PROTOCOL TEMPLATE: INTERVENTIONAL STUDY

Complete Title: Assessing the feasibility and acceptability of a Time Restricted Feeding intervention among older adults with Mild Cognitive Impairment
Short Title: Time Restricted Eating for Metabolic and Psychological Optimization (TEMPO)
Drug or Device Name(s): N/A
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Sponsor: National Institute of Aging
Protocol Date: 7/1/2025
NCT#: NCT05997316

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EXAMPLE: Protocol Signature page for Multicenter research where the PI at UNC is the overall PI.

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Short Title: Time Restricted Eating for Metabolic and Psychological Optimization (TEMPO)

Lead Investigator:
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Version Date: 7/1/2025

I confirm that I have read this protocol and understand it.
Principal Investigator Name: Patrick J. Smith, PhD, MPH

Principal Investigator Signature: 

Date: 7/1/2025

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PROTOCOL SYNOPSIS: Obesity and related metabolic comorbidities have been associated with more than a 4-fold increased risk of incident cognitive impairment, including Alzheimer's disease and related dementias (ADRD). Dysfunctional metabolic flexibility is increasingly recognized as a critical mechanism linking metabolic risk factors to risk of cognitive impairment, although few studies portable behavioral strategies to enhance metabolic function among individuals at risk for ADRD. The TEMPO trial examined the feasibility and acceptability of a 12-week time restricted feeding intervention among individuals with mild cognitive impairment (MCI), as well as assessing changes in cognitive and metabolic function.

BACKGROUND AND RATIONALE:

A.1. Public Health Significance of Mild Cognitive Impairment and Alzheimer's and Related Dementias. The United States population is increasingly older and overweight, with nearly 50% of adults projected to meet criteria for obesity by 2030.[38] In parallel, older adults (aged ≥ 65 years) will represent an increasingly high proportion of the American population, at an estimated 73 million individuals. As a corollary, the prevalence of Alzheimer's and Related Dementias (ADRD) is also projected to increase from 26.6 million to over 106 million worldwide by mid-century.[39-41] In addition, many more older adults will develop subclinical cognitive impairments that substantially impair quality of life and independent functioning without reaching criteria for dementia, including mild cognitive impairment (MCI).[52] Recent estimates have suggested that ADRD may account for up to $215 billion annually in public health expenditures[42] and is projected to increase.

A.2 Metabolic Function, MCI, and ADRD. Metabolic dysfunction is increasingly recognized as a 'a key [causal] player in dementia pathology', increasing the risk of disease progression and cognitive impairment.[43] Obesity and associated metabolic risk factors are associated with increased risk of MCI,[44,45] elevated ADRD biomarkers, [46-48] and faster progression from MCI to ADRD.[1,48-50] The adverse impact of obesity on the brain is not surprising, given that obesity is associated with an array of cardiovascular and metabolic abnormalities,[51] including hypertension,[52] insulin resistance, and dyslipidemia; all of which increase ADRD risk,[53-61] worsen ADRD biomarker profiles,[62] and are modifiable with weight loss.[63,64] The presence of obesity appears to increase ADRD risk independent of comorbid vascular risk factors [65] or genetic risk.[66]
Despite the robust association demonstrated between peripheral metabolic dysfunction and cognitive impairment, primary prevention efforts have been hampered by a lack of mechanistic insight delineating the pathways by which peripheral impairments in metabolic function impair central nervous system (CNS) metabolic function. This is particularly important as neurocognitive benefits following exercise-based lifestyle modification appear to be age-dependent,[67-71] with larger benefits in middle-aged relative to older samples, leading some investigators to hypothesize a metabolic 'tipping point' for intervention efficacy.[72-74] In addition, the beneficial effects of weight loss on cognition do not appear to correlate consistently with improved aerobic fitness or weight loss from prior behavioral trials, [75,76] strongly suggesting that the beneficial effects of such interventions may be transmitted through alternative metabolic pathways.[37,77] This could explain why recent trials among participants with metabolic risk factors, such as the Diabetes Prevention Program (DPP)[78] and LOOK-AHEAD trials, found that behavioral weight loss may not improve cognition.[79-84] Elucidating metabolic pathways that enhance cognition is a critical knowledge gap.

A.2 Metabolic Switching, Ketone Metabolism, and MCI. An emerging line of research suggests that the brain's ability to shift between metabolic energy substrates is a critical, understudied mechanism linking obesity to cognitive impairment. The ability to metabolically switch between peripheral energy resources between times of negative energy balance and positive energy balance (i.e. excess energy intake relative to output) appears to play an important role in healthy aging, systemic metabolic function, and CNS metabolic efficiency.[85] In addition, experimental evidence linking dietary changes to neuroimaging biomarkers suggests that greater time spent utilizing ketones as the brain's primary fuel supply has a stabilizing effect on brain network connectivity and improves cognitive function, whereas the opposite pattern is observed for glucose.[86] The capacity for the brain to change fuel sources, referred to as 'metabolic switching', declines with age[86,87] and is impaired among those with metabolic conditions, such as diabetes.[88] Despite constituting only 2% of body mass, the brain disproportionately utilizes 20% of systemic energy resources and decreases in metabolic

efficiency with older age. Systemic insulin resistance has a well-documented, deleterious effect on brain glucose utilization, blunting the effects of CNS energy resources, accelerating cognitive aging, and increasing the likelihood of ADRD by 2-3 fold.[14] Despite the profound effects of systemic metabolism on brain function, ketogenic energy resources appear relatively spared from the effects of biological aging and appear to remain efficient among older adults.[16] Notably, although CNS hypometabolism is a cardinal feature of ADRD brain function, utilization of ketone bodies appears unaffected by this ongoing neurodegenerative process and chronic engagement in hypocaloric dietary patterns appears to preserve synaptic plasticity and cognitive function in animal models.[89] Few studies have attempted to examine the effects of ketone manipulation on neurocognitive function[15,90,91] or the potentially mediating role of increased ketone production for neurocognitive improvement in the context of lifestyle modification interventions.

Available evidence is therefore consistent with alterations in ketones playing a critical mechanistic role by which lifestyle improves cognitive function. Ketones are the preferred fuel source for cerebral functions and are over-represented in the prefrontal cortex,[92] consistent with the effects of behavioral weight loss on executive functions and learning / memory consolidation.[69,70,72,73] A recent pilot study among older adults with memory complaints or impairments demonstrated that dietary modification increased cerebral ketone metabolism and memory performance.[93] In addition, recent meta-analytic studies suggest that trials eliciting even mild ketosis result in moderate cognitive improvements among individuals with mild cognitive impairment or ADRD.[90]

A.3 Time Restricted Feeding to Improve Metabolic Function. A rapidly emerging body of literature suggests that time restricted feeding (TRF) / intermittent fasting is a feasible intervention to enhance metabolic function[32] among older adults.[30,35,94] Recent pilot studies have demonstrated that even a one-month TRF intervention among older adults (aged ≥ 65 years) with metabolic risk factors results in substantial weight loss (~5lbs) and was associated with high levels of treatment adherence (meeting goals on 84% of days).[35] Importantly, available data from both human and animal studies suggests that TRF is unique from other 'whole diet' interventions in its impact on metabolic mechanisms, mitochondrial biogenesis, and cellular plasticity, resulting in overall enhanced metabolic efficiency. [95] TRF has also been suggested play an important protective role in protecting against cognitive decline both by increasing overall cerebral health and by enhancing the brain's ability to adapt during acute metabolic fluctuations by recruiting additional energy resources, such as ketones.[19] Recent thought leaders in the field of TRF have advocated for "Future randomized controlled IF trials should use biomarkers of the metabolic switch (e.g., ketone levels) as a measure of compliance and of the magnitude of negative energy balance during the fasting period". [85] Our overarching conceptual hypothesis is that chronic metabolic dysfunction results in an impaired CNS metabolic efficiency and cognitive function, both of which may be improved by TRF (**Figure 1**).

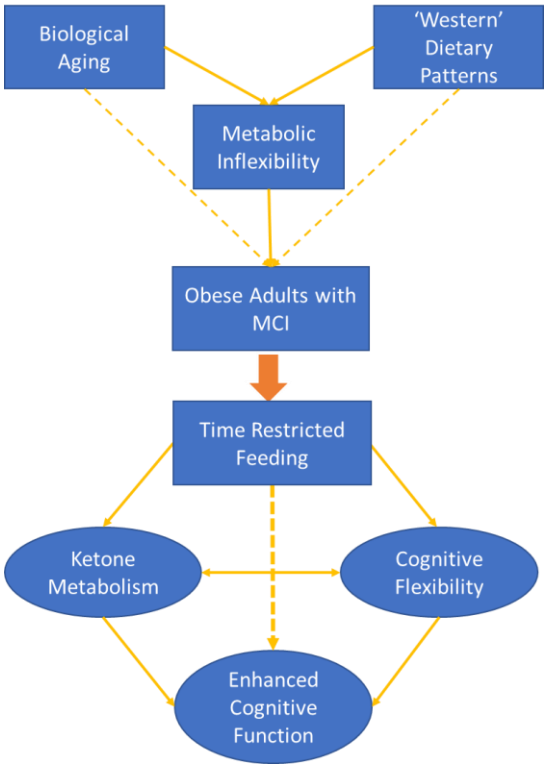


Figure 1. Conceptual model linking metabolic inflexibility, cognitive function, and obesity in MCI.

B. INNOVATION. The proposed project has a number of innovative features. **First**, the project is innovative in its focus on using a potentially portable, low-cost intervention approach for a highly prevalent, very costly public health problem. Despite the prevalence and lack of treatments to stabilize MCI, no studies have examined experimentally manipulated fasting or its mechanisms in this vulnerable patient group. **Second**, our focus on temporal patterns of eating behavior is unique and represents a critical departure from prior work examining either caloric restriction or modifying overall dietary patterns. Prior multimodal interventions have suggested that dietary interventions have among the lowest adherence rates when compared to other behavioral intervention components, such as exercise or vascular risk modification.[96,97] Recent evidence among older adults suggests that TRF is more feasible and therefore represents a more portable intervention approach. Therefore, if the proposed intervention is successful, it holds great importance as a first-line strategy to enhance prevention efforts among individuals with MCI. **Third**, our focus on multiple markers of metabolic switching is novel and an important innovation that diverges from conventional 'whole diet' or single nutrient approaches, which target

basal metabolic function. **Fourth**, Duke is among leading institutions in the United States in its examination of metabolic mechanisms linking lifestyle factors, such as physical activity and eating patterns, with metabolic disease processes. The present proposal solidifies new collaborations between investigators within the Duke Molecular Physiology Institute (DMPI: Huffman and Muoio) and investigators within aging and behavioral interventions in MCI (PI Smith and co-I Strauman).

C. PRELIMINARY STUDIES. Our team has conducted research in three broad areas relevant to the proposed study, including 1) dietary modification and weight loss, 2) MCI trials, and 3) metabolic mechanisms:

1) Metabolic Mechanisms of Caloric Restriction: Drs. Huffman, Parker, and Muoio have conducted and/or evaluated metabolic responses to multiple translational studies linking lifestyle modification to therapeutic mechanisms. In young, normal to slightly overweight (BMI 22-27.9 kg/m2) adults, 12 months of ~12% CR (versus ad libitum (AL)) increased NMR- assessed fasting acetone and, after 24 months, fasting β-hydroxybutyrate (both groups, P<0.04) (**Figure 2**).[98] In CALERIE Phase 1, six months of 25% CR, 12.5% CR plus 12.5% caloric deficit from exercise training, and weight maintenance control diet were compared. Despite being matched for caloric deficit with confirmation by similar weight loss and body composition changes, CR alone and CR displayed unique metabolic responses for amino acids, acylcarnitines (fatty acid oxidation by products), and fatty acids. For CR alone, acylcarnitine concentrations increased and were consistent with greater amounts of complete fatty acid oxidation.[99] Additionally, CR alone improved metabolic flexibility, assessed as a greater ability to shift substrate utilization from the fasting to fed state with post-prandial reductions in fatty acids and acylcarntines, exceeding improvements in CR + exercise.[100]

2) Lifestyle Trials, Metabolism, and Cognitive Function: Our investigative team has conducted numerous RCTs examining the associations between improved metabolic function and cognitive function.[37,70,101-107] Dr. Patrick Smith's previously published findings from the ENCORE trial of middle-aged adults with obesity and hypertension demonstrated that 4 months of weight loss program improved executive functioning, memory, and learning, and these results were strongest when weight loss was enhanced using the DASH diet (d = 0.56, P = .008).[37] Dr. Smith was also instrumental to the design[106] and implementation of the ENLIGHTEN trial of aerobic exercise and the DASH diet among older adults with vascular comorbidities and cognitive impairment,[12,102,108,109] many of whom had MCI. Results demonstrated that exercise participants exhibited significant improvements in executive function (d = 0.32, P = .046), with smaller improvements among DASH participants (d = 0.30, P = .059), and the largest improvements among participants randomized to receive both (d = 0.40; p = 0.046)[109] that were sustained at 18-months.[110]

	Ad libitum group (n=75)	Calorie restriction group (n=143)	Between-group p-value
Total ketone bodies (μM)			
Baseline	196.9 (10.9)	218.8 (11.5)	0.8678
Change at month 12	9.04 (19.05)	47.57 (14.09)***	0.0952
Change at month 24	-4.62 (16.71)	34.47 (12.77)**	0.0546
β-hydroxybutyrate (μM)			
Baseline	117.0 (7.1)	128.3 (7.6)	0.9137
Change at month 12	-0.76 (11.70)	23.23 (8.66)**	0.0903
Change at month 24	-7.90 (10.27)	17.95 (7.86)*	0.0385*
Acetoacetate (μM)			
Baseline	52.2 (3.5)	56.5 (2.8)	0.3975
Change at month 12	10.20 (5.88)	20.18 (4.37)***	0.1629
Change at month 24	6.51 (5.06)	17.37 (3.89)***	0.0791
Acetone (μM)			
Baseline	27.7 (2.1)	34.0 (2.6)	0.4360
Change at month 12	-2.77 (3.07)	4.86 (2.27)*	0.0429*
Change at month 24	-5.39 (2.24)*	-0.33 (1.72)	0.0645

Figure 2: CALERIE Phase 1 group differences for circulating ketone concentrations. Ketones were measured use nuclear magnetic resonance-based methods.

3) Peripheral metabolic mechanisms of ADRD risk: We have published numerous studies examining metabolic mechanisms of cognitive change.[102,104,105,111,112] Our research group has focused primarily on examining the overlap between cardiometabolic risk factors (CMRFs), subclinical carotid atherosclerosis, and endothelial dysfunction on cognition,[102,111,112] demonstrating that these subclinical risk markers may mediate the associations between clinical CMRFs (e.g. hypertension) and neurocognitive impairment.[112] We examined mechanisms linking physical activity, aerobic fitness, the DASH diet, and cognition, focusing on CMRFs and inflammatory biomarkers.[102] We found that higher levels of fitness and the DASH diet were associated with better cognition among individuals with CIND, and that these associations were partially mediated by CMRFs, suggesting that these interrelated factors were additively associated with outcomes.[102] In addition, we found that obese participants exhibited worse executive function at baseline and that this association was mediated by impaired metabolic biomarkers, including insulin and leptin resistance.[36] Similar findings emerged from baseline assessments of our ongoing behavioral weight loss trial among treatment-resistant hypertensives, the majority

of whom are obese. We found that greater obesity (β = -0.19, P = .029) and HOMA-IR (β = -0.46, P <.001) associated with worse executive function,[36] with HOMA-IR mediating this association.[113]

Co-Investigators' Expertise. The proposed R21 integrates work from several areas to provide an integrated behavioral approach to enhance metabolic functioning through TRF among individuals with MCI.

Dr. Patrick Smith completed postdoctoral fellowships in both behavioral medicine and clinical neuropsychology and has served as the PI or co-I on multiple MCI studies, including lifestyle trials (HL109219)[12,106,109,110,113] and identification of MCI patients using functional connectivity metrics (AG042599). Dr. Smith also serves as one of two core clinical neuropsychologists on the recently funded Duke-UNC Alzheimer's Disease Research Center. His work has focused on enhancing neurocognition using behavioral weight loss, such as dietary modification and exercise,[12,36,37,70,104,113-117] most of which integrated Dr. Krista Ingle, our study interventionist, as the primary behavioral weight loss interventionist. Dr. Smith recently served as the PI for a trial examining the effects of behavioral weight loss on cerebrovascular and endothelial mechanisms of cognitive enhancement (HL130237).[36,118] Drs. Kim Huffman and Deborah Muoio have performed extensive work examining metabolic and inflammatory mechanisms of lifestyle modification.[100,119-124] Dr. Huffman has also mentored Dr. Daniel Parker, a geriatrician focusing on biomarkers and mechanistic treatment targets for ADRD-related dementias. Finally, Dr. Timothy Strauman is an expert in interventions to enhance self-regulatory function across multiple clinical populations.[125-132] He has collaborated extensively with Dr. Smith on prior trials[37] and related reviews.[70]

RESEARCH STRATEGY: D. R21 APPROACH

Methodological Features: Our intervention approach has been informed both by contemporary pilot studies in healthy older adults,[35,133,134] adults with cardiometabolic risk factors,[135-138] and our own work among adults with cardiometabolic risk factors[37,115,139-141] and cognitive impairment.[12,36,109,110,113,142] In terms of our behavioral intervention approach for TRF, our primary conceptual underpinning is therefore based on temporal self-regulation theory,[143-148] in which adults with MCI participate in TRF using behavioral (e.g. hunger) and environmental context (e.g. home and time of day) to enhance context-specific responsivity for self-regulation. Several key features were prioritized in developing the initial treatment approach for the proposed intervention, including 1) appetite awareness training,[37,139,149] 2) enhanced psychological flexibility and experiential acceptance of aversive hunger cues,[150-152] 3) stimulus control through environmental modification,[153-155] and 4) cognitive control techniques derived from the Motivationally Enhanced Compensatory Cognitive Training for Mild Cognitive Impairment (ME-CCT-MCI) protocol (see details in Human Subjects).[156-158] Although our a priori focus be on intervening on an individual level with the participants, we recognize that many participants will have social support members who may wish to participate. We will therefore allow but not require participation by study partners, consistent with our prior intervention approaches.[12,142,159,160] For participants with study partners, we will incorporate elements from Multi Contextual Treatment Approach, which focuses on strategy generation and metacognitive process components to enhance transfer of behavioral skills.[161-166]

Table 1. Time-Restricted Feeding Focus Group and Pilot Testing

Participatory Design Focus Group
Participatory focus groups will be conducted (n = 6/group) to guide investigators in developing the TRF protocol and modify elements of the intervention approach. Focus groups will be developed based on our: 1) prior experience using dietary modification, behavioral weight loss, and appetite awareness training among older adults, 2) clinical experience among individuals with MCI, 3) empirical work from prior behavioral interventions in MCI, particularly the ME-CCT-MCI treatment protocol, and 4) prior experience using affect regulation approaches to increase psychological flexibility among individuals with impulsivity and executive dysfunction.
Intervention Development Focus Groups
Two intervention development focus groups will be conducted to have MCI participants and their study partners evaluate the TRF protocol materials. We will plan to conduct these groups in-person and using telehealth video interfaces to accommodate distancing restrictions and enhance translation of intervention materials to participants home environment.
Intervention Evaluation Focus Groups
The final focus group will have individuals with MCI and their study partners evaluate the fully developed TRF protocol. Participants will provide feedback to be incorporated into any final protocol modifications.

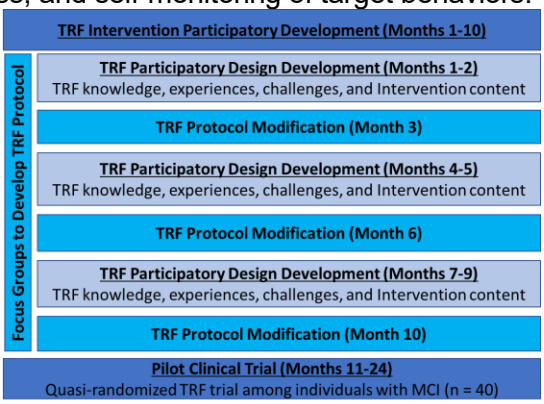
We anticipate that early sessions will focus on **motivational and organizational factors**, including 1) identifying motivational factors leading to study enrollment through values clarification and self-discrepancy exercises[129,167,168] to enhance the personal salience of TRF goals, 2) collaborative goal-setting using SMART (Specific, Measurable, Achievable, Relevant, and Time-bound),[169] and 3) organizational strategies to enhance self-monitoring and success with early TRF sessions. The intervention will then shift to focus on **coping skills to enhance affect regulation and inhibitory control**. Approaches will include 1) appetite awareness training with mindfulness,[37] 2) relaxation and distress tolerance techniques,[170] and 3) cognitive defusion approaches.[171] Following the deployment of affect regulation strategies, we will then shift to **cultivating cognitive compensatory strategies** to enhance 1) attention modulation, 2) encoding of TRF information, and 3) problem-solving approaches. In the final stage of the trial, we plan to focus on **relapse prevention training** through 1) self-reinforcement strategies, 2) contingency management, and 3) stimulus control.[150] Throughout the intervention, we will deploy behavioral intervention strategies known to be efficacious among individuals with MCI, in which environmental cues and other aspects of implementation intentions are leveraged to

encourage initiation of target behaviors. Environmental modifications will therefore be recommended to enhance automatic cues for TRF success in the participant's home, such as using a centralized white board. Common barriers to organization will be discussed, with potential self-management strategies offered for participants to choose a personalized strategy to enhance adherence. Intervention approaches will be personalized using baseline executive function profiles with a particular focus on individual differences in inhibitory control. We note that the proposed intervention components above and detailed in the Human Subjects section will serve as a general template or 'roadmap' for intervention development, which will be iteratively adapted based on participant feedback in order to optimize acceptability.
TRF intervention components: Prior studies have demonstrated the greatest feasibility using a 16-hour based fasting period (16:8), deployed twice per week (5:2). Initial TRF recommendations will be to fast during two days during the next week, at least two days apart, with a fasting period of 14 hours and eating period of 10 hours. This will gradually be titrated up to a 16 hour fast with 8 hours of unrestricted eating (16:8) on two days per week, consistent with the prevailing 5:2 trial approaches. Participants typically place their 16-hr fasting period as beginning following dinner (e.g. 8pm) and ending at lunch the following day (e.g. 12pm). We will *a priori* target the 16:8 fasting on a 5:2 schedule to maximize acceptability. A minimum of 14-hrs will be used during the early stages of fasting training, as needed. During the fasting periods, participants will be allowed to drink water but will be instructed to refrain from eating, snacking, or consuming sugar-sweet beverages.

Importance of Executive Functioning: Executive functioning is a key driver of self-regulatory behaviors and is highly predictive of habitual behavioral modifications. Participants with greater inhibitory control, working memory, and mental flexibility should have greater ability to both make and sustain behavioral changes over time. Baseline levels of executive functioning will therefore play a major role in personalization of intervention techniques. Individuals with poorer inhibitory control, for example, will be preferentially trained to increase the amount of behavioral 'friction' for dietary indiscretions during fasting periods. This could include 1) engaging in activities away from their home (and easily accessible food sources) during fasting periods, 2) removing all easily accessible snacks from their kitchen and/or pantry in order to reduce their primacy, and 3) substituting pleasurable distractions such as spending time with others, watching a movie, or engaging in other value-consistent activities to help distract them from hunger cues.

Phasic Intervention Approach: Recent behavioral intervention development approaches have placed an emphasis on the use of phased intervention approaches to enhance acquisition and extension of new behavioral skills. Our intervention team was persuaded by recent data from the Science of Behavior Change (SOBC)[172] initiative demonstrating that behavioral intervention strategies are most effective when tailored to intervention stage, with strategies to improve self-efficacy yielding the largest benefits in behavioral adoption / initiation phase, self-regulatory and stimulus control strategies to modify contextual cues yielding the largest benefits in the implementation phase, and strategies to modify self-monitoring and expectations in the maintenance phase. Reinforcement frequency and potency as well as self-monitoring techniques, have been found to be optimally utilized when deployment varies by the phase of treatment, with more frequent reinforcement during skills acquisition (e.g. adoption phase [1-3]) and variable reinforcement during skills implementation and maintenance phases (e.g. implementation phase [4-8]). This dual-process intervention approach maximizes habitual elements of behavior changes by modifying contextual cues, emphasizing behavioral rehearsal, and reducing behavioral friction to the initiation of healthy behaviors in early intervention phases to reduce the amount of intentional effort required in later intervention phases.

The present TRF intervention was designed using components successfully utilized in our prior trials, including enhanced tolerance of satiety cues, mindful appetite awareness, and self-monitoring of target behaviors. In developing the proposed intervention approach, In addition, recognizing that participants will differ in their prior training experiences and behavioral compliance with exercise and diet at baseline, early content-focused sessions will be tailored to the individual needs of the participant. The proposed intervention schedule below is therefore intended to provide a basic overview of the intervention schedule, which will be tailored to individual participants using baseline behavioral data and background information to personalize training targets based on their individual needs. Consistent with contemporary intervention practices emphasizing processes elements as critical to behavior change,[172-



[174] our research team sought to integrate process-based components from several frameworks targeting enhanced self-regulatory skills,[172] including social cognitive theory,[175] relational frame theory,[176,177] self-systems theory,[130] and Habit Theory.[178]

D.2. ASSESSMENT PROCEDURES

Assessment of Feasibility and Acceptability. Study feasibility will be assessed by examining attrition (i.e., study completion) and adherence (i.e., completed intervention sessions and assessments). Consistent with prior TRF trials, adherence to the intervention will be assessed using daily diaries, with additional verification through calls by the study coordinator. Acceptability will be assessed using by participant satisfaction using the Client Satisfaction Questionnaire 10-item version.[179]

Assessments of Cognitive Function. The primary focus of the proposed study will be on cognitive performance within domains known to be most sensitive to early metabolic disruptions, including executive function / complex processing speed[64,180] and learning efficiency under interference conditions.[181-184] These domains of performance are also highly prognostic of future impairments in instrumental activities of daily living, development of MCI and ADRD. Our test battery chosen for its sensitivity to subclinical disruptions in metabolic function and its prognostic association with future cognitive decline and ADRD. The tasks are streamlined with standard discontinuation rules applied to reduce subject frustration and overall burden. The battery will consist of Executive Function / Processing Speed (Trail Making Test,[185] Stroop Test,[186] Controlled Oral Word Association Test,[187] Animal Naming Test,[188] Digit Span Forward and Backwards,[189] Digit Symbol Substitution Test, and the Ruff 2 & 7 Test[190]). We will also assess Learning / Memory (Loewenstein-Acevedo Scales Semantic Interference and Learning,[183,184] California Verbal Learning Test-II [CVLT-II], [191] and the Benton Visual Memory Test – Revised [BVMT-R]).[192]

Assessments of Metabolic and Inflammatory Function. Metabolic function and flexibility will be assessed using a diverse array of outcomes, including glucose, insulin, insulin-like growth factor, HbA1c, lipids, triglycerides, non-esterified fatty acids, total ketones, brain derived neurotrophic factor (BDNF), beta-hydroxybutyrate, lactate, amino acids, plasma kynurenine, kynurenic acid, and tryptophan.
non-esterified fatty acids, total ketones, beta-hydroxybutyrate, lactate, amino acids, and acylcarnitines. We will also measure conventional clinic markers of metabolic function, including blood pressure, body mass index, and metabolic syndrome severity score. Inflammatory markers will also be obtained, including IL-6, TNF-alpha, high sensitivity C-reactive protein (CRP), IL-1β, IL-8, IL-10, myostatin, and glial fibrillary acidic protein (GFAP). Finally, samples will be obtained for the purposes of assessing gene expression profiles.[124,193]

Fasting-Dependent Changes in Cognitive and Metabolic Functions. In order to assess state-dependent changes in cognitive and metabolic functions, we will conduct ancillary assessments at pre- and post-treatment following an 18-hr fasting period. In contrast to the assessments above, this will allow us to better delineate cognitive and metabolic changes occurring in the context of elevated metabolic demand, providing a 'metabolic stress test'. In order to assess subtle changes in tests most sensitive to early decline, a brief assessment of cognition will be obtained using the Trail Making[185] and Stroop Tests[186] for Executive Function / Processing Speed and the Loewenstein-Acevedo Scales Semantic Interference and Learning[183,184] for Learning / Memory. We will also repeat our markers of metabolic function, as described above.

Select Methodological Issues:

Study Sample: We discussed various study samples at length, including selecting individuals with metabolic syndrome, central adiposity instead of BMI, or using alternative measures of excess weight, as well as potentially selecting a wider age range for inclusion. We elected to use overweight and obesity based on recent reviews suggesting that alternative measures of adiposity have measurement limitations and would further limit the external validity of any findings.[194] **Study Intervention:** Our choice of study intervention to improve metabolic function was a topic of considerable discussion in our investigative team, because the proposed metabolic mechanisms may also be impacted by exercise. We elected to focus on TRF because of its portability and specific impact on ketones and other markers of 'metabolic switching'. We also feel the proposed study intervention will lessen overall participant burden by focusing on TRF as the target behavior.

RESEARCH STRATEGY: Data Management and Analysis

Data will be entered into a centrally managed Redcap database. Assessments of TRF feasibility and acceptability will be assessed by carefully characterizing accrual, adherence, and retention for the 12-week TRF trial (**Aim 1**). Feasibility will be assessed by accrual in the study timeline, 90% adherence to study procedures, and 90% of participants completing the protocol. For our analyses of cognitive and metabolic changes following TRF (**Aim 2**) we will use repeated measures, linear mixed effect models in which cognitive

performance is modeled using mean rank approach with in each cognitive domain,[106] as recommended by O'Brien.[243] Within these analyses, we will adjust for age, biological sex, and pretreatment levels of the respective outcome, with the time effect as our variable of interest. This composite approach has several advantages over testing multiple individual endpoints, including increased reliability, enhanced precision of the treatment estimates, improved power, and minimization of Type I Error.[244, 245] Analyses are powered to detect differences in the primary 'gatekeeper' model at the P = .05 level.[195,196] If significant, examination of components of the global score are examined in secondary, explanatory analyses in which the significance level is propagated forward.[197] A parallel model will be used to examine changes in metabolic function, in which diverse measures of metabolic function and flexibility are combined into a global mean-rank score. For our analyses of fasting-dependent changes in cognitive and metabolic function (**Aim 3**), we will explore fasting-dependent changes utilizing a parallel, mixed effect modeling strategy with fasting state (non-fasted vs. fasted) as an additional categorical predictor, with the time X fasting state interaction as our predictor of interest. Patterns of missing data will be characterized using Rubin's[198] criteria and managed accordingly using Harrell's multiple imputation (mult.impute) procedure in R. We will supplement our primary regression analyses with an examination of the treatment effect among completers[199] using Rubin's Complier Average Causal Effect (CACE) model[200] using SAS (Cary, NC) or R. **Power Analysis**: Power for **Aim 2** was based previous estimates from our lifestyle trials.[37,109] We conducted our power analyses with the following assumptions: 1) an initial sample size of 40 participants with 15% attrition at 4-months, 2) alpha of 0.05, and 3) an R^2 of 0.50 between model covariates and the outcome of interest. Based on these assumptions, we anticipate power to detect improvements of d = 0.70 between baseline and post-treatment assessments, paralleling improvements from our recent behavioral weight loss trial in adults with resistant hypertension.[36]

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO HUMAN SUBJECTS

1a. *Human Subjects Involvement, Characteristics and Design*

Subjects will include 40 men and women aged 65-85 years with amnestic Mild Cognitive Impairment (Montreal Cognitive Assessment Battery score [MoCA] total score 19-25 or a phonemic fluency score of ≤12 with MoCA > 25 or semantic fluency score ≤ 15 with MoCA score > 25;[201] and score of ≥ 1.0 on the Mail-in Cognitive Function Screening Instrument)[202], obese (body mass index 27.5-40 kg/m^2), sedentary, and be willing to participate in all aspects of the proposed intervention. Reasons for participant exclusion will include secondary causes of obesity, evidence of clinical dementia (MoCA score ≤ 18), severe CKD (eGFR <45 ml/min/1.73m^2), heart failure, high grade arrhythmias, severe valvular heart disease, severe asthma or chronic obstructive lung disease, diabetes requiring insulin, musculoskeletal or neurologic problems that would preclude participation in aerobic exercise training, a major psychiatric disorder, a history of drug abuse, alcohol consumption >14 drinks/week, gastric bypass surgery, non-English speaking, or a life-limiting comorbid medical condition such as cancer.

1b. *Sources of Materials*

Medical, clinical, and questionnaire data will be provided by participants for research purposes.

1c. *Potential Risks*

Risks of serious injury during the trial is considered negligible. TRF has been shown to have adequate acceptability and a low prevalence of adverse events in older adults with obesity.[35] Participants may occasionally experience headaches, light-headedness, or nausea, which occur infrequently and appear to peak approximately two weeks into treatment. [135] Although unlikely, there is the possibility that changes in dietary behavior could result in excessive metabolic derangements in some participants, which we will monitor and manage as needed. Participants also will be carefully monitored for clinically significant changes in neurocognitive function and Dr. Daniel Parker, a board-certified behavioral neurologist, will assess participants exhibiting significant neurocognitive change to make additional referrals as needed. There is also some risk of loss of confidentiality of cognitive performance data.

2. ADEQUACY OF PROTECTION AGAINST RISKS

2a. *Recruitment and Informed Consent*

If the volunteer clearly meets all of the study eligibility criteria, he/she will be asked to read and sign a Duke University Medical Center IRB-approved informed consent form. A research assistant will confirm a statement in the consent form that to qualify for participating in the study, additional weight measurements will be made to verify eligibility criteria. If overweight / obesity criteria are met, then the participant will be administered the Montreal Cognitive Assessment Battery[203] in order to determine if his or her cognitive status meets criteria for the proposed study. Physician approval will be required for participants to enroll in this study. Potential participants will be recruited from physician referrals at Duke, the Durham VA, Duke Raleigh Hospital and their affiliated community-based clinics, as well as the Durham Veterans Affairs Hospital.

The Duke / UNC Alzheimer's Research Center has recently been awarded, with a focus on recruiting diverse older adults with cardiometabolic risk factors at risk for ADRD. Dr. Smith is one of only two core neuropsychologists working on the ADRC project, which will afford unique opportunities to leverage emerging recruitment opportunities to enhance enrollment efforts.

The Duke Family Medicine Clinic follows about 13,000 participants annually, with more than 50% being African American and 65% women. Duke Family Medicine received recognition from the National Committee for Quality Assurance (NCQA) as a Level 3 Patient-Centered Medical Home in June 2012 under the PCMH 2011 Standards. In 2018, the clinic was actively following 5,121 individuals with BMIs 25-40 kg/m^2.

The Durham VA is a large, high complexity facility that provides primary care to 40,000 veterans in 3 main sites (two hospital-based clinics in Durham and a community-based clinic in Raleigh). Of these registered participants, previous estimates have suggested up to 80% are overweight or obese.[204] We have previously used VA recruitment to achieve 100% of our enrollment targets for behavioral intervention studies.[109]

2b. *Protection Against Risk*

A number of special precautions will be taken to ensure participant safety:

Prospective study participants will be carefully screened before initiating the proposed TRF program. Potential subjects with clinical evidence of ischemic heart disease, heart failure, or other major medical or psychiatric problems will be excluded. In addition, subjects who have evidence of severe valvular disease, ECG evidence of ischemia on recent exercise testing, an abnormal BP response, or complex ventricular ectopy will be excluded from the study and referred for appropriate treatment. At the conclusion of the trial, participants will be referred back to their treating physicians. In the event that participants do not have a physician, several well-established outpatient programs at Duke University Medical Center, Duke Raleigh, or UNC are equipped to receive referrals from our research program. We believe that these facilities, in addition to private practitioners in the community, provide a comprehensive range of appropriate referral sources for participants needing further treatment. We are confident that careful screening and monitoring of all participants entered into our protocol, and tracking of all participants following the completion of the interventions, will minimize risk to study participants. The study personnel, including physicians, psychologists, internal medicine physicians, and the physician's assistant, have the training and experience to provide the necessary safeguards for participation.

Participants included in our clinical databases contribute clinical information based on their neuropsychological assessment, biomarker assessments, clinical history, laboratory results, and cerebrovascular risk factor information pertinent to their neurocognitive function. The data are used specifically for research purposes. Release of patient information is carefully controlled through the Institutional Review Board (IRB). All project staff will have fulfilled Duke University's mandatory HIPAA training requirements. All aspects of the study protocol will meet HIPAA requirements specified by the Human Studies Committee and the Privacy Office at Duke University. The protocol will be approved by the Duke University Medical Center IRB and University of North Carolina Hospitals before it is implemented. All investigators have completed the required education and certification in the protection of human research participants.

In the unlikely event of an adverse medical event during assessment or any other on-site phase of study participation, the patient's attending physician and/or the emergency services at DUMC will be contacted immediately. In addition, the principal investigator and medical director of the study will be notified of all such events. Any patient who develops new cardiac symptoms or experiences a significant deterioration of cognitive function will be referred for additional evaluation at the discretion of the study neurologist (Dr. Parker). Also, if any patient exhibits significant psychopathology or becomes acutely suicidal they will be escorted to the Duke emergency room for immediate treatment.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

This study will likely have several important potential benefits. First, participants receiving the TRF intervention will very likely experience weight loss, may achieve improved metabolic function, reduced cerebrovascular risk factors, and potentially improved neurocognition. We will also explore treatment response in relationship to age, pre-treatment neurocognitive function, cerebrovascular burden, and phospholipid metabolism. This may make it possible to identify participants who are especially likely to respond well to TRF. The information gathered could enhance health care professionals' ability to advise participants about the effects of voluntary weight loss and may enable health care providers to identify, in a timely fashion, participants who might benefit most from an intensive lifestyle intervention.

Potential benefits to society include the identification of an effective strategy to reduce the incidence of neurocognitive decline, elucidate metabolic mechanisms of neurocognitive improvement, and gain a better understanding of the mechanisms underlying the relationship between obesity and Alzheimer's Disease and Related Dementias (ADRD). If the TRF intervention shows preliminary benefits in improving neurocognitive and metabolic function, it could be used as a potential preventive strategy among individuals at risk for ADRD and implemented as part of conventional rehabilitation approaches. In addition, because there are no current pharmacological treatments to reduce the prevalence and development of neurocognitive decline, interventions that improve neurocognition have significant implications for the management and treatment of individuals with obesity, who may be at particularly higher risk for the development of ADRD.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Our prior work has highlighted the efficacy of lifestyle change to enhance metabolic and neurocognitive function. What is not yet known is the degree to which older adults at risk for ADRD may be able to utilize TRF as a strategy to maintain brain health and reduce ADRD risk. The proposed intervention therefore introduces a portable and potentially impactful behavioral approach to mitigate the progression of cognitive decline and reduce ADRD risk in a highly vulnerable and increasingly common patient population.

Dissemination of our findings involves the transfer of our research results to participants, health care providers, and decision makers to modify the lifestyle behaviors of participants and inform health care providers about optimal ways to manage participants with risk factors for cognitive decline. A major strategy will be the presentation of the study design and results at various national meetings including the International Neuropsychological Society, the American Psychiatric Association, the American Psychological Association, and the American Heart Association. Another key strategy will be the rapid publication of the study design and results in major journals. We hope to publish our findings in the best journals available to both the general medical community (e.g., *JAMA, NEJM, Lancet*), as well as to specialty journals in neurology, neuropsychology, internal medicine, and psychiatry.

5. Data and Safety Monitoring Plan:

Adverse events will be systematically monitored at the time of enrollment, initiation of the study intervention, and at the conclusion of the 4-month TRF program. Although we anticipate few adverse events, we note that any intervention-related adverse events in metabolic or cognitive change will be reviewed by Drs. Parker and Huffman on a regular basis. For the purposes of the present, an adverse event is defined as any undesired, noxious, or pathological change in a participant, as indicated by symptoms or laboratory changes that occur in association with our additional assessments. In addition, as noted above, participants exhibiting a MoCA < 18 during baseline assessments will be excluded and participants reporting or exhibiting clinically worrisome cognitive changes during the 4-month intervention or post-treatment assessments will be referred for additional neurological evaluation at the discretion of Dr. Parker. Pre-existing conditions that worsen during a study are considered adverse events. Serious Adverse Events (SAE) are defined as any adverse event that results in any of the following outcomes:

- Death or a life-threatening illness including active suicidal ideation/attempt (such as drug overdose)
- A persistent or significant disability/incapacity
- A requirement for hospitalization ≥24 hours

After careful screening, patients who are judged at risk (e.g., because participation in the treatment is medically contraindicated) will be excluded from the study and referred for appropriate treatment. Participants who exhibit significantly abnormal metabolic functioning suggesting clinically significant instability or who cannot otherwise participate in the TRF program also will be excluded from the study and referred to their

primary care physician for treatment. Drs. Huffman and Parker will be fully apprised of this information on a regular basis. All staff involved in the design or conduct of the study will receive the required education on the protection of human research participants prior to funding of the project. Dr. Smith will be available 24/7 for emergent and/or urgent study-related issues.

6. Data Sharing Plan: An anonymized dataset with key study-related data will be made available to investigators upon request one-year after the publication of the primary study findings. Investigators will be able to make requests through Drs. Smith and Pieper, who can facilitate such data management tasks. In addition, we will plan to provide a complete, anonymized dataset for deposition into online data repositories within three years of publication, for use in subsequent follow-up analyses or meta-analytic studies. We will also make annotated statistical analytical code available for public usage, in order to increase the reproducibility of our findings for future studies.

7. Protocol Development: Source Materials for Behavioral Intervention

The behavioral portion of our TRF intervention was developed using source materials from our prior behavioral interventions,[12,37] strategies to enhance self-regulatory functioning,[125,126,129] and behavioral intervention components with previously demonstrated efficacy among individuals with MCI.[205,206] An example of a TRF protocol is provided below. We note that the proposed intervention schedule below is intended to provide a roadmap for development and will be enhanced with feedback from participants throughout the trial. We also anticipate that our intervention approach will be flexibly implemented, with personalization based on individual participant characteristics, background profile of cognitive impairments, and individual goals.

WEEK 1: Overview of TRF training, review the pathophysiology of TRF on metabolic function and cognition, and an introduction to the relation between self-regulatory function and TRF success. The importance of self-monitoring techniques and environmental modifications will be emphasized. In addition, the importance of self-regulatory coping techniques will be emphasized as self-management skills that can be mastered through regular practice. The patient will also be asked to describe their MCI and medical history, as well as identifying underlying values motivating them to participate. An autobiography, which we have used in our prior work also will be employed as a way of allowing the patient to tell his or her own "story" and identify key motivational factors and personal barriers that will need to be addressed during treatment. Participants will also undergo a values clarification and self-discrepancy exercise to enhance the personal salience of TRF goals. Finally, patients will be instructed in the use of self-monitoring tools, which will be monitored. Participants will also be asked to engage in collaborative goal setting for the first week of TRF by first identifying the best days of the week for establishing their 5:2 routine. Initial TRF recommendations will be to fast during two days during the next week, at least two days apart, with a fasting period of 14 hours and eating period of 10 hours. This will gradually be titrated up to a 16 hour fast with 8 hours of unrestricted eating (16:8) on two days per week, consistent with the prevailing 5:2 trial approaches.

WEEK 2: Self-Monitoring and Organizational Strategies. Participants will engaged in discussion of activities to cultivate TRF routines, both as a method to enhance TRF adherence and also to reduce cognitive burden. Using weekly calendars, reminder strategies, and other compensatory techniques to cue participants to prepare and engagement in TRF. For example, cultivating a routine for the night before TRF begins. Environmental modifications will be recommended to enhance automatic cues for TRF success in the participant's home, such as using a centralized white board. Common barriers to organization will be discussed, with potential self-management strategies offered for participants to choose a personalized strategy to enhance adherence. For those successfully adhering to the intervention, behavioral goals will be titrated towards their 16:8 fasting goal. For those who have not yet achieved their initial goals, a focus on identifying and managing barriers will remain the treatment target focus to ensure success. Intervention approaches will be personalized using baseline executive function profiles with a particular focus on individual differences in inhibitory control.

WEEK 3: Appetite Awareness Training with Mindfulness. Participants will be trained in mindfulness exercises modified from the Motivationally Enhanced Compensatory Cognitive Training for Mild Cognitive Impairment (ME-CCT-MCI). Participants will engage in mindfulness training exercises to enhance attention control, increase cognitive flexibility, and to develop a take-home practice routine. Process targets will include enhancing awareness and cognitive defusion of hunger pangs, redirecting attention away from food cues using distraction techniques, and to build insight regarding automatic thoughts related to satiety cues. Use of experiential acceptance techniques, paradox of control, self-soothing techniques, suffering in the service of health and other values. Participants will be encouraged to cultivate and practice distraction techniques during

fasting periods to enhance tolerability of hunger cues.

WEEK 4: Relaxation and Distress Tolerance Techniques. Participants will be instructed on relaxation techniques to help manage anxiety and elevated distress. Techniques will include mini-practices, distress tolerance techniques, and progressive muscle relaxation. An explicit focus on using these techniques as a way of managing hunger pangs and when experiencing impulses to over-eat. Relaxation and distress tolerance will be framed as affective self-regulatory skills to help manage transient increases in distress, frustration, hunger, and impulsive feelings. Techniques will include distraction, self-soothing, and imagery.

WEEK 5: Attention and Concentration. Strategies for enhancing attention and concentration will be introduced to enhance TRF compliance, including the STEP BACK energy conservation principles. Behavioral strategies to enhance participants' ability to modulate attention will also be deployed, including 'spotlight' attention strategies (e.g. detailed observation of a painting) and LEAP principles to enhance conversational attention. Consistent with temporal self-regulation theories, attention and concentration resources will be characterized as a 'muscle' that can be strengthened over time and that will fatigue with overuse. Focused periods of attention during TRF will be cultivated and strengthened through the intervention, with an intentional focus on periods of more active attention and periods of rest and recovery.

WEEK 6: Learning and Memory. Participants will be trained in memory techniques to help augment their adherence to TRF. Strategies will be linked to deployment of self-monitoring and organizational skills from session 2, as well as attention strategies in session 5. External memory strategies will include reminder systems, calendars, and timers. Internal reminder enhancements will include dual-mode encoding, visual imagery, self-talk, internal rehearsal, chunking, and 'overlearning' approaches. Retrieval strategies will also be discussed, such as mental retracing, recreating the context, and using previously learned organization and relaxation skills.

WEEK 7: Problem-Solving Techniques. Participants will collaboratively with an emphasis on active problem-solving of barriers to PA. Problem-solving will be modeled and encouraged in all subsequent sessions. participants will be instructed in systematic ways to approach daily problems (e.g., defining the problem, identifying elements of the problem, brainstorming, selecting approach, evaluating effectiveness).

WEEK 8: Self-Reinforcement Techniques. Participants will collaboratively discuss different self-reinforcement approaches, including both intrinsic and external reinforcers. Intrinsic reinforcement will be cultivating using self-monitoring of self-reported fatigue and energy levels, weight loss, enhanced sense of self-efficacy, and improvements in body image. External reinforcement strategies will include selecting pleasurable activities to engage in after meeting behavioral compliance targets. These might include getting new clothes, watching a movie of interest, or participating in other pleasurable activities.

WEEK 9: Contingency Management Techniques. Participants will collaboratively develop approaches for anticipating and managing relapse behaviors, such as missing a day of TRF or accidentally eating during TRF. Goals will include processing behavioral antecedents of relapse behaviors, identifying alternative coping strategies, and using organizational aids to anticipate future barriers to relapse over the next several weeks. Behavioral analysis will be reviewed closely to 1) identify potential discrepancies between short-term goals and TRF engagement and 2) highlight potential behavioral patterns contributing to TRF non-compliance. As in our prior intervention studies, identification of problematic behavioral patterns will be discussed in order to manage potential TRAPs (Trigger, Response, and Avoidance Pattern) in order to cultivate adaptive response patterns (TRACs [Trigger, Response, Alternative Coping response]). Review will focus on value engagement and not on avoidance of aversive symptoms.

WEEK 10: Stimulus Control / Committed Action**:** This session will focus on any additional modifications to environment or within participants' social support system to enhance sustained compliance with TRF. Strategies for both groups will include increasing behavioral friction for impulsive eating, visual stimuli to increase the salience of long-term valued action, and eliciting social support to increase accountability to TRF goals. This could include placing a picture of one's children or grandchildren near workout gear (family as value) or prominently placed quotes embracing struggle as a means of spiritual enhancement (religious value).

WEEK 11-12: Remediation and Review**:** This session will focus on review of previous intervention materials and remediation of any coping skills deficits. The interventionist will also spend time revisiting the participants' personal values, long term goals, areas of strength observed during the intervention, and individualized TRAPs and TRACs.

8. Assessment of Neurocognitive Performance: The primary outcome of interest from the present study will be from assessments of neurocognitive performance. While neurocognitive changes observed in obese

individuals have been documented in multiple domains,[207,208] impairments are most common on tests of frontal lobe functioning, including "executive functions",[209-212] such as slowed information processing, set-shifting, and working memory.[213-216] However, we also recognize that impairments in episodic and declarative memory performance are prototypically observed among individuals at risk for ADRD and also are common among individuals with obesity.[217-222] We therefore adopted a 45-60 minute test battery as recommended by the Neuropsychological Working Group for vascular cognitive disorders,[180] which provides an assessment of both executive functioning, memory, and processing speed across multiple subtests. We have used similar test batteries in our prior studies with success.[37,107-109,223,224] The neuropsychological test battery will be administered in a fixed order with alternative forms, and we will alternate the order of test versions using a counterbalanced sequence in order to minimize practice effects. Tests will be streamlined with standard discontinuation rules applied to reduce subject frustration and overall burden. The neuropsychological test battery will be administered in a fixed order with alternative forms. We also will alternate the order of test versions using a counterbalanced sequence in order to minimize practice effects. The battery will consist of:

Executive Function / Processing Speed

Trail Making Test:[185] This test is used to measure visuomotor attention and executive function. For Part A of the test, participants draw lines to connect consecutively number circles; for Part B, participants connect consecutively numbered and lettered circles by alternating between the two sequences (1-A-2-B-3-C, etc).

Stroop Test:[186] This test assesses executive function and set-shifting ability. The standardized version of the Stroop test used in the proposed study consists of three sections: word, color, and color-word.

Controlled Oral Word Association Test:[187] This tests verbal flexibility and executive function as demonstrated by rapidly generating words to a particular letter (C-F-L; P-R-W; F-A-S) in 60 seconds.

Animal Naming Test:[188] This tests semantic fluency and verbal flexibility/executive function as demonstrated by rapidly generating words a specified category (in this case, animals) within a 60 seconds.

Digit Symbol Substitution Test:[189] This test from the Wechsler Adult Intelligence Scale measures executive functioning and attention. Participants are asked to draw symbols that match one of 10 digits copied from a key. Scores on this task are the number of correct symbols drawn in a 120-second time period.

Digit Span Forward and Backwards:[189] This test from the Wechsler Adult Memory Scale – IV assesses auditory attention and working memory. Participants repeat digits of increasing length, first in the forward direction as they have heard the numbers and then in reverse order.

Memory

Hopkins Verbal Learning Test – Revised: One of three equivalent forms of the HVLT-R will be used to assess verbal memory, retention, and recognition.

Brief Visual Memory Test – Revised (BVMT-R):[192,219,225] One of three equivalent alternate forms of the BVMT-R will be used to measure nonverbal learning, recognition, and delayed recall.

Cognitive Complaints

Everyday Cognition Scale (ECog): Detailed information regarding subjective cognitive compliants will be obtained using the ECog at both baseline and post-treatment assessments. The ECog measures an individual's ability to perform everyday tasks relative to their reported ability 10 years ago. This instrument has been widely validated in MCI samples[234] and correleates with the degree of underlying neuropathological burden.[235] The ECog consists of 39 items rated from 1 ('no change or actually performs better than 10 years ago') to 4 ('performs the task much worse than 10 years ago'). A Global Cognition score is calculated by averaging score ratings on all 39 items. Scores are also provided within six subdomains corresponding to Memory, Language, Visuospatial function, Planning, Organization, and Divided Attention.

9. Ancillary Markers of Behavioral and Psychosocial Process Measures

The following assessment procedures will be conducted on all participants at baseline and following completion of the intervention. These measures are designed to assess psychological processes that may have important, mechanistic associations with participant uptake and engagement of intervention materials.

Acceptance and Action Questionnaire-II (AAQ-II):[236] The AAQ-II is a 7-item measure of psychological inflexibility or the degree to which participants are able to remain mentally present and fully accepting of the

present moment, without interference from distracting thoughts and feelings. Participants respond to items using a 7-point Likert scale from 1 (*not at all true*) to 7 (*completely true*).[236]

Brief Experiential Avoidance Questionnaire (BEAQ):[237] The BEAQ is a 15-item measure of experiential avoidance. Experiential avoidance provides an assessment of participants' tendency to engage in cognitive or behavioral strategies to avoid uncomfortable internal experiences, including behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. Sample items include: "The key to a good life is never feeling any pain" and "I would give up a lot not to feel bad".

General Self-Efficacy Scale (GSE):[238] The GSE is a widely used instrument for measuring general levels of self-efficacy, a key psychological mechanistic marker within behavioral interventions. The GSE assesses individuals' ability to maintain a broad and stable sense of personal competence and deal effectively with a variety of stressful situations.

Perceived Stress Scale (10-item Version; PSS-10):[239] The PSS is one of the most widely used psychological instruments for assessing participants' perception of stress or the degree to which individuals appraise their life as stressful. Items assess the degree to which individuals feel their life is unpredictable, uncontrollable, and how overloaded they experience their lives to be.

10. Ancillary Markers of Metabolic Risk Factors and Function

Metabolic Function and Flexibility Markers: Lipids, triglycerides, glucose, insulin, insulin-like growth factor, HbA1c, non-esterified fatty acids, total ketone bodies, brain derived neurotrophic factor, beta-hydroxybutyrate, lactate, amino acids, plasma kynurenine, kynurenic acid, tryptophan, non-esterified fatty acids, and acylcarnitines will all be assayed from fasting blood samples drawn between 0800 and 0900 hr at a local LabCorp facility, which we have used in prior research.

Inflammatory Markers: Inflammatory markers will be obtained using similar methodology as described above for our metabolic outcomes. Inflammatory markers will include IL-6, TNF-alpha, high sensitivity C-reactive protein (CRP), IL-1β, IL-8, IL-10, myostatin, and glial fibrillary acidic protein (GFAP). We will also obtain samples for the purposes of assessing gene expression profiles.[124,193]

Clinic Blood Pressure: Clinic SBP and DBP will be obtained during participant screening using standardized procedures. BP assessments will be repeated following completion of the 4-month protocol. BP assessments will be obtained following Joint National Committee (JNC 8) guidelines,[240] in which BP is assessed in a quiet, temperature-controlled room within our clinical research facility. Participants will have been asked to refrain from smoking or ingesting caffeine for at least 30 minutes prior to their appointment time. BP measurements will be standardized for cuff size, position, environment, time of day, and medication dosing. After 5 minutes of quiet rest, four seated BP readings, each 2 minutes apart. The last three readings will be averaged to define clinic BP.

Metabolic Syndrome Severity: Metabolic syndrome severity will be quantified using previously published z-score methods, in which metabolic syndrome components are aggregated using sex- and race-specific risk formulae, including waist circumference, triglycerides, HDL-C, SBP, and glucose.[241]

Body Weight and Nutritional Habits: Baseline and post-intervention body weight will be determined by a *calibrated medical balance beam* scale. We will assess dietary changes using widely validated report measures, including a *4-day food diary*[242,243] and a standard Food Frequency Questionnaire.

Framingham Stroke Risk Profile: To quantify the degree of cerebrovascular risk in the sample, stroke risk factors will be aggregated using the revised Framingham Stroke Risk Profile Score,[244] which incorporates data on SBP, antihypertensive medication use, diabetes status, prevalent CVD, atrial fibrillation, and left ventricular hypertrophy using gender-specific risk estimates.

Cardiometabolic Medication Burden: To facilitate assessment and quantification of commonly used cardiometabolic medications that may influence the interpretation of metabolic outcomes data, we will quantify total cardiometabolic medication burden using the Daily Defined Dose (DDD), a standardized methodology developed by the World Health Organization.[245,246] The DDD is a system for quantification of drug amount designed to enable comparison across drug classes (e.g., 1×DDD=150 mg irbesartan or 5 mg amlodipine),[246] which we have previously used in the context of behavioral trials.[109,139] We will specifically explore the influence of statins on any observed associations, given their possible influence on markers of phospholipid change.

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Data Management and Analysis
Data will be entered into a centrally managed Redcap database. Assessments of TRF feasibility and acceptability will be assessed by carefully characterizing accrual, adherence, and retention for the 12-week TRF trial (**Aim 1**). Feasibility will be assessed by accrual in the study timeline, 90% adherence to study procedures, and 90% of participants completing the protocol. For our analyses of cognitive and metabolic changes following TRF (**Aim 2**) we will use repeated measures, linear mixed effect models in which cognitive performance is modeled using mean rank approach with in each cognitive domain, as recommended by O'Brien. Within these analyses, we will adjust for age, biological sex, and the pretreatment level of the respective outcome, with the time effect as our variable of interest. **Biological sex** will be addressed both by adjusting for biological sex in our regression analyses and testing for potential moderation of any observed changes in cognitive or metabolic outcomes by biological sex. This composite approach has several advantages over testing multiple individual endpoints, including increased reliability, enhanced precision of the treatment estimates, improved power, and minimization of Type I Error. Within this modeling framework, analyses are powered to detect differences in the primary 'gatekeeper' model at the P = .05 level. If the primary model is found to be significant, examination of individual components of the global score are examined in secondary, explanatory analyses in which the significance level is propagated forward. A parallel model will be used to examine changes in metabolic function, in which diverse measures of metabolic function and flexibility are combined into a global mean-rank score. For our analyses of fasting-dependent changes in cognitive and metabolic function (**Aim 3**), we will explore fasting-dependent changes utilizing a parallel, mixed effect modeling strategy with fasting state (non-fasted vs. fasted) as an additional categorical predictor, with the time X fasting state interaction as our predictor of interest. Patterns of missing data will be characterized using Rubin's criteria and managed accordingly using Harrell's multiple imputation (mult.impute) procedure in R. We will supplement our primary regression analyses with an examination of the treatment effect among completers[199] using Rubin's Complier Average Causal Effect (CACE) model[200] using SAS (Cary, NC) or R.
Power Analysis: Power for **Aim 2** was based previous estimates from our lifestyle trials. We conducted our power analyses with the following assumptions: 1) an initial sample size of 40 participants with 15% attrition at 4-months, 2) alpha of 0.05, and 3) an R_2 of 0.50 between model covariates and the outcome of interest. Based on these assumptions, we anticipate power to detect improvements of d = 0.70 between baseline and post-treatment assessments, paralleling improvements from our recent behavioral weight loss trial in adults with resistant hypertension.[36]

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