Multicultural Healthy Diet to Reduce Cognitive Decline and Alzheimer's Disease Risk

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FULL PROTOCOL TITLE

Multicultural Healthy Diet to Reduce Cognitive Decline & Alzheimer's Disease Risk

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PRECIS

Study Title: Multicultural Healthy Diet to Reduce Cognitive Decline & Alzheimer's Disease Risk

Objectives: This pilot study is designed to investigate whether consuming a healthy diet that is based on the **Dietary Inflammatory Index (**DII) and tailored to a multicultural cohort hereafter known as the Multicultural Healthy Diet (MHD) can be adapted for a multicultural middle aged (40-65 yr) middle income cohort in Bronx, New York and whether it improves cognition compared to consuming a usual diet. We propose this study in a middle-aged population because early indicators of cognitive aging may manifest long before old age and because lifestyle factors, such as diet, may have their largest impact during this age period.

The primary objectives are:

1. Show that the MHD can be adapted for a diverse middle-aged cohort in the Bronx.
2. Test whether a MHD intervention can benefit cognitive function in a middle-aged population.
3. Identify components of the MHD associated with stable or improved measures of cognition.

The secondary objective of this pilot is to provide a necessary foundation for understanding how lifestyle interventions (such as the MHD) during midlife impacts clinical endpoints at older ages.

Design and Outcomes

The proposed study **design** is a two-arm randomized clinical trial. Participants in the experimental intervention arm will be exposed to an intervention over an 18 month period (four in-person visits in small groups with the interventionist over a two month intensive phase & monthly telephone coaching starting in month 3 of the intervention till month 18). Assessment visit cover a 27month period (run-in, baseline, months 9 & 18 and 27) at the Aging Research Center (Van Etten Building) at the Albert Einstein College of Medicine (Einstein).

Comparison participants will only have access to general health recommendations such as the US Dietary Guidelines-2015. Health educators/coaches will deliver the intervention and comparison sessions. Comparison participants will receive the information in same modality as the intervention namely four in-person and bi-weekly for first two months, then monthly by phone till month 18. The comparison sessions will focus on self-care/management matters.

To assess dietary effects on cognition (primary **outcome will consist of a z-score global composite measure of three ambulatory cognitive tasks**.), we will use a "measurement-burst" design, consisting of 35 brief assessments of a range of cognitive functions administered via smartphones during week-long measurement-bursts; this will be repeated three times at nine-month intervals over a follow-up period of 27 months. This intensive measurement approach will allow assessment of cognitive function in "real-time", thereby providing a more reliable index of function, which will also be more sensitive to change. We will randomize 290 participants (145 in intervention; 145 in comparison) into a two arm study to test whether a MHD diet can benefit cognition compared to a usual or comparison diet.

Interventions and Duration

Dietary Component of the Intervention: This will be a small group intervention with tailored phone calls after the core sessions. Participants will undergo an 18 month intervention (four semi-monthly small group sessions for 2 months followed by monthly phone calls for 16 months). The small group sessions will last 2 hours for 3-4 participants. Monthly phone calls last 20 minutes and are focused on dealing with specific challenges such as dealing with social situations, eating at fast food outlets. The intervention will be hands-on and delivered using a motivational interviewing approach and include a virtual visit to the supermarket in session 2 with the small group format, with a focus on structuring one's own environment to maximize adherence to the study. While some participants may lose a small amount of weight on this diet, weight loss is not a primary goal and dietary intake will be reviewed as eucaloric. The core sessions are:

1. Key components of the MHD Diet & Hit List
2. Shopping Smart & Price Wise: Reading Nutrition Facts Labels, & Shopping Cart Check
3. Understanding portion sizes and monitoring tools to keep track
4. MHD diet at home and outside the home: photo of contents of home fridge/contents of cupboard (photo-optional activity)
5. Monthly calls start as tailored to participant using motivational interviewing approach

Behavioral Component of the Intervention. We will use a motivational interviewing approach to enhance motivation for adherence to the intervention. We propose to use validated Social Cognitive Theory (SCT) constructs to implement the intervention with emphasis on the social-physical environmental (e.g. modification of the home environment) and behavioral (individual level) changes. The following principles will be applied to issues related to dietary change: self-monitoring, stimulus control, problem solving, goal setting and individual feedback. **Self-monitoring** promotes behavior changes by promoting awareness of eating habits and creates self-efficacy. Participants will be offered a variety of tools from web-based systems or apps such as MyFitnessPal or ChooseMyPlate super tracker or paper-based food diaries to self-monitor in a manner tailored to individual needs.

Attendance and **monthly self-monitoring of three days' intake** will be tracked as process measures to determine participant adherence. Non-adherent participants (as demonstrated by missed sessions or unreachable by phone) will receive up to ten additional phone contacts at different times of day/ day of week. If no contact is established after ten contacts, the participant will be considered as limited contact or no follow-up status. However, each participant will be considered on a case-by-case basis and contact may be established at a later date as determined by participant and study staff.

Participants in the experimental intervention arm will be exposed to an intervention over an 18 month period (four in-person visits in small groups with the interventionist over a two month intensive phase & monthly telephone coaching starting in month 3 of the intervention till month 18). Assessment visits cover a 27month period (run-in, baseline, months 9 & 18 and 27) at the Aging Research Center (Van Etten Building) at the Albert Einstein College of Medicine (Einstein). Participants in the intervention arm are expected to follow the diet over the 27 month period they participate in the study.

Sample Size and Population

Study staff will screen, recruit and retain 290 eligible diverse participants aged 40 to 65 yr for this project who live, work, visit, attend school in Co-op City or in adjacent communities. Co-op City is a diverse cooperative housing development in the northeast section of Bronx County. Co-op City's size (>50,000 residents), diversity (60.5% African American, 27.7% Hispanic), median age (42 years), income ($50,900) and proximity to the Einstein Medical complex make it an ideal population center from which to recruit a representative sample. The 290 participants will be randomized (145 in intervention; 145 in comparison) into a two arm study to test whether a MHD diet can benefit cognition compared to a usual or comparison diet.

STUDY TEAM ROSTER

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1 STUDY OBJECTIVES

1.1 Primary Objective

The direct costs of caring for individuals with AD and related dementias (ADRD) in the US in 2016 are estimated to be over $236 billion, and costs are estimated to increase to $1 trillion (in today's dollars) by 2050. Today, 5.4 million Americans live with AD; 5.2 million are 65 yr or older, and 200,000 are <65 yr. By 2050 it is estimated that up to 13.8 million will have the disease (1). Given these staggering numbers, strategies to prevent or delay cognitive decline are urgently needed especially among diverse populations as in the Bronx, New York. According to the Einstein Aging Study, Bronx blacks were at higher risk, compared to whites for non-amnestic mild cognitive impairment (2) and Bronx Hispanics of Dominican and Puerto Rican descent in the Hispanic Community Health Study/Study of Latinos had lower neurocognitive scores compared to other Hispanics (3). Diet is increasingly recognized as an influence on cognitive health in aging adults; however methodological differences in assessment of both diet and cognitive function have shown inconsistent results (4-7). The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet combines the Mediterranean and the Dietary Approaches to Stop Hypertension (DASH) or its combination known as the MIND dietary pattern (8, 9) may decelerate cognitive decline and reduce incidence of AD in dementia-free older adults. However to date these studies were based on observational studies, or a unique population (e.g. Euro-American), or used biased measurement methods or lacked biomarker evidence. The key mechanism for the action of MIND diet appears to be anti-inflammatory factors. The Dietary Inflammatory Index (DII) can be therefore better focused on these factors

and an anti-inflammatory diet based on the DII can potentially be equally or more effective and we further hypothesize that this diet will be readily adapted to multicultural populations (10).

Therefore, **a clinical trial in a multicultural population using sensitive measurement methods to assess the impact of an anti-inflammatory diet on cognition is needed to validate these findings.** Here, we propose a pilot study to investigate whether consuming a healthy diet that is based on the DII and tailored to a multicultural cohort hereafter known as the Multicultural Healthy Diet (MHD) can be adapted for a multicultural middle aged (40-65 yr) middle income cohort in Bronx, New York and whether it improves cognition compared to consuming a usual diet. We propose this study in a middle-aged population because early indicators of cognitive aging may manifest long before old age and because lifestyle factors, such as diet, may have their largest impact during this age period (11). Previous studies (12, 13) have used global mental function tests and relied on designs with relatively few and widely spaced repeated measurements--factors which can compromise the ability to detect cognitive change. To overcome these limitations, we propose to assess dietary effects on cognition using a "measurement-burst" design, consisting of 35 brief assessments of a range of cognitive functions administered via smartphones during week-long measurement-bursts; this will be repeated three times at nine-month intervals over a follow-up period of 27 months. This intensive measurement approach will allow assessment of cognitive function in "real-time", thereby providing a more reliable index of function, which will also be more sensitive to change (12). We will randomize 290 participants (145 in intervention; 145 in comparison) into a two arm study to test whether a MHD diet can benefit cognition compared to a usual or comparison diet. Our specific aims are to:

A1. Show that the MHD can be adapted for a diverse middle-aged cohort in the Bronx.

Evaluate pre- and post-intervention serum biomarkers indicative of a MHD diet pattern, specifically total folate, tocopherols, carotenoids, vitamin B12 and fatty acid profile; and self-reported intake of food groups such as fruits and green leafy vegetables, to compare study arms. We hypothesize that there will be no differences between arms in these biomarkers at baseline and that, at the post-intervention time-points, biomarkers of the MHD will be higher in the intervention arm.

A2. Test whether a MHD intervention can benefit cognitive function in a middle-aged population.

Assess cognitive domains known to be sensitive to normative cognitive aging and risk for ADRD including visuospatial working memory, short-term associative memory "binding", and processing speed, using real-time ambulatory assessments over a 7-day period every 9 months to evaluate the time course over which positive impacts are detectable. We also assess inflammatory markers C-reactive protein & IL-6 as possible mechanisms of action. We hypothesize that participants randomized to the MHD diet will have more stable and possibly improved cognitive function relative to baseline, whereas comparison participants will have measurable decline.

A3. Identify components of the MHD associated with stable or improved measures of cognition.

Evaluate biomarkers indicative of a MHD diet pattern (see A1) and relate to cognitive function measures.

1.2 Secondary Objectives

If successful, the MHD can be used as a widely accessible and potentially powerful strategy to enhance or maintain cognitive health and reduce risk of AD to benefit society at large. Dietary factors are an established risk factor for AD (57) that are thought to be especially salient as individuals move from midlife into older ages (11). By evaluating short-term dietary effects on cognitive health during midlife and early old age, the proposed study will provide a necessary foundation for understanding how lifestyle interventions (such as the MHD) during midlife impacts clinical endpoints at older ages.

2 BACKGROUND AND RATIONALE

2.1 Background: Evidence base for Diet & Cognition

There is emerging evidence that Alzheimer Disease (AD) has microbial origins and that therefore anti-inflammatory diets may be especially helpful with reducing inflammation (14). A Western diet is pro-inflammatory and associated with a smaller hippocampus, which is implicated in cognitive decline (15). Anti-inflammatory dietary patterns such as the Mediterranean diet are characterized by higher intake of nutrient-dense foods such as vegetables, fruit, whole grains and fish and are associated with enhanced mental and cognitive health (16-19). The MIND diet, a hybrid of the Mediterranean and DASH diet highlights ten dietary components that were associated with slower cognitive decline with age and possibly decreased AD risk in an observational study in a primarily Euro-American cohort (8, 9). These foods are whole grains, olive oil, green leafy vegetables, other vegetables, berries, beans, nuts, wine, fish and poultry. On the other hand the Multicultural Healthy Diet (MHD), which is based on the DII and a focus of our study, draws from an international/regional base of foods. Each food is scored according to its inflammatory potential; as such the diet can be adapted to the population under study by increasing intake of anti-inflammatory foods. The MHD is based on 45 food parameters and includes whole foods, nutrients and other bioactive compounds such as alcohol, vitamins B12 to garlic, ginger, n-3 fatty acids, onions, green tea, flavonones, thyme, and oregano each of which is rated according to its inflammatory potential. For an example of an anti-inflammatory diet pattern see Table 1. Hydration is a focal aspect of MHD because 75% of the brain is comprised of water and dehydration can impact cognitive control. It is especially important to be hydrated upon waking up (20).

Table 1. Example of Anti-Inflammatory Diet Pattern
Whole grain cereals 1/day
Vegetables such as broccoli 2/wk
Mixed vegetables with carrots 2/wk
Other vegetables such as sweet peppers, bok choy, eggplant, beets 1/day

Bananas 1/day
Cantaloupe or mango or papaya 1/day
Onions 1/day
Tomatoes or tomato juice 1/day
Garbanzo, kidney, red beans, black-eyed, yellow split or Chinese peas 1/day
Lentils 2/wk
Nuts/nut butters 1/day
Garlic, chives or scallions 1/day
Coffee or tea 2-3/day
Pumpkin pie or sweet potato pie 1/wk
Beef stew 1/wk
Ice cream 1/wk
DII Score - 4.67 Highly Anti-Inflammatory*
Score ranges from -8.87 maximally anti-inflammatory to +7.98 maximally pro-inflammatory

Anti-inflammatory foods in the MHD include fruits, vegetables, nuts, whole grains and fish; the anti-inflammatory properties of fish are related to long chain omega-3 polyunsaturated fatty acids (21). Variety in fruit and vegetable intake has been associated with improvements in cognition in middle-aged and older Hispanics (22). Anti-inflammatory diets have also improved mood, long-term attention, and global cognition (23-25). Nutrients in the Mediterranean diet associated with brain health include vitamin D, choline, and monounsaturated fatty acids (4, 26-28) and flavanols such as epicatechin were associated with increases in connectivity in the brain and with mitigating age-related cognitive decline related to dentate gyrus--a region in the hippocampal formation, a possible source for age-related memory decline and dysfunction (29-31). Anthocyanins, present in berries, have been associated with increased neuronal signaling in brain centers mediating memory function as well as improved glucose disposal, benefits that would be expected to mitigate neuro-degeneration (32). It is noteworthy that low carbohydrate diets were associated with decrements in spatial memory and reverse digit symbol substitution (33) and children consuming diets higher in saturated fats and cholesterol exhibited impaired ability to maintain multiple tasks sets in working memory and poorer efficiency for cognitive control processes involved in task switching; when faced with greater cognitive challenge, a high fat diet was associated with decreased flexibility in thinking (34).

2.2. Study Rationale and Justification for a Multicultural Healthy Diet based on the Dietary Inflammatory Index (DII)

2.2.1. Rationale for Study

Prevention by modifiable lifestyle factors such as diet is a potentially effective strategy as whole foods, nutrients and bioactive compounds can impact cognition through various mechanisms including vascular, antioxidant and anti-inflammatory pathways (35); however the data are far from clear and the differential effects of short vs. long term changes in diet on cognition are unknown**.** While the MIND diet was associated with reduced incidence of AD in a primarily Euro-American cohort in Chicago, the anti-inflammatory diet based on the DII has been associated with higher cognitive status in a middle-aged cohort in France (36) and more recently with lower risk of mild cognitive impairment and dementia onset among 7,109 participants from the Women's Health Initiative (37). Moreover this diet can be tailored to global multi-cultural contexts as it is not necessary to consume specific foods such as berries or olive oil as in the MIND diet to obtain cognitive benefits (36). Recent evidence indicates that individuals of non-Mediterranean ancestry who are less accustomed to consuming olive oil may benefit less from

high olive oil consumption than individuals of Mediterranean ancestry with respect to reduction of Type 2 diabetes mellitus risk (38). The anti-inflammatory diet is assessed using the dietary inflammatory index (DII), that is an index that assesses diets based on their effect on six inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein (10). It is a population-based index based on published data that compares populations worldwide on the inflammatory potential of their diets and incorporates commonly consumed bioactive components including flavonoids, spices such as turmeric, saffron and tea. The overall score takes into account the whole diet, not just the individual nutrients or foods and does not depend on specific population means or recommendations of intake.

Folate & Cognition

In addition to specific dietary patterns, little is known of the specific effect of nutrients on cognition, as findings on nutrients such as B vitamins (folic acid, B6, B12) are inconsistent and indicate a possible range beyond which intake may be harmful; for example excess folic acid intake may lead to adverse effects on cognition, while an optimum level of intake is needed to enhance cognition (39, 40). Most randomized controlled trials involving nutritional supplements with B vitamins have not yielded positive results for cognition suggesting that supplements may be of less value than food derived intake (41***).*** Folate is a water-soluble B vitamin that is naturally present in some foods, added to others and also available as a dietary supplement (42). Food sources include leafy vegetables (spinach, broccoli, cabbage, lettuce), liver, kidney, beans, avocadoes, bananas, whole grains, eggs and some fish. Folic acid is added to the food supply in the US and 46 other countries/territories (43). When ingested it is converted into forms of reduced folate that are identical to naturally occurring folate from foods. Fortification of the American diet was projected to increase folic acid intake by approximately 100 mcg/day, but the program actually increased mean folic acid intake in the US by about 190 mcg/day (44). While supplementation was designed to benefit women of childbearing age, some population groups such as the elderly and perhaps adolescents may be exceeding the recommended level of 1,000 mcg day primarily due to folic acid from supplementation (45). It is not known whether the excess is harmful because little is known about its biological effects. Young folic acid-supplemented rats had deficits in motivation and spatial memory, raising concerns about potential deleterious effects of excess supplementation during adolescence (46). While there is evidence that low folate levels are related to decreased cognitive function, the impact of excess folic acid intake may have similar effects especially in presence of low vitamin B12 levels (40, 47). There may also be an association between unmetabolized folic acid and cognitive decline (48, 49).

Assessing Cognitive Status via Burst Measures

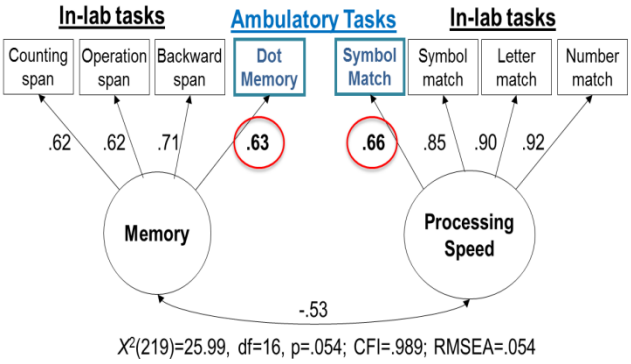
Traditional methods for assessing cognitive function involve performing a single assessment that needs to be repeated at periodic intervals months or years later in order to track changes in cognitive function and take place in physical and social environments that are fundamentally dissimilar to the environments in which people perform cognitive tasks in their daily lives. Natural variation in performance at the time of a single test can increase measurement error and diminish sensitivity for detecting cognitive decline (13). To overcome these barriers, we propose to conduct week-long ambulatory monitoring (using smartphones) of people's behavior and cognitive function in their natural environments. By repeatedly assessing cognitive function

across a variety of situations and contexts, ambulatory cognitive assessment can result in a much lower margin of error than traditional single-assessment neuropsychological tests (13). Ambulatory approaches to cognitive assessment have been used successfully in older adult samples, for healthy adults and individuals with neurologic disorders (13, 50, 51). Other studies support the feasibility of this approach (52, 53), and we report data from our preliminary work below that illustrates the validity and reliability of our ambulatory cognitive battery construct. Using repeated 7-day "bursts" of ambulatory assessments, we will be able to track changes from pre- to post-intervention (intra-class correlations >0.90), and examine real-time associations between diet and cognitive function (12).

2.2.2. Justification of Study

This study is novel in its combination of ecological momentary assessment of cognitive function using smartphones and tablets with dietary measures to assess the impact of a MHD dietary pattern on composite cognitive measures. Assessments take place in real-time in the participant's natural setting and include additional information from biomarkers so that the subtle impact of the MHD diet on cognition can be measured. Additionally as the differential effects of short vs. long-term dietary changes on cognition are unknown, we will innovatively be able to detect subtle changes in a shorter duration of time. The innovation in approach of this study lies in: 1) examination of short-term (days, weeks) and "mid" term effects (months) of diet on cognition, 2) linking those effects to biological and psychological (mood) mediators/mechanisms, 3) improved precision/efficiency for ascertaining cognitive outcomes. The use of the smartphone enables multiple cognitive assessments in English or Spanish without requiring attendance at a clinic. Telephone calls from bilingual coaches after initial in-person intervention allow for flexibility in scheduling and wide reach. Self-report of diet in combination with objective biomarker assessment (54-56) strengthens analyses of diet-disease hypotheses.

Figure 1



2.2.3 Feasibility- *Preliminary Studies*

Measurement Burst Design: Feasibility and Participant Compliance:
Dietary patterns and cognition: Preliminary findings from tests of global cognitive function from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (n=8,829, 45-74 yrs of age), a cohort that includes participants from Co-op City, Bronx, indicated in a model including age, ethnicity, sex, income and energy intake, the Alternative Healthy Eating Index (AHEI- a diet quality score that assesses the degree to which the diet adheres to the US Dietary Guidelines, was significantly associated with tests assessing verbal episodic learning and memory: the Spanish English Verbal Learning Test (SEVLT) 3 trials and SEVLT Recall. A 10 unit increase in

AHEI-2010 was associated with significant increase in these cognitive scores (β= 0.49, 95% CI: 0.18, 0.80, P=0.002), (β= 0.21, 95% CI 0.06, 0.36, P=0.005) respectively.

Dr. Sliwinski (investigator) has conducted several NIH-NIA funded measurement burst studies (57) and is currently conducting an NIH-NIA funded R01 (The ESCAPE [Effects of Stress on Cognitive Aging, Physiology, and Emotion] Study) and P01 measurement burst study in the Bronx (The Einstein Aging Study). The ESCAPE study uses smartphones to conduct ambulatory assessments of cognitive function, health behaviors, stress and emotional status in a diverse probability sample (N=304) that has been drawn from the same neighborhoods and resemble the proposed sample in terms of socioeconomic (i.e. education & income) status, age (up to 65) and racial diversity and literacy. Despite the duration and intensity of measurements (14 days, 5 times per day), participants have exhibited excellent compliance, completing over 80% of the smartphone assessments, and excellent retention over a 1year follow-up (12% attrition) (58). Given that the proposed study utilizes a less demanding assessment protocol, we expect similar levels of compliance and retention. Ambulatory cognitive testing by smartphones in naturalistic settings is reliable and valid: as part of ESCAPE, Dr. Sliwinski developed and validated smartphone-based cognitive tests of memory and processing speed in a diverse sample (58). This study used a sample that will resemble the proposed sample in terms of age (up to 65 yr), race and other demographics. Participants were prompted at 5 quasi-random times per day for 14 days to complete brief visuospatial working memory (Dot "Grid" Memory) and processing speed (Symbol Search) tasks on study-provided smartphones. These tasks are described in detail in section 2c2. Scores for each person were calculated by taking their average performance across all assessments. Reliability for the average scores was 0.97 and 0.98 for the Grid Memory and Symbol Search, respectively. Figure 1 illustrates construct validity of the smartphone-based ambulatory cognitive tasks, which were designed to measure visuospatial working memory (Grid Memory) and processing speed (Symbol Search). Both tasks had high factor loadings (>0.60) on their target constructs.

Recruitment & Retention Experience at Einstein: WHI, HCHS/SOL & ESCAPE:
Our team has previously successfully recruited 4,000 diverse post-menopausal women from New York City to the Women's Health Initiative (WHI), a landmark NIH-funded study at forty sites nationwide using direct mail from purchased lists, enhanced by advertising and other community promotions. We have also recruited over 4,000 Hispanic/Latinos from the Bronx to HCHS/SOL, a NIH-funded epidemiologic study of Hispanic/Latinos at four sites in the United States including Bronx, New York (3, 59, 60). Recruitment in HCHS/SOL was achieved via probabilistic community-based sampling, with 19,389 households visited to yield a final sample of 4,156 participants in three years of follow-up, retention was >85%. The ESCAPE study (58) used systematic probability sampling to recruit a racially and economically diverse sample of 25-65 year olds from Co-op City, a Bronx housing cooperative of >50,000 residents.

Intervention Studies at Einstein: Adherence and Monitoring by Self-Report & Biomarkers:
In the Women's Health Initiative (WHI) Dietary Modification Trial, which was designed to increase fruit and vegetable intake to five servings per day, intake of fruits and vegetables in the intervention group (n=19,470) increased from 3.6 (SD, 1.8) servings at baseline and stayed at 4.7 (SD, 2.4) servings by year 9 of the intervention while the intake of comparison participants (n=29,216) rose only to 3.8 (SD, 2.0) one year after baseline and was 3.7 servings (SD, 2.0) at

year 9 (WHI-Semi-Annual progress report, 2/29/2004.) Overall, 517 participants at the New York City field center who initially enrolled in the study, or 81.6% were still active in the last yr (yr 10) of the intervention. The remainder had stopped the intervention (9.7%) or had stopped/ lost to follow-up (4.5%) or were deceased (4.3%) (Data from WHIPO444 3/15/05). These data indicate the durability of the intervention, not just nationwide, but also at the New York City site, which included participants primarily from the Bronx. Biomarker data from the nationwide study indicated relative increases comparing intervention to comparison participants even at year 3 at which point intervention sessions had decreased from 18 sessions in year 1 to 4 sessions in subsequent years: total carotenoids, (5%) tocopherols (1%), beta-cryptoxanthin (7%), lutein (3%), and retinol (2%). Gamma-tocopherol levels difference between intervention and control decreased 15% indicating a decrease in fats/oil intake in the intervention group (61).

Additionally we adapted the intervention materials to the cultural context. Examples include the alternative self-monitoring tools, an effort that was co-led by Dr. Mossavar-Rahmani (62). Our pharmacy pilot study of n=22 pharmacy clients representative of Co-op City Bronx participants indicated that 94% of women & 83% of men state desire to change eating behaviors. Fifty percent of men and 44% of women also stated eating French Fries/chips in the past week and only 58% of men and 44% of women stated eating a fruit every day (63).

Summary of Significance: **The significance of this study lies in our ability to do the following: 1) Assess adoption of a MHD in mid- and late adulthood in a multicultural cohort; 2) Determine whether adoption of a MHD can enhance cognitive aging; 3) Identify components of the diet associated with enhanced cognition.**

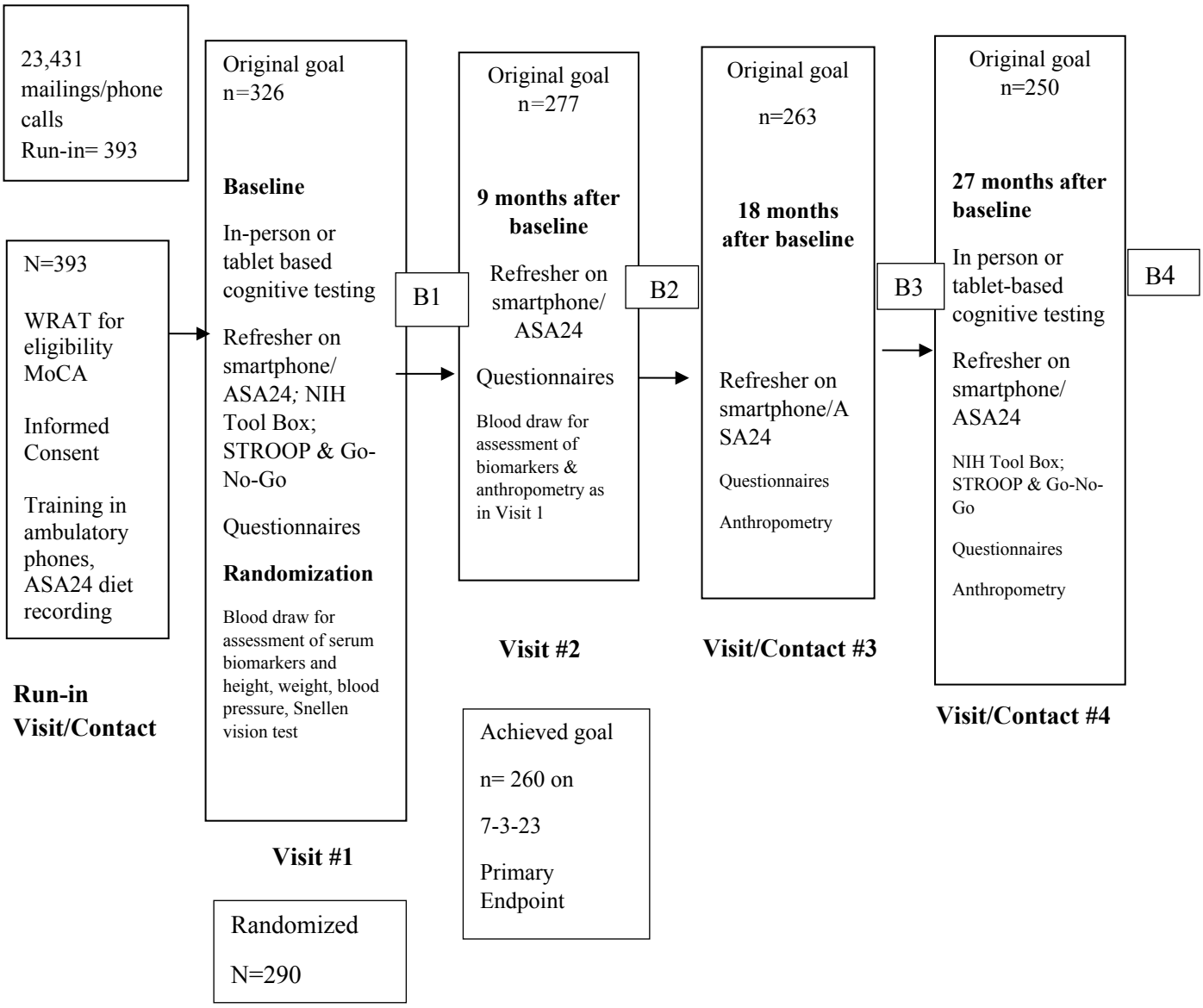
3 STUDY DESIGN

The proposed study design is a **two-arm randomized clinical trial**. Participants in the **experimental intervention arm** will be exposed to an intervention over an 18 month period (four in-person visits in small groups with the interventionist over a two month intensive phase & monthly telephone coaching starting in month 3 of the intervention till month 18). Assessment visit cover a 27 month period (run-in, baseline, months 9 & 18 and 27) at the Aging Research Center (Van Etten Building) at the Albert Einstein College of Medicine (Einstein). The study will also be mentioned at community events at Co-op City and interested participants will be invited to provide contact information so that the recruitment letter can be sent to them.

Comparison participants will only have access to general health recommendations such as the US Dietary Guidelines-2015. Health educators/coaches will deliver the intervention and comparison sessions. This approach models the Care Management Organization of our health system, Montefiore Medical Center (64). Comparison participants will receive the information in same modality as the intervention namely four in-person and bi-weekly for first two months, then monthly by phone till month 18. The comparison sessions will focus on self-care/management matters as: maintaining dental hygiene, flu vaccinations, choosing shoes that fit, considerations for long-term care insurance, having a health care proxy, dealing with aches and pains of aging, eye health, etc.

Figure 2: Schedule of Clinic Visits: Original vs. Revised Goals

Note: One week burst measures occur after clinic visits (B1-4); we revised missingness rate from 15% in original proposal to 10% and missingness rate assumption is 5% from B2 to B4



Based on a revised sample estimate that better reflect ability to recruit, study staff will screen, recruit and retain 290 eligible diverse participants (from original estimate of n=326 revised to n=277 plus buffer of additional n=13 participants- see section 9.2- Sample Size & Randomization) aged 40 to 65 yr for this project who live, visit, work or attend school in Co-op City or in adjacent communities. Co-op City is a diverse cooperative housing development

designed to provide affordable housing in the northeast section of Bronx County. Co-op City's size (>50,000 residents), diversity (60.5% African American, 27.7% Hispanic), median age (42 years), income ($50,900) and proximity to the Einstein Medical complex make it an ideal population center from which to recruit a representative sample. Additionally, as residents have ownership rights to their unit, turnover of residents in this housing complex is low. The staff will recruit the target sample and implement methods to maximize participation and retention based on Mody et al., 2008 (65). To minimize selection bias, we will use telephonic recruitment methods that have been developed and validated for use in the Einstein Aging Program Project (NIA P01AG003949) since 1993. These procedures consist of obtaining Registered Voter Lists (RVL) from the New York City Board of Elections for the Co-op city zip code, which define a sampling block covering more than 90% of individuals listed in U.S. Census tabulations for that area. Individuals on the RVL will be categorized into 10-year age intervals and assigned to age, race and gender sampling stratified sampling blocks. Letters of introduction will be sent to members of each sampling block, explaining the project and its goals, how the recipient of the letter was identified, and that they will be contacted by telephone within two weeks. The letter includes a telephone number for individuals to call if they do not wish to be contacted by telephone; all individuals doing so will be removed from the sampling blocks. During the recruitment call recruiters will establish rapport, identify exclusions and screen for basic computer use skills. Interested and eligible individuals will then be enrolled. ***For recruitment, we*** sent letters to 23,431 individuals inviting them to the study and n=393 participants enrolled for run-in activities. Of the n=393, 73% or n=290 were randomized to the study. We achieved a final sample size of n=260 by the second visit (Visit #2) indicating retention of 89.7% of randomized participants. Eligibility by phone screening call or at community-based events will be based on: residing, working, visiting or attending school in Co-Op City, Bronx or neighboring communities, age (between 40-65 yrs), willingness to participate in a study where weight loss is not a primary goal, and to track food intake. Eligibility criteria: willing to participate in study for 27 months; employment that does not interfere with ability to respond to prompts (for example a shift worker who needs to tend to patients may not be a good candidate); willingness to accept either study condition (comparison or intervention). Exclusion criteria includes a history of neurologic condition or disease producing cognitive dysfunction; history of traumatic brain injury; current psychiatric disorder known to significantly affect cognition (e.g., major active depression, history of eating disorders, PTSD); participants with type 2 diabetes who are on medications that cause hypoglycemia (e.g. insulin, sulfonylureas, and meglitinides) and have had hypoglycemic episodes, previous history of cardiovascular disease; participant primarily interested in weight loss as judged by discussion with participant and any severe chronic illness, low literacy or other medical or other conditions that would preclude completion of study activities; history of alcohol or drug dependence; hematologic disease or malignancy not in remission for more than 5 years; visual, auditory, or motor impairment that precludes cognitive testing.

In-Clinic Cognitive Assessments: Participants will also perform computer based versions of the dot-memory, symbol search and memory binding tasks, to provide us with a point of comparison

for other studies of dietary effects on cognitive function. Other in-clinic cognitive tests include the Stroop Test for processing speed (done visits 1-4 -see descriptor) and tests from the NIH Tool Box (https://www.nia.nih.gov/research/resource/nih-toolbox) that will be done at visits 1 & 4- these tests were discontinued during the pandemic as of 3/12/20:

Toolbox Flanker (executive function attention)

Toolbox Picture Vocabulary (language)

Toolbox Dimensional Card sort (EF-judgment/flexibility)

Toolbox Pattern Comparison (processing speed)

WMS Episodic Memory (WMS paired associates)

These tests are accompanied by participant complaints questionnaire used in the Einstein Aging Study at visit 1 (see form) at visit 1 (baseline) and the 6 item Promis v1.0-Applied Cognition-General Concerns-Short Form 6a in follow-up visits.

The Wide Range Achievement Test (WRAT) literacy test will be given once at run-in. *In-Clinic Questionnaires: Participants will also be* asked to complete questionnaires regarding past medical history, concomitant medication, socio-demographic information, education, income, marital status, alcohol, physical activity, smoking and drug use including smoking. APOE4 allele, the gene for apolipoprotein E which is a risk factor for AD will also be assessed. These questionnaires are based on ESCAPE study and have acceptable participant burden drawing on participants from Co-op City (see Appendix and Table 1 in Scott et al., 2015 (66).

Assessment Visits- Run-In: After eligibility is determined over the phone, each participant will be scheduled for a run-in visit at which time they will receive instructions on the use of the smartphone or tablet for the burst measures for the cognitive exercises. The in-clinic test will also include a literacy test (67). Mild Cognitive Impairment (MCI) is rarely documented for adults <65 yr (our sample will be aged 40-65 yr). Pilot data in much older adults (aged 75+) with diagnosed MCI have shown them to be able to comply with a smartphone protocol similar to the one we proposed to use. Participants will not be excluded with baseline memory complaints or indications of cognitive problems because it may be precisely those individuals who could benefit from the dietary intervention. At this visit participants will also receive instructions for use of the National Cancer Institute Automated Self-Administered 24 hour dietary recalls (ASA24) for daily intake. The ASA24 is a web-based 24 hour dietary recall instrument (68) available in English/Spanish that has been used in studies with multicultural populations (69). It is available as an app on smartphones. It includes an optional module to query about dietary supplement intakes based on supplements reported in the 2007-08 National Health and Nutrition Examination Survey (NHANES). Based on our experience in ESCAPE, of this number, we expect 80% of participants to succeed in the run-in activities (80% of compliance for activities that run several days). Only participants capable of complying with this protocol will be invited to the study. We will carefully characterize those who do not qualify for the study on demographic and functional (e.g., literacy) variables to ascertain the extent of

selection bias and inform future iterations of this protocol.

Visit #1: When judged to be compliant based on satisfactory completion of cognitive function by smartphone/tablet and dietary intake via ASA24, participants will be invited to Visit #1. At this visit there will be cognitive testing, a short review on use of the smartphone, and completion of questionnaires before randomization. A fasting blood draw to assess serum biomarkers associated with diet will be scheduled close to the date of the baseline visit, at which time weight and height will also be assessed. Anthropometric measures include height and weight for the calculation of body mass index (BMI), waist-hip measures and blood pressure. Measurement of weight will be recorded in kilograms. Scales will be calibrated with fixed known standard weights and certified annually by the local Bureau of Weights and Measures. Height will be recorded in centimeters and measured with a stadiometer attached to the wall. BMI in kg/m^2 will be calculated from measured weight and height. After Visit #1, participants will undergo cognitive and behavioral measurements in burst fashion for a 7-day period every nine months over a 27-month study period in tandem with completing 7 diet recalls. Daily measures of health behaviors such as sleep quality, physical activity, fatigue, stress/emotions, and social activity will be included along with the cognitive function measures over the one-week period (see Appendix for questionnaires.) Smartphones or tablets used for the burst measurements will either be mailed or returned after each burst when participants return for the blood draws.

Visit #2 will occur 9 months after baseline visit. At this visit, we will conduct cognitive testing along with a short refresher on use of smartphones to precede the 7 day burst measure for cognition and diet that follows this visit as well as after visits #2-4. Participants will be scheduled for the follow-up blood draw for serum biomarkers and anthropometric measures. **Visit #3** will occur 9 months after Visit #2 and will consist of cognitive testing and a similar refresher on use of smart-phone/ ASA24. The last **Visit #4** will occur 27 months after baseline or 9 months after visit # 4 and will include cognitive measurements.

Dietary Intake: Dietary and supplement intake data will be at baseline for a week in tandem with cognitive bursts and in three follow-up bursts of one week at each follow-up clinic visit collected using the ASA24 (68) We chose this method as it has low participant burden and can be completed in real-time and has been used by participants with diverse backgrounds (70). Improvements in technology now allow for digital images that assist with estimation of serving size (71). The ASA24 has been validated against interviewer-administered 24-hour dietary recalls and is available in both English and Spanish and includes audio to guide the user (72). Participants will be prompted to go online via smartphones to complete the assessment. Participants will undergo training to use the ASA24 at the run-in visit. The food database for ASA24 is from the Food & Nutrition Data Base for Diet Studies (FNDDS 11-12). If participants cannot find their foods in this system, they can use the "food not found functions" to list the foods and they can be added later.

Dietary & Other Biomarkers: Blood specimens will be collected close to the baseline visit and approximately 9 months later and frozen at minus 70 degrees C and sent to Advanced Research & Diagnostic Lab (ARDL) at University of Minnesota for the following analyses: Lipid panel [cholesterol (total), HDL (direct), triglycerides, LDL (calc)]; plasma tocopherols/carotenoids; serum folate; serum B12; plasma fatty acids; IL-6 and C-reactive protein, and APOE4. To assess

hydration, serum sodium and blood urea nitrogen (BUN) were added. To ascertain type 2 diabetes we added Hemoglobin A1C. A 5% blinded duplicate sample will be sent to the lab for quality control.

Ambulatory Measurement Protocol: The ecological momentary assessment (EMA) protocol follows established and validated procedures that we have used in previous work to construct brief assessments, train participants in the use of specially configured smartphones, and minimize participant burden to ensure good compliance with the study protocol (58, 66, 73, 74). During their clinic visit, participants will be trained to complete the EMA protocol on study-provided smartphones running a custom-designed mobile health application that allows them to report on their daily experiences and play "brain-games" that measure their cognitive function. Our custom software locks down the operating system, self-launches at appropriate times, and provides an intuitive and easy to use interface with limited response options. This protocol controls the study-provided Android smartphone so that the participant is guided through completion, and cannot navigate the directories or run other applications except related to the study such as the ASA24 diet recall. Those with visual difficulties will receive a mini-Android tablet instead of a smartphone. Participants will: (1) be signaled by the smartphone to provide data at four quasi-random times (stratified throughout waking hours) per day for 7 consecutive days, and (2) provide event contingent reports upon waking and prior to going to sleep. The 4 signal contingent assessments will take 4-5 minutes to complete; the waking-up & bedtime surveys will take 3-5 minutes to complete.

Data will be saved locally on each smartphone's internal storage for the duration of the data collection periods and retrieved via direct connection to a workstation over USB to a central secure server after phone is returned following each assessment. Participants will complete "wake-up" surveys upon waking up in the morning. Wake-up surveys consists of a brief assessment of the previous night's sleep (when they went to bed, when they woke up, sleep disruptions and sleep quality) and a reminder to note what they are eating by entering foods into the ASA24 as they consume them or all at once by the following morning for all foods eaten the previous day. Bedtime surveys will be completed immediately prior to going to bed, and will query individuals about the stress, physical symptoms and the fatigue they experience throughout the day. Participants will be alerted to complete the signal contingent surveys via beeps. The four signal contingent surveys will be administered randomly throughout the day and consist of questions regarding the participant's current location, mood, stress, activity level, who they are with, and the distractibility of their environment. Immediately following the Wake-up and signaled brief surveys, participants will complete five brief cognitive tasks (described below). Each wake-up, signal contingent and bedtime survey will also query whether the individual had any liquids and what he/she drank. Three additional 7-day measurement bursts will be completed at 9, 18 and 27 months post-baseline, resulting in up to 140 assessments across the follow-up period (35 assessments on each of 4 bursts). This intensive measurement approach will allow us to explicitly examine lead-lag relationships between "cognitive health friendly" eating patterns and especially role of eating patterns that have an adverse impact on cognitive function. The burst design will permit modeling of the temporal relationship between diet and cognitive function across days, months & years. Knowledge of the time sequence is important as it will allow us to determine how long the effects of a healthy food/nutrient lasts (e.g. blueberries or folate), what dose is effective and how it is affected by subsequent ingestion of a less healthy food (French fries). <u>The 27 month assessment period will provide three time points to assess cognitive status to establish trajectory.</u>

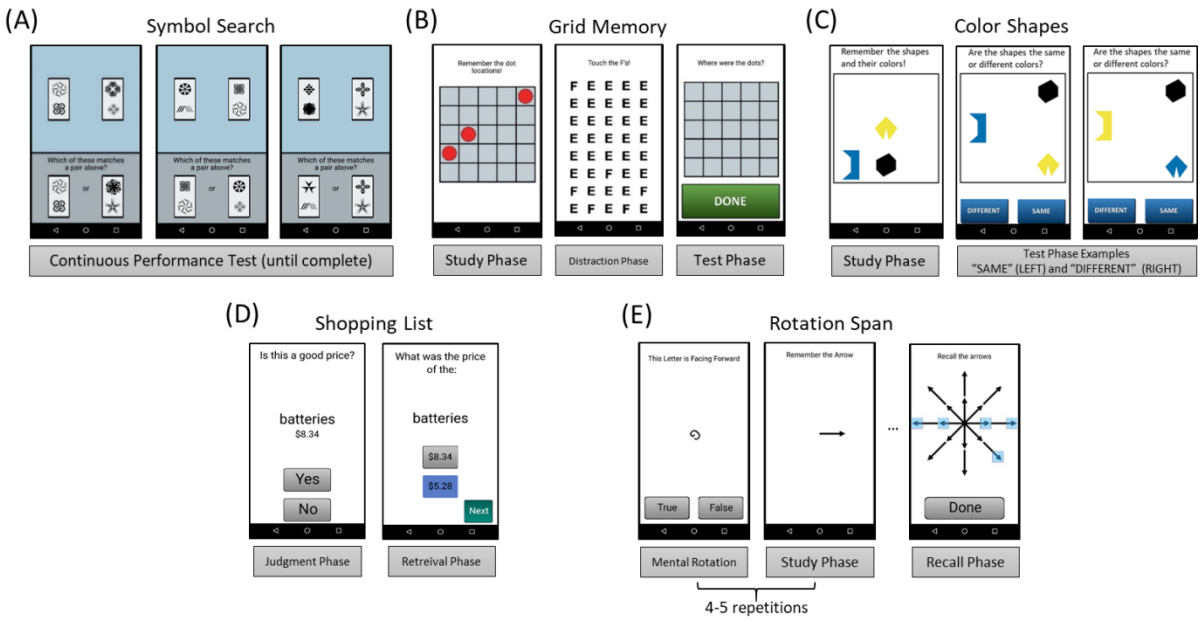


Figure 3. Mobile Cognitive Assessments in MHD. (A) Symbol Search task. (B) Grid Memory task. (C) Color Shapes task. (D) Shopping List task. (E) Rotation Span task.

Cognitive function measures: Typical clinic-based neuropsychological tests often involve multiple trials and take 5 to 10 minutes (or longer) to administer. Best practices for EMA studies indicate that each assessment should be very brief to minimize participant burden and encourage compliance (75). In addition to brevity, cognitive tests administered without supervision should have intuitive task demands to avoid confusion on the part of participants, and be designed to discourage cheating (e.g., writing down word lists). Finally, test stimuli should vary sufficiently across repeated administrations to eliminate unintended learning effects that might result from repeated practice with the same test items. Following these design principles, we implemented three previously validated ambulatory cognitive assessments to assess domains of processing speed, visuospatial working memory, and short-term associative memory "binding", as well as two new "exploratory" ambulatory assessments to assess domains of long-term associative memory and working memory capacity. We selected the following three ambulatory assessments as the primary endpoint of MHD due to the sensitivity of their respective cognitive domains to dietary habits, normative cognitive aging, and presence of preclinical AD (8, 24, 33). Specifically, we administered an assessment of visuospatial working memory (Grid Memory task) because recent work has shown that spatial pattern separation is sensitive to memory impairment in very early and preclinical AD (76, 77). We modeled the processing speed (Symbol Search) task after the Digit Symbol Substitution Test, which a meta-analysis has shown to be one of the earliest indicators of cognitive decline in preclinical dementia (78). Finally, the measure of short-term associative memory binding (Color Shapes task), was designed after the work of Parra and colleagues (2011) where it was shown to be a highly sensitive index of memory impairment in very early AD (79-82). The primary endpoint of MHD is a composite cognition score derived from performance on these three tasks.

Two additional ambulatory cognitive assessments were included in the EMA protocol as exploratory outcomes. The exploratory Shopping List task is longer-term associative memory task (>30s between study and test) modeled after the Paired Associates Learning task (83), and

has also been shown to be sensitive to early cognitive deficits in preclinical AD (84). Finally, we included an exploratory assessment of working memory capacity in the Rotation Span task (RSpan). The RSpan task is a complex span task of working memory, recently validated for remote EMA administration with M2C2 (85).

Ambulatory Cognitive Assessment Procedures. The Symbol Search task is a speeded two-alternative forced choice task where participants are asked to select the tile from the bottom of the screen that matches one of the tiles presented at the top of the screen. Target and sample stimuli for the task were rectangular 'tiles' containing two symbols, arranged stacked vertically (see Figure 3A). During each trial, two sample tiles were presented simultaneously at the top of the screen along with two choice tiles at the bottom of the screen. One of the choice tiles contained matching symbols in the same arrangement (top/bottom) as one of the sample tiles at the top of the screen. The other choice tile (the incorrect choice) contained either non-matching symbols (no overlap with either sample tile) or one symbol matching a sample tile ('lure' choice). Lure choices occurred on 50% of trials and were included to increase the attention (conjunction search) demands of the task. Participants were asked to select the tile at the bottom of the screen that matched one of the two tiles presented at the top of the screen as quickly and accurately as possible. Stimuli were presented until a response was made. Inter-trial interval was 1000ms and each trial began with the previous trial stimuli scrolling off the screen from right to left and the current trial stimuli scrolling onto the screen in the same direction. Participants completed 12 trials per assessment (~30 seconds per assessment). The primary outcome of the Symbol Search task is median response time (RT) for accurate trials.

The Grid Memory task is a delayed short-term recall task with a filled delay interval where participants are asked to recall the locations of three red dots presented in a 5 × 5 study array after a brief filled interval. Each trial of the Grid Memory task began with the presentation of an empty 5 × 5 study array for 1000ms (see Figure 3B). After this 1000ms warning interval 3 red dots appeared, occupying separate locations within the study array for a period of 3000ms. After the study period, a secondary letter-cancellation task was presented. The letter cancellation task involved the presentation of a 5 × 8 array of capital E's and F's for 7000ms. Participants were asked to locate all of the capital letter F's, which were removed from the screen after being tapped. After the letter cancellation task phase was complete an empty 5 × 5 recall array was presented and participants were asked to touch the locations occupied by the 3 red dots in the study array. The recall array was presented until participants submitted their choices. Participants completed 4 trials per assessment (~60 seconds per assessment). The primary outcome for Grid Memory is the mean error distance (Euclidean distance) of the red dots between study and recall arrays.

The Color Shapes task is a visual array change detection task where participants are asked to determine whether the combination of features (color and shape) among 3 visual objects distributed throughout the array change between study and test arrays. Each trial of the Color Shapes task began with an empty array for 500ms after which 3 colored abstract shapes appeared for a period of 2000ms (see Figure 3C). Participants were asked to study the specific combinations of shape and color present in these study array objects. After a brief 900ms delay period, the 3 colored shapes reappeared at different locations throughout the test array. The colored shaped at test could maintain the same combinations of color and shape (a "SAME" trial) or 2 of the shapes could have swapped colors (a "DIFFERENT" trial). Participants indicated whether they believed the combination of shapes and colors presented at test matched

the combinations present in the study array by pressing SAME or DIFFERENT buttons located at the bottom of the screen. Test array stimuli remained on the screen until response. Each trial had a 50% chance of being a SAME/DIFFERENT trial. Participants completed 6 trials per assessment (~45 seconds per assessment). The primary outcome for Color Shapes is corrected recognition rate (Hit-rate minus False-alarm rate).

The Shopping List task is a delayed recognition task where participants are asked to determine whether shopping list item-price combinations presented during a retrieval phase match the combinations judged during a price judgment phase of the task. The Shopping List task began with a price judgment phase where participants made subjective judgments of prices (in US dollars and cents) presented alongside hypothetical shopping list items (e.g. 'bananas'). Participants made 10 subjective price judgments in total during the price judgment phase by pressing "YES" or "NO" buttons in response to the question "is this a good price for [shopping item]" (see Figure 3D). Price judgment phase stimuli were presented for 3000ms each, with an inter-stimulus interval of 1000ms between items. Immediately following the price judgment phase, the retrieval phase began, involving 10 forced-choice recognition trials. Each recognition trial presented one of the shopping list items judged during the price judgment phase accompanied by two prices. One price always matched the price judged during the price judgment phase. The other, non-target price values were always within 9USD of the correct, target price. Both prices were always below 10USD. The order of shopping list item tested during the retrieval phase was randomized with respect to the price judgment phase presentation order. Retrieval phase trials were presented until response. The Shopping List task lasted approximately 60 seconds per assessment. The primary outcome for Shopping List was proportion correct responses during the retrieval phase.

The Rotation Span task is a complex span test of working memory capacity where participants are asked to memorize oriented arrows one at a time while performing interleaved mental rotation judgments on letter stimuli that were either forward or backward facing when oriented back to standard typeface orientation. Each trial of the Rotation Span task began with the presentation of a mental rotation trial (forward- or backward-facing versions of the capital letters G, F, R, and J were used for the mental rotation trials). After selecting "TRUE" or "FALSE" to the prompt "This letter is facing forward", an arrow study stimulus was presented for 1000ms (see Figure 3E). Arrow stimuli were oriented at 45deg increments around an invisible clock-face and were either short or long in total length, allowing for 16 possible orientation-length combinations. After completing a set of 4 or 5 rotation task/arrow memoranda pairs (set-size was randomized on every trial and across administrations), participants were asked to recall all of the oriented arrows memorized on the current trial by pressing the arrow heads of a full-report recall array. Participants completed 2 trials of the Rotation Span task (~60 seconds). The primary outcome of the Rotation Span task was total number of correctly recalled arrows ("partial credit" scoring criteria).

A recent study showed that a global measure of cognitive function, consisting of tasks which assess working memory and processing speed, was sensitive to a healthy diet (8). **Our primary outcome will consist of a z-score global composite measure of the Symbol Search, Grid Memory, and Color Shapes tasks**. In addition, our secondary outcomes will consist of examining dietary effects on each of the three tasks to determine whether observed intervention effects are attributable to specific cognitive domains. Exploratory outcomes will consist of short-

and long-term associations between dietary outcomes, responses to self-report EMA surveys, and performance on all five ambulatory cognitive assessments.

Figure 4: MHD Diet--A Typical Day--Based on the Dietary Inflammatory Index with adaptations to cultural context and emphasis on hydration. Drink a cup of water upon waking and water throughout the day
Breakfast: One cup whole grain cereal with ½ cup berries or sliced bananas and ¼ cup milk or whole grain bread with nut butter spread (e.g. almond, cashew) and fruit; green or regular tea or coffee with milk if desired and not more than 1 tsp sugar.
Snack: 1/3 cup cashews or almonds or fruit such as mango or banana and milk beverage (batida) made without sugar
Lunch: Sandwich with two slices whole wheat bread 1 oz low-fat mozzarella cheese or chicken slices and half an avocado mashed 1 or more cups of water or tea/coffee preferably without sugar
Salad: 1 cup romaine lettuce or baby kale or arugula; 1 cup fresh cucumber slices; ¼ cup chick peas;1/2 cup tomatoes; 1 Tbsp olive oil and vinegar dressing; 1 or more cups of water
Dinner: 4 oz broiled salmon or catfish or chicken or baked pork chops seasoned with chopped onions/tomatoes or turmeric, garlic, ginger or tarragon or vegetarian alternative: red beans or pigeon peas (gandules) and brown rice with chopped tomatoes, roasted peppers and green olives, cilantro, onions, bell peppers, and capers; ½ cup whole grain (quinoa, brown rice) and/or 1 cup lentils,½ cup squash or beets
Salad: ½ cup arugula or baby spinach, ½ cup tomatoes, ½ cup cucumbers, 1Tbsp olive oil & vinegar dressing
Dessert: Sweet potato custard made with evaporated skim milk with 6 grams of sugar per serving or fruit (orange, kiwi, etc.)

Behavioral Component of the Intervention. We will use a motivational interviewing approach to enhance motivation for adherence to the intervention (86-90). We propose to use validated Social Cognitive Theory (SCT) constructs to implement the intervention with emphasis on the social-physical environmental (e.g. modification of the home environment) and behavioral (individual level) changes (91). The following principles will be applied to issues related to dietary change: self-monitoring, stimulus control, problem solving, goal setting and individual feedback. **Self-monitoring** promotes behavior changes by promoting awareness of eating habits and creates self-efficacy. Participants will be offered a variety of tools from web-based systems or apps such as MyFitnessPal or ChooseMyPlate super tracker or paper-based food diaries to self-monitor in a manner tailored to individual needs (62).

Cognitive Strategies: Participants will work with the coach to identify whether perfectionism, pessimism, and all-or-none thinking apply to them and if yes, identify strategies to counter negative thinking through the use of thought stopping and/or positive statements. Likewise, the influence of emotions on eating will be discussed. Attention will be given to motivational issues and relapse prevention. We will use a relapse prevention model to instruct participants to reframe inappropriate eating episodes as temporary slips. Participants will have the option of bringing significant others to in-person sessions by obtaining prior permission from the coach. Participants will also learn how to shop economically by using coupons, frozen vegetables, frequenting farmer's markets and buying foods in bulk when and where practical. Cooking demos demonstrating make-overs of meals with anti-inflammatory compounds such as spices will be provided.

Training of Coaches: Coaches will receive on-site training on the delivery of the comparison and intervention materials and motivational interviewing from Dr. Mossavar-Rahmani (92).

Training will cover the content and delivery of the four in-person and telephone participant contacts. The nutrition coach will target nutrition intervention activities, while the general health coach will deliver the comparison activities focussed on general health-related topics.
Evaluation of the Protocol: We will evaluate the clinic visit protocol and the intervention sessions in the first month and every six months for standardized delivery.

Retention Plan: To maximize retention, the study will provide incentives for data collection activities after randomization. Participants will receive $20 compensation for each of four completed clinic-based assessments (Baseline, 9 month, 18 month, 27 months) and $80 for each battery of completed one-week measurement bursts (cognitive test and diet assessment). Participants will also receive a $5 bonus for completing 80% of daily assessments and an additional $10 for completing 90% of all assessments.

Data Management for this study will be overseen by Ms. Katz and her team, similar to that used in the ESCAPE study. Drs. Sliwinski & Hakun will be responsible for data collection and quality control related to cognitive function tasks and ambulatory assessments captured on the smartphone. Dietary data will be downloaded from the NCI ASA 24 web-site and all data will be compiled by the data analyst at Einstein. Data collected using conventional paper and pencil methods for other study instruments are entered by the study coordinators through the relational data base structured specially for this study. The study database system tracks enrollment, participant flow, clinic evaluations, number of follow-up evaluations, and deaths and dropouts in real-time. It also includes summary reports of assessments and interventions longitudinally across bursts. This system includes procedures for documenting the creation and distribution of data sets for specific analyses, and archiving of each data set according to purpose and date of creation. Biospecimens are initially maintained in the Einstein Clinical & Translational Service Award (CTSA) lab, the Biomarker Analytic Research Core (BARC) and shipped to Advanced Research & Diagnostic Lab (ARDL) *at University of Minnesota for analysis*. Laboratory results from outside labs will be electronically transferred, and will undergo quality control checks. Cleaned data will be uploaded through a secure transfer system using the HIPPA compliant Box system and uploaded to the main database. Data will be maintained in a secure environment and subject data will be protected from unauthorized access. The study staff will prioritize protection of the subject privacy, and ensure that access is only given to authorized investigators without compromising a subject's right to privacy. The data server and all computers feeding into it are connected by a local area network (LAN) that is <u>not</u> connected to the Internet. The LAN is a stand-alone network of password protected computers with no connection to any other computers within or outside the institution, which decreases security threats from viruses and virtually eliminates the threat of external "hacking." The computerized data collected will be subjected to SSL 256-bit encryption. There is a similar server at PSU where encrypted ambulatory data are stored. Only encrypted data are transmitted from the ambulatory data collection devices to the servers and from server to server. The servers have been granted an SSL certificate verified by InCommon. This encryption protects participants should the data be intercepted as it is transmitted to the servers. In the unlikely event that interception occurs, the data could not be decoded without the unique encryption key that is held by investigators at both Einstein and PSU. The servers are housed in secure offices at Einstein and PSU and can only be accessed by trained administrators. When data are to be uploaded for access to outside investigators for

analysis, they are de-identified and transferred to an external hard drive and brought to a secure computer with Internet/FTP access.

When the COVID-19 pandemic occurred, participants, investigators and staff were unable to travel into the Einstein clinic facilities. Remote administration of the study protocol put into place. The established LAN system could not be used since access to the clinic site where the physical server, workstations and data reside was not possible. Therefore, the local server environment was temporarily converted to a web-based environment so participant records and data were accessible to authorized personnel via the Internet. The virtual server is protected via a multi-layered encrypted firewall utilizing IP filtering, Windows login security and SQL server authentication. Real time network intrusion software, anti-malware and anti-virus programs run concurrently. No users have the ability to export or download any data. Once the study is able to operate from the clinic site, data collection will return to the original setup.

All of the databases and data entry programs are stored on a dedicated server and maintained by Ms. Katz, the highly experienced data manager. Multiple automated back-up procedures are implemented nightly to store copies of data and programs at both on- and off-site locations. Data sets are be frozen on a semi-annual basis. Specific codebooks are generated for each frozen dataset to document contents, frequencies of included variables, documentation of editing and cleaning procedures, and code used to create calculated variables. Potentially identifiable data will be sent to Kaiser Permanente Washington Research Institute for statistical analyses using Montefiorebox and de-identified data to the University of Minnesota for biospecimen laboratory analyses.

Adaptations to the Pandemic

Beginning with the Covid-19 pandemic on March 13, 2020 all group intervention and comparison sessions were conducted on Zoom. Before the start of the Covid-19 pandemic, in-clinic measures were obtained during site visits that occurred prior to a 2-day baseline "Run-in" period (Run-in Visit), a 7-day Baseline measurement burst (Baseline Visit), 9-, 18-, and 27-month measurement bursts (Follow-up Visits). Beginning with the pandemic all cognitive assessments were conducted online via Zoom except for the NIH Toolbox which was discontinued. We resumed biospecimen collection and anthropometry in-person starting July 16, 2020, after a four month hiatus due to the pandemic.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Study staff will screen, recruit and randomized n=290 eligible diverse participants distributed participants aged 40 to 65 yr for this project from Co-op City or adjacent communities, a diverse cooperative housing development designed to provide affordable housing in the northeast section of Bronx County. Co-op City's size (>50,000 residents), diversity (60.5% African American, 27.7% Hispanic), median age (42 years), income ($50,900) and proximity to the Einstein Medical complex make it an ideal population center from which to recruit a representative sample. Additionally, as residents have ownership rights to their unit, turnover of residents in

this housing complex is low. The staff will recruit the target sample and implement methods to maximize participation and retention based on Mody et al., 2008 (66). To minimize selection bias, we will use telephonic recruitment methods that have been developed and validated for use in the Einstein Aging Program Project (NIA P01AG003949) since 1993. These procedures consist of obtaining Registered Voter Lists (RVL) from the New York City Board of Elections for the Co-op city zip code, which define a sampling block covering more than 90% of individuals listed in U.S. Census tabulations for that area. Individuals on the RVL will be categorized into 10-year age intervals and assigned to age, race and gender sampling stratified sampling blocks. Letters of introduction will be sent to members of each sampling block, explaining the project and its goals, how the recipient of the letter was identified, and that they will be contacted by telephone within two weeks. The letter includes a telephone number for individuals to call if they do not wish to be contacted by telephone; all individuals doing so will be removed from the sampling blocks. During the recruitment call recruiters will establish rapport, identify exclusions and screen for basic computer use skills. Interested and eligible individuals will then be enrolled.

4.1 Inclusion Criteria

Eligibility criteria for the study will include:

- Living, working, visiting (e.g. for shopping, doctors' visits, etc.) or attending school in Co-op City, Bronx or adjacent communities and between 40-65 yr of age
- Willing to participate in study for 27 months
- willing to track food intake
- employment that does not interfere with ability to respond to prompts (for example a shift worker who needs to tend to patients may not be a good candidate)
- willing to accept either study condition (comparison or intervention)
- willing to participate in a study where weight loss is not a primary goal
- participant with controlled hypertension
- access to a smartphone that can work with any HTML5 compliant web browser to enter food records.
- reliable access to the internet

4.2 Exclusion Criteria

Exclusion criteria for the study will include:

- history of neurologic condition or disease producing cognitive dysfunction
- history of traumatic brain injury; current psychiatric disorder known to significantly affect cognition (e.g., active major depression, history of eating disorders, active PTSD)
- participants with type 2 diabetes who are on medications that cause hypoglycemia (e.g. insulin, sulfonylureas, and meglitinides) and who have had hypoglycemic episodes
- previous history of cardiovascular disease (CVD): myocardial infarction, heart failure, stroke (that affects physical functioning), hospitalization for CVD event or procedure.
- uncontrolled hypertension defined as blood pressure ≥ 140/90 mm Hg
- participant primarily interested in weight loss as judged by discussion with participant and any severe chronic illness

- low literacy or other medical or other conditions such as pregnancy or breastfeeding that would preclude completion of study activities
- history of alcohol or drug dependence
- hematologic disease or malignancy not in remission for 5 years or more
- visual, auditory, or motor impairment that precludes cognitive testing.
- participating in weight loss programs such as: Weight Watchers', Atkins or extreme dieting programs
- participating in programs that enhance cognition such as playing brain games
- taking medications that impact cognition such as Aricept

- diagnosis of kidney/renal disease on dialysis or special diet
- diagnosis of liver disease
- Using Continuous Positive Airway Pressure (CPAP) and experiencing disrupted sleep

4.3 Study Enrollment Procedures

To minimize selection bias, we will use telephonic recruitment methods that have been developed and validated for use in the Einstein Aging Program Project (NIA P01AG003949) since 1993. These procedures consist of obtaining Registered Voter Lists (RVL) from the New York City Board of Elections for the Co-op city zip code, which define a sampling block covering more than 90% of individuals listed in U.S. Census tabulations for that area. Individuals on the RVL will be categorized into 10-year age intervals and assigned to age, race and gender sampling stratified sampling blocks. Letters of introduction will be sent to members of each sampling block, explaining the project and its goals, how the recipient of the letter was identified, and that they will be contacted by telephone within two weeks. The letter includes a telephone number for individuals to call if they do not wish to be contacted by telephone; all individuals doing so will be removed from the sampling blocks. During the recruitment call recruiters will establish rapport, identify exclusions and screen for basic computer use skills. Interested and eligible individuals will then be enrolled.

The recruitment phase consists of the following:

- Letter of Introduction to the study (see appendix) is sent to individuals
- After 7-10 days of the letter being sent, attempt to reach the individual by phone.
- If contact is made with the individual, oral consent is obtained to proceed with the telephone interview (see appendix IRB oral consent).
- Telephone screen will be administered to determine eligibility

During the recruitment phase, recruiters will complete an entry in a Screening Log for each in the sampling block. The Screening Log will contain the following information:

- # of phone attempts to reach the individual
- Whether the individual was reached
- Whether the individual agreed to a phone interview
- If they agreed to phone interview, were they eligible
- If not eligible, reason for ineligibility

In addition to telephonic methods, we will attend community events (fairs, events at local malls and businesses) and also use email blasts, ResearchMatch newspaper articles and distribute flyers to recruit participants. We will recruit from the Montefiore Medical Group in Co-op City (Bartow) for participants who live, work, visit (for shopping, doctor's appointments) attend school in Co-op City or neighboring communities and will also use electronic medical records from the Montefiore Medical Group in these communities to create recruitment lists that we will use to contact participants . Our recruiter will describe study to participants in waiting area and provide contact information about the study or sign up interested participants. Flyers will be provided. Physicians in the practice may also provide flyers about study to participants and refer them to study recruitment phone line or email address.

Once it has been determined that an individual is eligible to participate and he/she agrees, an appointment is made for two screening visits. At these visits, participants perform run-in such as using the smartphone for assessing cognition and mood and also learn to track foods using the smartphone. They are also given home assignments to assess ability to perform the study tasks. Randomization occurs after screening visit #2 when participants return to the clinic with the smartphones and are judged to be eligible to proceed to study activities.

The tasks at each visit are outlined below:

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

If assigned to the Multicultural Healthy Diet, participants will:

- follow an anti-inflammatory healthy dietary pattern over the 27 month duration of the study
- attend four 1-2 hour groups sessions on shopping & cooking healthy diet in the first 2 months at Co-op City or other convenient location (up to 8hr)
- write down foods eaten 3 times/month for 18 months (18 hr)
- receive 16 monthly 20 minute phone calls and/or online program materials from coaches on following diet after the group sessions end; for participants who are difficult to reach, up to three sessions can be completed in one phone call (5 hr, 20 minutes)

Dietary Component of the Intervention: This will be a small group intervention with tailored phone calls after the core sessions. Participants will undergo an 18 month intervention (four semi-monthly small group sessions for 2 months followed by monthly phone calls for 16 months). The small group sessions will last 2 hours for 3-4 participants. Monthly phone calls last 20 minutes and are focused on dealing with specific challenges such as dealing with social situations, eating at fast food outlets. The intervention will be hands-on and delivered using a motivational interviewing approach and include a visit to the supermarket in session 2 with the small group format, with a focus on structuring one's own environment to maximize adherence to the study. While some participants may lose a small amount of weight on this diet (see

example in Figure 6), weight loss is not a primary goal and dietary intake will be reviewed as eucaloric and have the following distribution of macronutrients: 33% fat, 38-41% carbohydrate and 26% protein, (may vary as MHD is individualized). The core sessions (Table below) are:

1. Key components of the MHD Diet & Hit List
2. Shopping Smart & Price Wise: Reading Nutrition Facts Labels, & Shopping Cart Check
3. Understanding portion sizes and monitoring tools to keep track
4. MHD diet at home and outside the home: photo of contents of home fridge/contents of cupboard
5. Monthly calls start as tailored to participant using motivational interviewing approach

MHD Diet sessions, components targeted and assessment/monitoring method

Core Session Topic & Learning Objectives	**MHD Component Targeted**	**Biomarker for assessment and/or monitoring method**
#1 Key components of MHD Diet Understanding inflammation and role in cognitive health Identifying and preparing foods that reduce inflammation	Embrace foods high in anti-inflammatory properties such as: cantaloupe, broccoli, green leafy vegetables, nuts, berries, beans, whole grains, fish, poultry, other vegetables, fish, water upon waking; seasonings/herbs such as ginger, turmeric, saffron, rosemary, thyme, oregano, cloves; vegetable/bean soups encouraged to increase hydration; choose healthy oils for salads, cooking (e.g. olive oil)	Positive biomarker: Levels of serum B12, tocopherols/ carotenoids (for yellow, orange and green vegetables), levels of metabolized folate (for green leafy vegetables, beans, avocadoes, bananas, whole grains, fish) , fatty acid panel; Negative biomarkers: C-reactive protein, IL-6
Hit List	Limit red meats, butter/stick margarine, cheese, pastries/sweets, fried/fast food	
#2 Shopping Smart: Label Reading at Supermarket	Get to know the produce sections of your supermarket (fresh/frozen/canned); being savvy about nutrition facts labels	Participant brings photo of fridge/cupboard for self-assessment
Hit list	Limit processed foods	
#3: Power of Habits & Self-monitoring	Establish MHD habits and stay hydrated; adapt cooking techniques to add spices/herbs	Participant self-monitors food intake; Participant learns ways to add anti-inflammatory compounds such as herbs/spices in food preparation
Hit list	Limit butter, margarine, pastries, sweets, fast/fried foods, soda, hot dogs, sugar-sweetened beverages	
#4 Dealing skillfully with social situations & food selection	Behavioral strategies to deal with social situations and slips/setbacks	Participant brings photo of fridge/cupboard for self-assessment
Monthly calls to month 18	Tailored to participant using motivational interviewing	Motivational interviewing approach

If assigned to the Usual Diet, participants will:

- continue usual diet
- attend four 2 hr group sessions at Einstein on topics related to aging (8hr)
- receive 16 monthly 20 minute phone calls and/or online program materials on topics related to aging (5 hr, 20 minutes)

5.2 Handling of Study interventions

Session materials and a manual describing the materials will be used for delivering the intervention.

Blinding: Assessment staff for clinic visits (for anthropometry, cognitive testing, etc.) will be blinded to study assignment and participants will be asked not to divulge their randomization status**.**

5.3 Concomitant Interventions

5.3.1 Allowed interventions

Participants randomized into the study may continue to take medications per primary physician recommendation and should follow their primary physician recommendation re: food allergies, prohibited foods (e.g. participants on blood thinning medications should avoid consuming large amounts of foods high in vitamin K such as green leafy vegetables) if on the Intervention Diet.

5.3.2 Required interventions

Other than the food based anti-inflammatory diet that is eucaloric and the usual diet, no other interventions are required.

5.3.3 Prohibited Interventions

Any intervention that may impact exposure (diet) and outcome (cognition) are prohibited and included in exclusion list. These include the following:

- Participating in any diet or weight loss programs such as: Weight Watchers', Atkins or extreme dieting programs
- Participating in programs to enhance cognition such as playing brain games
- Taking medications that impact cognition such as Aricept, Ritalin and other medications for ADHD.

If participants are prescribed the above medications after randomization or they develop a health outcome that would have made them ineligible to participate in the trial (e.g. diabetes), they will

continue to be followed and the decision to continue in the study will be assessed on a case-by-case basis by investigators with input from the Data Safety Monitoring Board.

5.4 Adherence Assessment

Adherence to intervention:

Attendance and **monthly self-monitoring of three days' intake** will be tracked as process measures to determine participant adherence. Non-adherent participants (as demonstrated by missed sessions or unreachable by phone) will receive up to ten additional phone contacts at different times of day/ day of week. If no contact is established after ten contacts, the participant will be considered as limited contact or no follow-up status. However, each participant will be considered on a case-by-case basis and contact may be established at a later date as determined by participant and study staff.

Adherence to diet via biomarkers: In yr 1-2 we will assess preliminary results of assays in a 5% subsample for carotenoids, tocopherols, and folate. This will serve as a preliminary check for adherence to the intervention. All participant specimens will be analyzed by yr 4-5.

Contamination of Comparison and Intervention: Co-op City encompasses a large area with >50,000 residents and is almost the size of a mini-city; we do not anticipate that there will be much chance for comparison and intervention participants to meet each other as evidenced in our studies (94, 95). We will ask participants to keep their randomization status confidential and request that they not discuss the intervention with other Bronx residents or with their online social networks. Only one member per household will be permitted to be invited to the intervention to preserve independence. If during the course of the study a participant moves out of the Bronx, he/she will be asked to continue the intervention via telephone. Since there are only four visits with the interventionist (that may be completed by phone based on coach's determination) and assessment using the smartphone, moving should not be a barrier to participation.

STUDY PROCEDURES

6.1. Schedule of Evaluations

Assessment	Screening: Phone Assessment	Baseline, Enrollment, Randomiza-tion: Visit 1a (Run-in Visit)	Visit 1b (Baseline)	Visit 2 (W1)	Visit 3 (W2)	Follow-up: Final Visit (W3)
Informed Consent Form	X (oral)	X (written)				
Demographics	X	X		X	X	X
Medical History			X	X	X	X
Cognitive Examination			X	X	X	X
Ambulatory Assessments	X	X	X	X	X	X
Questionnaires		X	X	X	X	
Supplement Use		X	X	X	X	X
Current Medications			X	X	X	X
Blood Chemistries, spot urine			X	X		
Vital Signs & anthropometry: Blood pressure, height, weight, body composition, eye test, Waist/hip circumference			X	X	X	X
Inclusion/Exclusion Criteria	X	X				
Enrollment/Randomization			X			
Intervention/Comparison Meetings and Phone Calls			X	X	X	
Adverse Events				X	X	X

6.2 Description of Evaluations

Consenting Procedure

An oral consent is obtained during recruitment when recruiters reach participants by phone and assess eligibility.

Written informed consent is obtained at the first screening visit and will be administered by study staff who have completed required and appropriate IRB training. Recruiters/staff members who will be providing the informed consent will have at least a bachelor's level college degree. Two signed copies (signed by both participant and staff member providing consent) will be obtained. One will be provided to the participant and another copy will be kept in participant file. Bilingual (English/Spanish) consent will be provided as needed. The participant files will be kept in a locked cabinet behind locked doors.

6.2.1 Screening Evaluation

At screening visit #1 participants:

- complete a brief questionnaire,
- receive an explanation of the full study by the study staff
- receive instruction in and have a chance to practice using the smartphone to review activities, mood and play several brief "brain games"
- learn how to use the smartphone to track foods consumed.

At home between the visits (1 hour per day for 2 days)

Beginning the next morning after the visit, participants are asked over two days to:

- complete a review of their activities and mood
- enter food and drink intake using the smartphone
- complete a brief survey when they wake up in the morning and before going to bed
- upon receipt of a signal from the smartphone, play brief brain games several times during the 2 days
- answer follow-up questions by phone about the smartphone or study

Participants should allow about 20 minutes per day for the brain games and 40 minutes for entering your food and drink into the smart phone each day.

Screening Visit 2 (3-5 days after Screening Visit 1, 90 minutes)

During this visit, participants will have to:

- return the smartphone.
- complete questionnaires and exercises that involve memory, attention, vocabulary and response speed.
- They may receive a follow-up phone call to complete a few additional questions.

After this visit, eligibility to continue to the next part of the study will be determined.

6.2.2 Enrollment, Baseline, and Randomization

Enrollment

Participants are considered enrolled in the study after enrollment into one of two study arms.

If deemed to be eligible for the main part of the study, participants are randomly assigned to one of two groups: the Multicultural Healthy Diet group or the Usual or Comparison Diet group.

Baseline Assessments

- blood pressure, blood draw, height, weight, waist/hip circumference, body composition, eye test
- cognitive testing: Dot Memory Task (spatial memory- encoding, distraction, recall), Symbol Search (processing speed), memory binding test or short term memory (to detect early Alzheimer Disease), Operation Span ("letter memory") & Rotation Span ("arrow memory"), Symmetry Span ("location memory"), Go No-Go to assess working memory, verbal memory and spatial memory; Paired Associates Learning Task ("Shopping List") that is a test of verbal associative episodic long-term memory. In-Clinic assessments include the STROOP test, NIH Tool Box assessments and self-reported cognitive complaints as described in p. 18-19.

6.2.3 Follow-up visits

Clinic Visit #1 (Scheduled for eligible participants after Screening Visit #2, 2 hr)

At this visit, participants will:

- undergo cognitive testing at the clinic
- respond to questionnaires about medical history, moods & daily experiences
- receive randomization assignment to Usual Diet or Multicultural Healthy Diet
- schedule a 30 minute visit for eye test and body measurements: blood pressure, blood draw, spot urine collection, height, weight, waist/hip circumference, body composition.

At home after Visit #1 (1 hour per day for 7 days)

Participants are asked to do the following over the next seven days:

- enter food intake using the smartphone
- complete a brief survey when waking up in the morning and before going to bed
- play brief brain games four times during the day
- at the end of the 7 days, return the smartphone to the clinic after completing the exercises

Randomization

Randomization occurs after Clinic Visit #1 (Baseline) when body measurements are complete. When adequate numbers of participants (about 8-10) are randomized to start a comparison or intervention group, participants will be invited to the sessions. In the meantime they will receive informational materials about the study in preparation for the sessions.

Clinic Visit #2 (Scheduled 9 months after Visit #1, 2 hr)

This visit is identical to Visit #1.

At home after Visit #2 (1 hour per day for 7 days)

These activities are identical to at-home activities after Visit #1.

Clinic Visit #3 (Scheduled 9 months after Visit #2, 2 hr)

This visit is identical to Visit #1, except that there will be no blood tests or urine collection scheduled after the visit.

At home after Visit #3 (1 hour per day for 7 days)

These activities are identical to at-home activities after Visit #1.

Clinic Visit #4 (Scheduled 9 months after Visit #3, 2 hr)

This visit is identical to Visit #1, except that there will be no blood tests or urine collection scheduled after the visit.

At home after Visit #4 (1 hour per day for 7 days)

These activities are identical to at-home activities after Visit #1.

6.2.4 Completion/Final Evaluation

The final visit is Clinic Visit #4 after which the smartphones are returned to the clinic and study ends.

7. SAFETY ASSESSMENTS

Since participants are changing their diets from one that is pro-inflammatory to one that is anti-inflammatory, they will be asked to consume fruits/vegetables, legumes, nuts, fish, whole grains and other anti-inflammatory food components such as scallions or chives and other herbs and spices to their diet and reduce intake of processed and fried foods, sweets and foods high in saturated fats. They also need to make sure they are hydrated, especially upon waking up.

Participants will be screened for being on any diets that could preclude consumption of the MHD such as allergies that would make it difficult to stay on this dietary pattern. It is likely that

participants will see a benefit from consuming the MHD. These beneficial effects could include decrease in constipation, higher energy level. Participants will be asked to report any new developments related to their consumption of the MHD. If participants developed a medical issue that precludes continuation in the study, they may withdraw from the study.

7.1 Specification of Safety Parameters

All abnormal and incidental findings during the physical encounters from the ARC visits will be documented on a case report form and reviewed by ARC physician within 24 hours.

The dietary and other biomarkers to be collected in this study are: plasma tocopherols/carotenoids, serum folate, serum B12, plasma fatty acids, lipid panel, IL-6, C-Reactive Protein and APOE4. Given the high cost of the biomarker, the main laboratory analyses will not occur until yrs 4-5 of the grant that is about 1-3 years after the blood draw. Since these values may not be meaningful after such a long period has elapsed and that in some cases the clinical implication of some of these biomarkers may be unknown, we will not provide biomarker information to the participant.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

The MHD for healthy participants- the target of this study- is generally safe. Should participants develop health problems during the study that precludes staying on this diet (e.g. unintentional weight loss, eating disorders), the participants are advised to contact primary physician and decide the merits of continuing in the study and are free to discontinue participation. Participants are asked to report any such developments.

7.3 Adverse Events and Serious Adverse Events.

*An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are recorded regardless of their relationship to the study intervention.*

*A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.*

7.4 Reporting Procedures

All abnormal and incidental findings during the study visits will be reviewed by the study physician, Jelena Pavlovic, M.D., Ph.D. The abnormal findings will be documented on a case report form by Dr. Pavlovic within 24 hours. If necessary, an adverse report will be generated.

Reporting: All adverse events will be compiled and reported in summary form on an annual basis to the Einstein IRB local CCI/IRB and at the conclusion of the study. Serious adverse events whether related to the study or not will be reported to the CCI/IRB and Molly Wagster, Ph.D., Chief, Behavioral & Systems Neuroscience Branch, Division of Neuroscience & NIA official on DSMB & Nikolaos Scarmeas, MD, MS, DSMB Chair & Safety Officer by phone, email or fax upon discovery; for serious adverse events related to the study a completed local IRB Adverse Event Report will be submitted within 5 business days upon discovery to the Einstein IRB; serious adverse events unrelated to the study will be reported on the annual adverse events log submitted with the progress report to the Einstein IRB. All deaths will be reported to the IRB and Drs. Wagster and Scarmeas upon discovery by phone, email or fax upon discovery; a completed local CCI/IRB Adverse Event Report will be submitted within 10 days of initial CCI/IRB notification. All deaths will be reported to the CCI/IRB upon discovery. Deaths will be reported to the Einstein IRB within 30 days since last intervention.

7.5 Follow-up for Adverse Events

Adverse Events will be followed up on case-by-case basis until resolved or considered stable by the study physician.

7.6 Safety Monitoring

Data Safety Monitoring Plan
Adverse Event Monitoring**:** Process: Data and Safety Monitoring will be performed by external monitors: Adam M. Brickman, Ph.D, Associate Professor of Neuropsychology, Columbia University College of Physicians & Surgeons, Nikolaos Scarmeas, MD, MS (DSMB Chair & Safety Officer), Associate Professor of Clinical Neurology, Columbia University College of Physicians & Surgeons, and Juned Siddique, Ph.D, Associate Professor of Preventive Medicine (Biostatistics) and Psychiatry & Behavioral Sciences, Northwestern University Feinberg School of Medicine. Dr. Molly Wagster, Chief, Behavioral & Systems Neuroscience Branch, Division of Neuroscience, National Institute on Aging will also participate in the DSMB meetings. Dr. David Frankowski, Division of Neuroscience, National Institute on Aging will serve as alternate to Dr. Wagster.

8 INTERVENTION DISCONTINUATION

If participants have unintentional weight loss defined as 10% weight change, if BMI >=25 and 5% weight change if BMI <25 in past six months to one year or develop health issues that preclude participation in the study, the participant may be asked to withdraw or he/she may voluntarily withdraw from the study. Participants may withdraw voluntarily from participation in the study at any time and for any reason. Alternatively if the withdrawal is temporary (due to surgery or other health or other matter), they can be followed for study outcomes if practical and can rejoin study when ready. Each situation will be decided on a case by case basis.

We have considered an attrition rate of 15% from visit #1 to visit #2 and 5% thereafter between visits. However we may consider replacement of participants if the numbers projected for

attrition are higher –time permitting. If there is not enough follow-up time, then replacement will not be possible.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The primary hypothesis is that participants randomized to the MHD diet will have more stable and possibly improved cognitive function relative to baseline, whereas comparison participants will have measurable decline.

The secondary hypothesis is that at baseline there will be no differences between arms in serum biomarkers indicative of a MHD diet pattern, specifically total folate, tocopherols, carotenoids, vitamin B12 and fatty acid profile; and self-reported intake of food groups such as fruits and green leafy vegetables; however at post-intervention, biomarkers of the MHD and self-reported intake will be higher in the intervention arm.

9.2 Sample Size and Randomization

Our initial design was to randomize 326 participants, with an expected 15% attrition at 9-months (Visit 2), and 5% per year thereafter to yield a total of 250 participants at 27 months after baseline (Visit 4). This would yield sufficient power for both the primary endpoint at 9 months, and final time point at 27 months. With 125 participants per arm at Visit 4, we would have 80% power to detect an effect size of 0.35 SD, representing an absolute between-group difference of 0.16 in the within-person change in cognition score. Assuming a within-person correlation of 0.85 (0.5), we would have had 80% power to detect an absolute difference of 0.19 (0.35) in the change in scores. In a previous study (ESCAPE), the correlation of mean performance (averaged across all assessments) from one burst to the next was ~0.90 (Personal Communication: Martin Sliwinski, 7-6-2022). The 9-month timepoint was chosen as primary, as it was the time that potentially would have the greatest difference by arm due to the largest adherence.

Given the challenges with recruitment, due to the somewhat high participant burden of the protocol and challenges of the Covid-19 pandemic, we revised the sample size to an expected n=277 to be randomized. For our primary endpoint at 9 months, assuming 10% attrition (n=250), we will still have 80% power based on our original assumptions. Using pessimistic assumptions of 20% attrition at each 9-month visit, the power should be 54% based on n=143 at last follow up at 27 months or Burst 4 to detect these effect sizes.

Key secondary outcomes include between-arm comparisons of MHD related dietary intakes. Based on preliminary data from the Study of Latinos: Nutrition & Physical Activity Assessment Study, baseline mean (SD) for biomarker folate, alpha-tocopherol, and B12 are approximately 46 (17) nmol/L, 0.91 (0.28) mg/dL and 598 (330) pg/mL respectively (93). An effect size of 0.35 would be detectable with 80% power with 125 subjects per arm, a between-arm difference in change of at least 5.95 nmol//L, 0.10 mg/dL, and 116 pg/mL in these respective markers at 9 months assuming a within person correlation of at least 0.5.

Randomization

Stratified permuted block randomization with variable block sizes will be used to randomize participants to one of the two study arms in a 1:1 ratio. Randomization will be stratified on sex, age (<53, 53-65), and education level (no more than high school or equivalent, more than high school).

9.2.1 Treatment Assignment Procedures

The study statistician will generate the randomization lists, one for each strata, which will be uploaded into the study database. A randomization module will be created so that study staff remain blinded to study arm until after a participant has passed screening, signed the informed consent and is ready to be randomized.

9.3 Interim analysis and Stopping Rules

The study will be stopped for reasons of poor study performance such as slow accrual, high losses to follow-up or poor quality control.

While the possibility of this event is very low, should there be need to suspend the study due to safety issues such as high number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. Such findings are presented to the study statistician or to the Data and Safety Monitoring Board (DSMB) statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the DSMB or to the Safety Officer and/or NIA. The findings are used to determine what steps will be taken.

9.4 Outcomes

Primary Outcome:

The primary outcome is a global composite cognition score derived as an average of the three z-scores of the participant's performance on three of the M2C2 ambulatory cognitive assessments (Grid Memory, Symbol Search, and Color Shapes tasks) at 9 months post baseline. These assessments are validated measures of visuospatial memory, processing speed and short-term associative memory binding, respectively.

Secondary Outcomes

Several secondary outcomes relate to whether the MHD can be adapted for a diverse middle-aged cohort in the Bronx. We will evaluate the change from baseline for serum biomarkers indicative of a MHD diet pattern at 9 months, specifically total folate, tocopherols, carotenoids, vitamin B12 and fatty acid profile; and self-reported intake of food groups such as fruits and green leafy vegetables. In addition, secondary outcomes consist of performance on the individual ambulatory cognitive assessments (Grid Memory task, Symbol Search task, Color Shapes task)

contributing to the primary outcome to determine whether observed intervention effects are attributable to specific cognitive domains.

Exploratory Outcomes

The exploratory outcomes relate to short- and long-term associations between dietary patterns self-reported stress and affect collected during the M2C2 surveys, and all five of the ambulatory cognitive tasks, including two exploratory tasks related to long-term associative memory and working memory capacity (Shopping List and Rotation Span tasks). Short-term (momentary, day-to-day) and long-term (across 27 months of follow-up) associations between the intervention and the ambulatory assessments will be examined.

Because the laboratory specimens are analyzed in yr 4-5, the assessments relating to the diet biomarkers on the entire sample will not be available until later in the study. In addition there will be no interim analyses of outcomes because this is a low risk study of a pilot clinical trial of short duration and important end-points such as sustainability and timing of effects may not be observed if the trial is stopped early, we will not perform interim analyses. However we will monitor for safety and quality of conduct. We are assessing Alzheimer's Disease (AD) biomarkers P-tau 217 and neurofilament light chain (nfl) and other AD biomarkers. The clinical significance of these biomarkers in this younger age group is not known as little data exists for this age group. We are assessing these biomarkers to characterize these biomarkers in this population and age range. As these biomarkers were added after informed consent was obtained, we will send consent addendum documents by FedEx (or other expedited mailing system) or email or regular mail and ask that the signed consent be sent back by FedEx (or other expedited mailing system) or email, mail or text if needed. The consent is accompanied by a letter to the participants that describes why we are administering this new consent. The study coordinator will call the participants to introduce the consent as practically possible. Participants are free to call the study coordinator and principal investigator for questions they may have.

9.5 Data Analysis

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

The anthropometric and cognitive testing information collected at the study clinic visits will be done by a blinded staff member. Participant records will be kept in participant files in a locked cabinet. Participant information will be kept confidential and staff would need to undergo IRB (CITI) training. The Manual of Procedures describes the study forms.

10.2 Data Management

Data Management for this study will be adapted by Ms. Katz and her team. Dr. Sliwinski will be responsible for data collection and quality control related to cognitive function measures. Dietary data will be downloaded from the NCI ASA 24 web-site and all data will be compiled by the data analyst at Einstein. We will use the study database system to track enrollment, subject flow,

and clinic evaluations, number of follow-up evaluations, deaths and dropouts using specialized tracking systems on a real-time basis. This system will include a procedure for documenting the creation and distribution of data sets for specific analyses, and we will archive each data set according to purpose and date of creation.

10.3 Quality Assurance

10.3.1 Training

Staff would need to undergo appropriate IRB (CITI) training. With respect to cognitive testing, Ms. Katz, in collaboration with Dr. Sliwinski, is highly experienced in this area and will provide training along with her experienced team of cognitive testers. An experienced medical technician (phlebotomist) is available for this study.

10.3.2 Quality Control Committee

Ms. Katz or designee will oversee quality control related to clinic data; Dr. Sliwinski or designee will perform quality control regarding the cognitive data; Dr. Mossavar-Rahmani or designee will determine rules related to performing quality control related to the nutrition data (e.g. excluding participants with unreliable data, too high or too few calories, e.g. energy intake <500 kcal/day.)

10.3.3 Metrics

Participants in the run-in who complete 80% of the ambulatory assessments (cognitive and surveys- 75% rounded to 80% is also acceptable or 9/12 assessments) and complete two days of dietary intake satisfactorily will be enrolled into the study. Satisfactory completion of dietary intake is determined by reliable/implausible recalls and judgement by staff.

For the purposes of data analysis we will accept the following: 50% completion of ambulatory assessments (cognitive and surveys) for each seven day burst and survey responses completed in reasonable time (within 30 minutes of beep prompt). Quality control with respect to data transmission will also be undertaken to verify abnormal transmissions. We will use a Checksum function to evaluate each data record for completeness and ensure that the data were not corrupted during saving or transmission. Record duplication during data transmissions from the mobile client app to the server is uncommon (<0.1%). However, to ensure the uniqueness of each data record, we will use the mobile app to assign a unique session tag for each individual every time the mobile app is launched to identify and remove any duplicate records. With respect to food records, completion of at least one reliable/plausible food records of seven days assigned will be acceptable.

10.3.4 Protocol Deviations

Protocol deviations will be captured during periodic review of the case reports and data obtained from protocol questionnaires and assessments. Staff will be advised accordingly for awareness of aberrant data and additional training sessions will be held with the staff to develop systems for

corrections. The Manual of Operations includes a Protocol Deviation Form that is completed should a protocol deviation occur.

10.3.5 Monitoring

The Principal Investigator & Co-Investigators and staff (as appropriate) will review the informed consents, oversee quality assurance for the cognitive testing and other study measures. The data base will include checks for outliers and the team will be alerted to these values.

Quality control for the dietary intervention will be assessed via observations of group sessions and telephone coaching by Drs. Yasmin Mossavar-Rahmani, a member of the Motivational Interviewing Network of Trainers (MINT) or designee using motivational interviewing approaches for assessing fidelity.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (Appendix) and any subsequent modifications will be reviewed and approved by the IRB committee responsible for oversight of the study.

The Einstein Human Research Protection Program (HRPP) promotes and protects the rights and welfare of all human research participants. Einstein's two IRBs* (formerly known as the Committee on Clinical Investigations (CCI) and the Montefiore Medical Center IRB) facilitate excellence in human research by extending personalized guidance and support to the research community through timely and high quality service, education, review, and monitoring. Two IRB meetings are held monthly to review full board items while all other transactions are reviewed upon receipt on an ongoing basis.

**An Institutional Review Board is a committee, operating under Federal regulations, State laws, and institutional policy, that reviews research involving human subjects to ensure the ethical and equitable treatment of those subjects.*

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. We do not expect to enroll participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney) because a requirement to participate in the study is to be able to complete the informed consent on one's own. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record. Spanish only speaking participants will be provided with an informed consent that is in Spanish.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the Office of Health Research Protection (OHRP).

Biospecimens will be initially maintained in the Einstein Clinical & Translational Service Award (CTSA) lab, the Biomarker Analytic Research Core (BARC) and shipped to Advanced Research & Diagnostic Lab (ARDL) at University of Minnesota for analysis**.** University of Minnesota will send plasma vials from baseline and nine months follow-up to Dr. Zetterberg's lab in Sweden for analysis of Alzheimer's Disease related biomarkers such as p-tau 217 and neurofilament light chain (nfl). Dr. Zetterberg is a pioneer in assessing these biomarkers. Laboratory results from outside labs will be electronically transferred, and will undergo quality control checks. Cleaned data will be uploaded to the main database. Data will be maintained in a secure environment and subject data will be protected from unauthorized access. The study staff will prioritize protection of the subject privacy, and ensure that access is only given investigators without compromising a subject's right to privacy. The data server and all computers feeding into it will be connected by a local area network (LAN) that is not connected to the Internet. The LAN will be a stand-alone network of password protected computers with no connection to any other computers within or outside the institution, which decreases security threats from viruses and virtually eliminates the threat of external "hacking." The computerized data collected will be subjected to SSL 256-bit encryption. There will be another server PSU. The servers have been granted an SSL certificate verified by InCommon. This encryption protects participants should the data be intercepted as it is transmitted to the servers. Only encrypted data are transmitted from the ambulatory data collection devices to the servers and from server to server. In the unlikely event that interception occurs, the data could not be decoded without the unique encryption key that is held by investigators at both Einstein and PSU. The servers are housed in secure offices at Einstein and PSU and can only be accessed by trained administrators. When data are to be uploaded for access to outside investigators for analysis, they are de-identified and transferred to an external hard drive and brought to a secure computer with Internet/FTP access. All of the databases and data entry programs will be stored on a dedicated server and maintained by Ms. Katz, the highly experienced data manager. Multiple automated back-up procedures will be implemented nightly to store copies of data and programs at both on- and off-site locations. Data sets will be frozen on a semi-annual basis. A specific codebook will be generated for each frozen dataset to document contents, frequencies of included variables, documentation of editing and cleaning procedures, and code used to create calculated variables.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

The guiding ethical principles being followed are based on the *Declaration of Helsinki.* The institutional review boards of the Montefiore Medical Center/Albert Einstein College of Medicine and Pennsylvania State University, State College review and approve the study materials.

The Einstein Human Research Protection Program (HRPP) promotes and protects the rights and welfare of all human research participants. Affiliated organizations include all of the colleges and schools of Yeshiva University, Montefiore Medical Center, Jacobi Medical Center and North Central Bronx Hospital.

Einstein's two IRBs* (formerly known as the Committee on Clinical Investigations (CCI) and the Montefiore Medical Center IRB) facilitate excellence in human research by extending personalized guidance and support to the research community through timely and high quality service, education, review, and monitoring. Two IRB meetings are held monthly to review full board items while all other transactions are reviewed upon receipt on an ongoing basis.

**An Institutional Review Board is a committee, operating under Federal regulations, State laws, and institutional policy, that reviews research involving human subjects to ensure the ethical and equitable treatment of those subjects.*

13 COMMITTEES

Steering Committee will consist of the investigator group: Ms. Katz, Drs. Hakun, Mossavar-Rahmani, Shaw, Sliwinski & Wylie-Rosett.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee.

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15 APPENDIX (INFORMED CONSENT, STUDY FORMS)

(See pdf attachments)