against multicollinearity, which would inflate standard errors and make estimation unstable. We will also examine the distribution of factors between groups to assess whether covariate-adjustment is required.

All outcomes will be tested using an intent-to-treat (ITT) framework. Sensitivity will be explored using adherence to the intervention (e.g., per protocol). We will report reasons for dropouts and explore missing data mechanisms. To examine whether missingness is unrelated to other observed measurements (missing completely at random, MCAR) or to the observed measurements only (missing at random, MAR), testing for completely random dropouts will be carried out. Additional sensitivity analyses will be performed to test for informative dropouts. We will apply pattern-mixture models by stratifying our data by dropout patterns and fitting separate regression models to strata.

The latent factors and loadings for executive function and other cognitive constructs will be determined based on a confirmatory factor analysis using baseline data. Any missing cognitive data at baseline could influence the formulation of the latent factors from the factor analysis. To avoid this potential concern, we will conduct an analysis using only the collected baseline data to create the latent factors. But, then, we will conduct a secondary sensitivity analysis by imputing missing values in each of the outcomes for the missing baseline data and use these values for creating the factor scores. Only baseline data will be used for imputation and these data will be used for repeating the

factor analysis. Then, we will compare the factor analysis results with and without missing value imputation.

By creating the latent factors based on data collected at baseline we will not be introducing intervention-related biases in the creation of the factors since the factors would be determined by data collected before randomization. However, we also plan to conduct post-hoc confirmatory factor analyses on the data collected at the follow-up assessments to determine consistency in the factor loadings across measurement time points (i.e., factor invariance). But, the results from this post-hoc confirmatory factor analysis will not be used for the modification of the baseline factor analysis results and will not influence the testing of the primary aim. We propose to test our primary hypothesis about the effects of the exercise intervention on executive function using a general linear mixed model (GLMM) approach because we will have three assessments of cognitive function over the course of the trial (baseline, 6-months, 12-months). The GLMM model will include both a random intercept and a random slope for individual participants and a treatment-by-time interaction as a fixed effect. This technique will allow us to model the changes in the latent factor score for executive function as a function of both time and group while also including other potentially confounding variables (e.g., site) in the model. Dose-response effects will be tested using a linear contrast between two intervention groups to examine differences between the 150 min/week and 225 min/week groups.

All other analyses and questions pertaining to the MRI data, amyloid, blood biomarkers, genetics, DXA and PWV, questionnaires, etc. are considered secondary or tertiary. We also plan to test these outcomes in a similar manner as described above using an ITT framework and a GLMM approach using a treatment x time interaction.

We will use methods established by Preacher and Hayes [105,106] to test for mediation between the predictor X (type of treatment) on the outcome Y (e.g., cognitive function) by the mediator M (e.g., brain outcome). Although directional hypotheses have been posited for our mediation analyses, a more conservative significance will be set at 0.01 to limit inflation of type I error. Initially, we will fit simple mediational models (predictor, single mediator, single outcome) applying the change score method. Depending on the results from simple mediational modeling, we may also combine mediators into multiple or serial mediator models to develop a more comprehensive picture of these pathways.

Multiple regression will test potential moderators of the outcomes. We will test each potential moderator individually. A significant interaction term indicates effect moderation. Our primary hypotheses include the examination of age, genotype, and baseline amyloid. We will also explore other demographic variables that influence neurocognitive function including gender, race, and education.

3. Discussion

We have designed and are implementing a large, comprehensive, multi-site, Phase III clinical trial to test whether moderate-intensity aerobic exercise has the capacity to improve cognitive and brain outcomes in cognitively normal older adults. We expect that the exercise intervention will enhance executive function, increase hippocampal and prefrontal cortex volume, increase fMRI activity and cerebral blood flow, and do this in a dose-dependent manner. We also predict that the effects will be moderated by genotype such that those with a genetic predisposition for cognitive decline (i.e., APOE e4) and higher amyloid levels, will show greater improvements than those without a genetic risk and with lower amyloid levels. We also predict that exercise might attenuate the accumulation of amyloid, especially for individuals that are below thresholds of amyloid positivity. In addition, we expect the exercise intervention to influence numerous measures of physiological (e.g., fitness, body composition), functional (e.g., gait speed), mood (e.g., negative affect), and social function (e.g., social networks), among others, that could explain variation in adherence, individual variation

in the response to exercise, or partly mediate the benefits to brain and cognition.

Despite the numerous strengths of this study, there are several notable limitations. For example, the results from this study will be unable to determine whether other doses of exercise (volume, frequency, intensity) would produce different effects on cognitive and brain outcomes. Thus, we are inherently limited in drawing conclusions about the doses that we have prescribed. That being said, we do expect variation in adherence to the prescribed doses and have planned secondary analyses that would test the effects of exercise on our outcomes by using a continuous measure of volume of activity achieved per week. We also elected to not have a no-contact control group, so if the light intensity stretching and toning condition also improves cognitive and brain function, it might diminish the effect size of the aerobic exercise conditions on cognitive and brain outcomes. In addition, in developing the inclusion and exclusion criteria, we balanced goals about generalizability to a broad population while maintaining and ensuring safety of the participants. All participants require PCP clearance, must be MRI compatible, and ambulatory to participate in the study. As such, all results should be interpreted in the context of the sample characteristics. Finally, we have assembled a theoretically-derived list of possible mediators and moderators of the effects of exercise on brain and cognition, but clearly the list is not exhaustive of all possible molecular and system-level mediators.

Like any RCT this trial is not immune to challenges. Maintaining high adherence and compliance over the course of a 12-month intervention requires approaches that leverage social-cognitive principles for behavior change. Missing data, study withdrawals, adverse events, and random differences between groups that exist at baseline could all interfere with interpretation of the intervention effects.

In sum, the outcomes from this study will have far-reaching scientific and clinical implications and could help transform public health recommendations of physical activity and exercise for influencing cognitive and brain outcomes in older adults. Our trial will also be able to identify mechanisms and moderators of the effectiveness of regular exercise to influence cognitive and brain outcomes.

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References

- [1] C.N. Harada, M.C. Natelson Love, K. Triebel, Normal cognitive aging, *Clin. Geriatr. Med.* 29 (4) (2013) 737–752, <https://doi.org/10.1016/j.cger.2013.07.002>.
- [2] I.E.M. Evans, D.J. Llewellyn, F.E. Matthews, R.T. Woods, C. Brayne, L. Clare, Social isolation, cognitive reserve, and cognition in healthy older people, *PLoS ONE* 13 (8) (2018), <https://doi.org/10.1371/journal.pone.0201008>.
- [3] M.K. Scullin, D.L. Bliwise, Sleep, cognition, and normal aging: integrating a half-century of multidisciplinary research, *Perspect. Psychol. Sci. J. Assoc. Psychol. Sci.* 10 (1) (2015) 97–137, <https://doi.org/10.1177/1745691614556680>.
- [4] D.C. Park, G.N. Bischof, The aging mind: neuroplasticity in response to cognitive training, *Dialogues Clin. Neurosci.* 15 (1) (2013) 109–119.
- [5] P. Malinowski, L. Shalamanova, Meditation and cognitive ageing: the role of mindfulness meditation in building cognitive reserve, *J. Cogn. Enhanc.* 1 (2) (2017) 96–106, <https://doi.org/10.1007/s41465-017-0022-7>.
- [6] N. Scarmeas, Y. Stern, Cognitive reserve and lifestyle, *J. Clin. Exp. Neuropsychol.* 25 (5) (2003) 625–633, <https://doi.org/10.1076/jcen.25.5.625.14576>.
- [7] M.W. Beckett, C.I. Arden, M.A. Rotondi, A meta-analysis of prospective studies on the role of physical activity and the prevention of Alzheimer's disease in older adults, *BMC Geriatr.* 15 (2015), <https://doi.org/10.1186/s12877-015-0007-2>.
- [8] C.W. Cotman, N.C. Berchtold, Exercise: a behavioral intervention to enhance brain health and plasticity, *Trends Neurosci.* 25 (6) (2002) 295–301.
- [9] Stillman CM, Donofry SD, Erickson KI. Exercise, fitness and the aging brain: a review of functional connectivity in aging. *Arch. Psychol.* (in press).
- [10] K.I. Erickson, C. Hillman, C.M. Stillman, et al., Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines, *Med. Sci. Sports Exerc.* 51 (6) (2019) 1242–1251, <https://doi.org/10.1249/MSS.0000000000001936>.
- [11] J. Young, M. Angevaren, J. Rusted, N. Tabet, Aerobic exercise to improve cognitive function in older people without known cognitive impairment, *Cochrane Database Syst. Rev.* 4 (2015) CD005381, <https://doi.org/10.1002/14651858.CD005381.pub4>.
- [12] D.E. Barnes, W. Santos-Modesitt, G. Poelke, et al., The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults, *JAMA Intern. Med.* 173 (9) (2013) 797–804, <https://doi.org/10.1001/jamainternmed.2013.189>.
- [13] J.A. Blumenthal, C.F. Emery, D.J. Madden, et al., Long-term effects of exercise on psychological functioning in older men and women, *J. Gerontol.* 46 (6) (1991) P352–P361.
- [14] D. Forbes, E.J. Thiessen, C.M. Blake, S.C. Forbes, S. Forbes, Exercise programs for people with dementia, *Cochrane Database Syst. Rev.* 12 (2013) CD006489, <https://doi.org/10.1002/14651858.CD006489.pub3>.
- [15] J. Young, M. Angevaren, J. Rusted, N. Tabet, Aerobic exercise to improve cognitive function in older people without known cognitive impairment, *Cochrane Database Syst. Rev.* 4 (2015) CD005381, <https://doi.org/10.1002/14651858.CD005381.pub4>.
- [16] L.M.J. Sanders, T. Hortobágyi, B. Gemert S la, E.A. van der Zee, M.J.G. van Heuvelen, Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: a systematic review and meta-analysis, *PLOS ONE* 14 (1) (2019) e0210036, <https://doi.org/10.1371/journal.pone.0210036>.
- [17] S. Jacob, P. Jeremy, E.L. Ding, H.W. Kohl, H. William, I.-M. Lee, Dose response between physical activity and risk of coronary heart disease, *Circulation.* 124 (7) (2011) 789–795, <https://doi.org/10.1161/CIRCULATIONAHA.110.010710>.
- [18] J.E. Donnelly, S.N. Blair, J.M. Jakicic, American College of Sports Medicine Position Stand, et al., Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults, *Med. Sci. Sports Exerc.* 41 (2) (2009) 459–471, <https://doi.org/10.1249/MSS.0b013e3181949333>.
- [19] H. Arem, S.C. Moore, A. Patel, et al., Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship, *JAMA Intern. Med.* 175 (6) (2015) 959–967, <https://doi.org/10.1001/jamainternmed.2015.0533>.
- [20] T. Yates, S.M. Haffner, P.J. Schulte, et al., Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis, *Lancet Lond. Engl.* 383 (9922) (2014) 1059–1066, [https://doi.org/10.1016/S0140-6736\(13\)62061-9](https://doi.org/10.1016/S0140-6736(13)62061-9).
- [21] E.M. Reiman, K. Chen, X. Liu, et al., Fibrillar amyloid- β burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease, *Proc. Natl. Acad. Sci.* 106 (16) (2009) 6820–6825, <https://doi.org/10.1073/pnas.0900345106>.
- [22] A.M. Fjell, L.T. Westlye, H. Grydeland, et al., Critical ages in the life course of the adult brain: nonlinear subcortical aging, *Neurobiol. Aging* 34 (10) (2013) 2239–2247, <https://doi.org/10.1016/j.neurobiolaging.2013.04.006>.
- [23] N. Raz, P. Ghisletta, K.M. Rodrigue, K.M. Kennedy, U. Lindenberger, Trajectories

- of brain aging in middle-aged and older adults: regional and individual differences, *NeuroImage*. 51 (2) (2010) 501–511, <https://doi.org/10.1016/j.neuroimage.2010.03.020>.
- [24] N. Raz, U. Lindenberger, K.M. Rodrigue, et al., Regional brain changes in aging healthy adults: general trends, individual differences and modifiers, *Cereb Cortex N Y N* 15 (11) (2005) 1676–1689, <https://doi.org/10.1093/cercor/bhi044>.
- [25] K.M. Rodrigue, E.M. Haacke, N. Raz, Differential effects of age and history of hypertension on regional brain volumes and iron, *NeuroImage*. 54 (2) (2011) 750–759, <https://doi.org/10.1016/j.neuroimage.2010.09.068>.
- [26] M. Lövdén, F. Schmiedek, K.M. Kennedy, K.M. Rodrigue, U. Lindenberger, N. Raz, Does variability in cognitive performance correlate with frontal brain volume? *NeuroImage*. 64 (2013) 209–215, <https://doi.org/10.1016/j.neuroimage.2012.09.039>.
- [27] K.M. Kennedy, K.I. Erickson, K.M. Rodrigue, et al., Age-related differences in regional brain volumes: a comparison of optimized voxel-based morphometry to manual volumetry, *Neurobiol. Aging* 30 (10) (2009) 1657–1676, <https://doi.org/10.1016/j.neurobiolaging.2007.12.020>.
- [28] R.A. Sperling, P.S. LaViolette, K. O'Keefe, et al., Amyloid deposition is associated with impaired default network function in older persons without dementia, *Neuron*. 63 (2) (2009) 178–188, <https://doi.org/10.1016/j.neuron.2009.07.003>.
- [29] S.M. Marks, S.N. Lockhart, S.L. Baker, W.J. Jagust, Tau and β -amyloid are associated with medial temporal lobe structure, function, and memory encoding in Normal aging, *J. Neurosci.* 37 (12) (2017) 3192–3201, <https://doi.org/10.1523/JNEUROSCI.3769-16.2017>.
- [30] CDC, Physical Activity Basics|PhysicalActivity|CDC, Published February 18, 2019. Accessed March 20, 2019, 2019. <https://www.cdc.gov/physicalactivity/basics/index.htm>.
- [31] K.I. Erickson, S.E. Banducci, A.M. Weinstein, et al., The brain-derived neurotrophic factor Val66Met polymorphism moderates an effect of physical activity on working memory performance, *Psychol. Sci.* 24 (9) (2013) 1770–1779, <https://doi.org/10.1177/0956797613480367>.
- [32] D. Head, J.M. Bugg, A.M. Goate, et al., Exercise engagement as a moderator of APOE effects on amyloid deposition, *Arch. Neurol.* 69 (5) (2012) 636–643, <https://doi.org/10.1001/archneurol.2011.845>.
- [33] C.S. Jensen, A.H. Simonsen, V. Siersma, et al., Patients with Alzheimer's disease who carry the APOE ϵ 4 allele benefit more from physical exercise, *Alzheimers Dement. Transl. Res. Clin. Interv.* 5 (2019) 99–106, <https://doi.org/10.1016/j.trci.2019.02.007>.
- [34] J. Brandt, The Hopkins verbal learning test: development of a new memory test with six equivalent forms, *Clin. Neuropsychol.* 5 (2) (1991) 125–142, <https://doi.org/10.1080/13854049108403297>.
- [35] J.A. Yesavage, T.L. Brink, T.L. Rose, et al., Development and validation of a geriatric depression screening scale: a preliminary report, *J. Psychiatr. Res.* 17 (1) (1982) 37–49.
- [36] M.S. Albert, S.T. DeKosky, D. Dickson, et al., The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement.* 7 (3) (2011) 270–279, <https://doi.org/10.1016/j.jalz.2011.03.008>.
- [37] G.M. McKhann, D.S. Knopman, H. Chertkow, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement.* 7 (3) (2011) 263–269, <https://doi.org/10.1016/j.jalz.2011.03.005>.
- [38] T.A. Salthouse, Speed and knowledge as determinants of adult age differences in verbal tasks, *J. Gerontol.* 48 (1) (1993) P29–P36, <https://doi.org/10.1093/geronj/48.1.P29>.
- [39] Z.S. Nasreddine, N.A. Phillips, V. Bédirian, et al., The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment, *J. Am. Geriatr. Soc.* 53 (4) (2005) 695–699, <https://doi.org/10.1111/j.1532-5415.2005.53221.x>.
- [40] R.M. Reitan, Validity of the trail making test as an indicator of organic brain damage, *Percept. Mot. Skills* 8 (3) (1958) 271–276, <https://doi.org/10.2466/pms.1958.8.3.271>.
- [41] F. Newcombe, *Missile Wounds of the Brain: A Study of Psychological Deficits*, Oxford U. Press, Oxford, England, 1969.
- [42] A.L. Benton, Differential behavioral effects in frontal lobe disease, *Neuropsychologia*. 6 (1) (1968) 53–60, [https://doi.org/10.1016/0028-3932\(68\)90038-9](https://doi.org/10.1016/0028-3932(68)90038-9).
- [43] R.H.B. Benedict, D. Schretlen, L. Groninger, M. Dobraski, B. Shpritz, Revision of the brief visuospatial memory test: studies of normal performance, reliability, and validity, *Psychol. Assess.* 8 (2) (1996) 145–153, <https://doi.org/10.1037/1040-3590.8.2.145>.
- [44] D. Wechsler, *Wechsler Adult Intelligence Scale, 4th ed.*, Baltimore, MD, Williams & Wilkins, 1958 <https://www.pearsonclinical.com/psychology/products/100000392/wechsler-adult-intelligence-scale-fourth-edition-wais-iv.html> Accessed March 20, 2019.
- [45] Pearson Clinical Australia & New Zealand Boston Naming Test - Second Edition|Pearson Clinical Australia & New Zealand. Accessed March 20, 2019, <https://www.pearsonclinical.com.au/products/view/525>.
- [46] D. Wechsler, *Wechsler Memory Scale, 3rd ed.*, The Psychological Corporation, San Antonio, TX, 1997.
- [47] G. Bennett, H. Seashore, A. Wesman, *Differential Aptitude Test, The Psychological Corporation, San Antonio, TX, 1997*.
- [48] T.A. Salthouse, N. Fristoe, S.H. Rhee, How localized are age-related effects on neuropsychological measures? *Neuropsychology*. 10 (2) (1996) 272–285, <https://doi.org/10.1037/0894-4105.10.2.272>.
- [49] J. Raven, *Advanced Progressive Matrices, Set II*, London, England, H.K. Lewis, 1962.
- [50] P.D. Zelazo, J.E. Anderson, J. Richler, K. Wallner-Allen, J.L. Beaumont, S. Weintraub, NIH toolbox cognition battery (cb): measuring executive function and attention, *Monogr. Soc. Res. Child Dev.* 78 (4) (2013) 16–33, <https://doi.org/10.1111/mono.12032>.
- [51] K.I. Erickson, M.W. Voss, R.S. Prakash, et al., Exercise training increases size of hippocampus and improves memory, *Proc. Natl. Acad. Sci. U. S. A.* 108 (7) (2011) 3017–3022, <https://doi.org/10.1073/pnas.1015950108>.
- [52] J.M. Monti, G.E. Cooke, P.D. Watson, M.W. Voss, A.F. Kramer, N.J. Cohen, Relating Hippocampus to relational memory processing across domains and delays, *J. Cogn. Neurosci.* 27 (2) (2015) 234–245, https://doi.org/10.1162/jocn_a.00717.
- [53] A. Bechara, A.R. Damasio, H. Damasio, S.W. Anderson, Insensitivity to future consequences following damage to human prefrontal cortex, *Cognition*. 50 (1–3) (1994) 7–15.
- [54] T.A. Salthouse, R.L. Babcock, Decomposing adult age differences in working memory, *Dev. Psychol.* 27 (5) (1991) 763–776, <https://doi.org/10.1037/0012-1649.27.5.763>.
- [55] B. Balke, R.W. Ware, An experimental study of physical fitness of air force personnel, *U S Armed Forces Med J.* 10 (6) (1959) 675–688.
- [56] G.A.V. Borg, Psychophysical bases of perceived exertion, *Med. Sci. Sports Exerc.* 14 (5) (1982) 377–381, <https://doi.org/10.1249/00005768-198205000-00012>.
- [57] E. Edvardsen, E. Hem, S.A. Anderssen, End criteria for reaching maximal oxygen uptake must be strict and adjusted to sex and age: a cross-sectional study, *PLoS One* 9 (1) (2014) e85276, <https://doi.org/10.1371/journal.pone.0085276>.
- [58] J.D. Ragland, C. Ranganath, M.P. Harms, et al., Functional and neuroanatomic specificity of episodic memory dysfunction in schizophrenia: a functional magnetic resonance imaging study of the relational and item-specific encoding task, *JAMA Psychiatr.* 72 (9) (2015) 909–916, <https://doi.org/10.1001/jamapsychiatry.2015.0276>.
- [59] O. Esteban, D. Birman, M. Schaer, O.O. Koyejo, R.A. Poldrack, K.J. Gorgolewski, MRIQC: predicting quality in manual MRI assessment protocols using no-reference image quality measures, *bioRxiv* (February 2017) 111294, <https://doi.org/10.1101/111294>.
- [60] E.J. Auerbach, J. Xu, E. Yacoub, S. Moeller, K. Uğurbil, Multiband accelerated spin-echo echo planar imaging with reduced peak RF power using time-shifted RF pulses, *Magn. Reson. Med.* 69 (5) (2013) 1261–1267, <https://doi.org/10.1002/mrm.24719>.
- [61] K. Setsompop, J. Cohen-Adad, B.A. Gagoski, et al., Improving diffusion MRI using simultaneous multi-slice echo planar imaging, *NeuroImage*. 63 (1) (2012) 569–580, <https://doi.org/10.1016/j.neuroimage.2012.06.033>.
- [62] K. Setsompop, B.A. Gagoski, J.R. Polimeni, T. Witzel, V.J. Wedeen, L.L. Wald, Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty, *Magn. Reson. Med.* 67 (5) (2012) 1210–1224, <https://doi.org/10.1002/mrm.23097>.
- [63] J. Xu, S. Moeller, E.J. Auerbach, et al., Evaluation of slice accelerations using multiband echo planar imaging at 3 T, *NeuroImage*. 83 (2013) 991–1001, <https://doi.org/10.1016/j.neuroimage.2013.07.055>.
- [64] E. Kilroy, L. Apostolova, C. Liu, L. Yan, J. Ringman, D.J.J. Wang, Reliability of two-dimensional and three-dimensional pseudo-continuous arterial spin labeling perfusion MRI in elderly populations: comparison with 150-water positron emission tomography, *J. Magn. Reson. Imaging JMIR*. 39 (4) (2014) 931–939, <https://doi.org/10.1002/jmri.24246>.
- [65] D.J.J. Wang, J.R. Alger, J.X. Qiao, et al., Multi-delay multi-parametric arterial spin-labeled perfusion MRI in acute ischemic stroke - comparison with dynamic susceptibility contrast enhanced perfusion imaging, *NeuroImage Clin.* 3 (2013) 1–7, <https://doi.org/10.1016/j.nicl.2013.06.017>.
- [66] B. Langhammer, J.K. Stanghelle, The senior fitness test, *J. Physiother.* 61 (3) (2015) 163, <https://doi.org/10.1016/j.jphys.2015.04.001>.
- [67] J.M. Guralnik, E.M. Simonsick, L. Ferrucci, et al., A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission, *J. Gerontol.* 49 (2) (1994) M85–M94, <https://doi.org/10.1093/geronj/49.2.M85>.
- [68] B. Manor, W. Yu, H. Zhu, et al., Smartphone app-based assessment of gait during normal and dual-task walking: demonstration of validity and reliability, *JMIR MHealth UHealth* 6 (1) (2018), <https://doi.org/10.2196/mhealth.8815>.
- [69] E. McAuley, The role of efficacy cognitions in the prediction of exercise behavior in middle-aged adults, *J. Behav. Med.* 15 (1) (1992) 65–88.
- [70] G.V. Caprara, C. Barbaranelli, L. Borgogni, M. Perugini, The “big five questionnaire”: a new questionnaire to assess the five factor model, *Personal. Individ. Differ.* 15 (3) (1993) 281–288, [https://doi.org/10.1016/0191-8869\(93\)90218-R](https://doi.org/10.1016/0191-8869(93)90218-R).
- [71] R.E. Amariglio, M.C. Donohue, G.A. Marshall, et al., Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's disease cooperative study cognitive function instrument, *JAMA Neurol.* 72 (4) (2015) 446–454, <https://doi.org/10.1001/jamaneurol.2014.3375>.
- [72] S. Cohen, W.J. Doyle, D.P. Skoner, B.S. Rabin, J.M. Gwaltney, Social ties and susceptibility to the common cold, *JAMA*. 277 (24) (1997) 1940–1944.
- [73] C. Randler, Validation of the full and reduced composite scale of morningness, *Biol. Rhythm. Res.* 40 (5) (2009) 413–423, <https://doi.org/10.1080/09291010902731213>.
- [74] M.D. Miller, C.F. Paradis, P.R. Houck, et al., Rating chronic medical illness burden in geropsychiatric practice and research: application of the cumulative illness rating scale, *Psychiatry Res.* 41 (3) (1992) 237–248, [https://doi.org/10.1016/0165-1781\(92\)90005-N](https://doi.org/10.1016/0165-1781(92)90005-N).
- [75] G. Block, M. Woods, A. Potosky, C. Clifford, Validation of a self-administered diet

- history questionnaire using multiple diet records, *J. Clin. Epidemiol.* 43 (12) (1990) 1327–1335, [https://doi.org/10.1016/0895-4356\(90\)90099-B](https://doi.org/10.1016/0895-4356(90)90099-B).
- [76] S.T. Farias, D. Mungas, B.R. Reed, et al., The measurement of everyday cognition (ECog): scale development and psychometric properties, *Neuropsychology*. 22 (4) (2008) 531–544, <https://doi.org/10.1037/0894-4105.22.4.531>.
- [77] M.F. Janssen, A.S. Pickard, D. Golicki, et al., Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study, *Qual. Life Res.* 22 (7) (2013) 1717–1727, <https://doi.org/10.1007/s11136-012-0322-4>.
- [78] E. McAuley, C. Cox, T.E. Duncan, Long-term maintenance of exercise, self-efficacy, and physiological change in older adults, *J. Gerontol.* 48 (4) (1993) P218–P224.
- [79] C.E. Cutrona, D.W. Russell, The provisions of social relationships and adaptation to stress, *Adv. Social Relationships* 1 (1987) 37–67.
- [80] B. Resnick, S.I. Zimmerman, D. Orwig, A.-L. Furstenberg, J. Magaziner, Outcome expectations for exercise scale Utility and psychometrics, *J. Gerontol. Ser. B* 55 (6) (2000) S352–S356, <https://doi.org/10.1093/geronb/55.6.S352>.
- [81] D.M. Hann, M.M. Denniston, F. Baker, Measurement of fatigue in cancer patients: further validation of the fatigue symptom inventory, *Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil.* 9 (7) (2000) 847–854.
- [82] J.A. Schinka, A. McBride, R.D. Vanderploeg, K. Tennyson, A.R. Borenstein, J.A. Mortimer, Florida cognitive activities scale: initial development and validation, *J. Int. Neuropsychol. Soc.* 11 (1) (2005) 108–116, <https://doi.org/10.1017/S1355617705050125>.
- [83] G. Godin, R.J. Shephard, A simple method to assess exercise behavior in the community, *Can. J. Appl. Sport Sci. J. Can. Sci. Appl. Au Sport.* 10 (3) (1985) 141–146.
- [84] A. Maetzel, L.C. Li, J. Pencharz, G. Tomlinson, C. Bombardier, Community hypertension and arthritis project study team. The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study, *Ann. Rheum. Dis.* 63 (4) (2004) 395–401.
- [85] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, *Acta Psychiatr. Scand.* 67 (6) (1983) 361–370.
- [86] M.P. Lawton, E.M. Brody, Assessment of older people: self-maintaining and instrumental activities of daily living, *Gerontologist* 9 (3, Part 1) (1969) 179–186, https://doi.org/10.1093/geront/9.3.Part_1.179.
- [87] E. McAuley, S.P. Mullen, A.N. Szabo, et al., Self-regulatory processes and exercise adherence in older adults: executive function and self-efficacy effects, *Am. J. Prev. Med.* 41 (3) (2011) 284–290, <https://doi.org/10.1016/j.amepre.2011.04.014>.
- [88] T.E. Seeman, E. Crimmins, M.-H. Huang, et al., Cumulative biological risk and socio-economic differences in mortality: MacArthur studies of successful aging, *Soc. Sci. Med.* 58 (10) (2004) 1985–1997, [https://doi.org/10.1016/S0277-9536\(03\)00402-7](https://doi.org/10.1016/S0277-9536(03)00402-7).
- [89] R. Melzack, The short-form McGill pain questionnaire, *Pain.* 30 (2) (1987) 191–197, [https://doi.org/10.1016/0304-3959\(87\)91074-8](https://doi.org/10.1016/0304-3959(87)91074-8).
- [90] J. MacKillop, E.J. Anderson, Further psychometric validation of the mindful attention awareness scale (MAAS), *J. Psychopathol. Behav. Assess.* 29 (4) (2007) 289–293, <https://doi.org/10.1007/s10862-007-9045-1>.
- [91] S. Cohen, Perceived stress in a probability sample of the United States, *The Social Psychology of Health. The Claremont Symposium on Applied Social Psychology*, Sage Publications, Inc, Thousand Oaks, CA, US, 1988, pp. 31–67.
- [92] M.R. Umstatt, R. Motl, S. Wilcox, R. Saunders, M. Watford, Measuring physical activity self-regulation strategies in older adults, *J. Phys. Act. Health* 6 (Suppl. 1) (2009) S105–S112.
- [93] K.R. Fox, C.B. Corbin, The physical self-perception profile: development and preliminary validation, *J. Sport Exerc. Psychol.* 11 (4) (1989) 408–430.
- [94] D.J. Buysse, C.F. Reynolds, T.H. Monk, S.R. Berman, D.J. Kupfer, The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research, *Psychiatry Res.* 28 (2) (1989) 193–213, [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4).
- [95] J.F. Fries, B. Bruce, D. Cella, The promise of PROMIS: using item response theory to improve assessment of patient-reported outcomes, *Clin. Exp. Rheumatol.* 23 (5 SUPPL. 39) (2005) S53–S57.
- [96] R.W. Robins, H.M. Hendin, K.H. Trzesniewski, Measuring global self-esteem: construct validation of a single-item measure and the Rosenberg self-esteem scale, *Personal. Soc. Psychol. Bull.* 27 (2) (2001) 151–161, <https://doi.org/10.1177/0146167201272002>.
- [97] E. Diener, R.A. Emmons, R.J. Larsen, S. Griffin, The satisfaction with life scale, *J. Pers. Assess.* 49 (1) (1985) 71–75, https://doi.org/10.1207/s15327752jpa4901_13.
- [98] J.E. Ware, C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection, *Med. Care* 30 (6) (1992) 473–483.
- [99] J.Y. Chau, H.P. van der Ploeg, S. Dunn, J. Kurko, A.E. Bauman, A tool for measuring workers' sitting time by domain: the Workforce Sitting Questionnaire, *Br. J. Sports Med.* 45 (15) (2011) 1216–1222, <https://doi.org/10.1136/bjsports-2011-090214>.
- [100] E. Orehek, A.L. Forest, S. Wingrove, People as means to multiple goals: implications for interpersonal relationships, *Personal. Soc. Psychol. Bull.* 44 (10) (2018) 1487–1501, <https://doi.org/10.1177/0146167218769869>.
- [101] D. Russell, L.A. Peplau, C.E. Cutrona, The revised UCLA loneliness scale: concurrent and discriminant validity evidence, *J. Pers. Soc. Psychol.* 39 (3) (1980) 472–480, <https://doi.org/10.1037/0022-3514.39.3.472>.
- [102] E. Nord, The validity of a visual analogue scale in determining social utility weights for health states, *Int. J. Health Plann. Manag.* 6 (3) (1991) 234–242, <https://doi.org/10.1002/hpm.4740060308>.
- [103] F.P. Morgeson, S.E. Humphrey, The Work Design Questionnaire (WDQ): developing and validating a comprehensive measure for assessing job design and the nature of work, *J. Appl. Psychol.* 91 (6) (2006) 1321–1339, <https://doi.org/10.1037/0021-9010.91.6.1321>.
- [104] H. Barthel, H.-J. Gertz, S. Dresel, et al., Cerebral amyloid- β PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study, *Lancet Neurol.* 10 (5) (2011) 424–435, [https://doi.org/10.1016/S1474-4422\(11\)70077-1](https://doi.org/10.1016/S1474-4422(11)70077-1).
- [105] A.F. Hayes, Partial, conditional, and moderated moderated mediation: quantification, inference, and interpretation, *Commun. Monogr.* 85 (1) (2018) 4–40, <https://doi.org/10.1080/03637751.2017.1352100>.
- [106] K.J. Preacher, A.F. Hayes, Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models, *Behav. Res. Methods* 40 (3) (2008) 879–891.