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Predicting outcomes of lifestyle and stress reduction interventions for obesity with DNA methylation and psychological measures

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OBJECTIVES/GOALS: Obesity has been classified as a global epidemic and origin of numerous health issues. The central hypothesis of this study is that psychological measures, DNA methylation, and gene transcription will predict obesity-related outcomes after lifestyle interventions, and such interventions may alter DNA methylation profiles. METHODS/STUDY POPULATION: This study consisted of a randomized-controlled trial examining the effects of lifestyle +/- stress reduction interventions in 285 highly stressed parents with obesity, followed for 2 years. Full participants received nutrition and activity counseling, and were randomized to either a stress reduction intervention or a contact control. Those who otherwise qualified for the study but unable to fully participate were included in a no intervention control group. The intervention consisted of 12 weeks of nutrition and activity counseling +/- 2-hour weekly stress reduction interventions using MBSR and CBT-based strategies. DNA methylation was assessed using Illumina EPIC arrays. RESULTS/ANTICIPATED RESULTS: Using linear mixed models (LMMs), this study will first examine the hypothesis that baseline psychological measures and pre-existing methylation sites associated with obesity and glycemic control (e.g., ABCG1, ATP10A, TXNIP, SREBF1, RNF39, and SOCS3) predict changes in BMI, HOMA-IR, and HgbA1C post-intervention and at 1 and 2 year follow-ups. Using sites that demonstrate statistical significance, we will develop a polymethylation risk score predictor of change in BMI. Next, we will examine the hypothesis that interventions which reduce obesity may also lead to improvements in epigenetic aging using LMMs to determine if changes in BMI or HOMA-IR predict changes in epigenetic age acceleration over the course of the study. DISCUSSION/SIGNIFICANCE OF IMPACT: This work examines whether psychological factors and/or epigenetic markers may be used in patient stratification at initiation of treatment, enabling improved treatment selection, fewer years of obesity and decreased risk of comorbidities. This proposal also asks whether lifestyle interventions impact the aging process itself.

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A CTS team approach to investigate skeletal muscle diseases and countermeasures in a donor-derived bioengineered muscle platform*

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OBJECTIVES/GOALS: Our team has developed a 24-well donor-derived skeletal muscle microphysiological system (MPS) to study signaling pathways associated with a variety of muscle diseases. 3D muscle will be utilized to evaluate pharmacologic interventions for these muscle conditions to improve both muscle mass and function. METHODS/STUDY POPULATION: In this study, muscle MPS were formed from healthy young female and male subjects. 3D muscle underwent a 21-day differentiation with an electrical stimulation (e-stim) regimen twice daily beginning on Day 14. Functional assessments in permeabilized fibers of both sexes included isometric and isotonic calcium-induced contractions, allowing for the characterization of force-pCa (-log[Ca2+]), force-velocity and force-power relationships. Samples from Day 17 and Day 21 will be assessed for pro-growth protein signaling via western blotting and a subset of samples will be analyzed by histology and microscopy for fiber type and size. Finally, culture media pre- and post-terminal e-stim on Day 21 will be collected for extracellular vesicle (EV) isolation and EVs will be assessed by standard proteomics analysis. RESULTS/ANTICIPATED RESULTS: Permeabilized fibers from both sexes reproduced the well-established sigmoidal force-pCa and the curvilinear force-velocity and force-power relationships reported in native striated muscle. Maximum specific force and force-pCa relationship were not different between sexes. Isotonic contractile measurements revealed that these male and female fibers also exhibit similar force-velocity and force-power relationships. We anticipate that 3D muscles from day 17 compared to day 21 will exhibit higher levels of pro-growth protein signaling due to e-stim application and no differences in fiber type or size between sexes. Additionally, we expect that EV quantity will depend upon 3D muscle maturity and presence of e-stim. DISCUSSION/SIGNIFICANCE OF IMPACT: This study demonstrates the similarities of functional characteristics and exercise (or e-stim) adaptation between native human skeletal muscle and 3D bioengineered skeletal muscle. Ultimately, this data further validates the muscle MPS system to study muscle diseases and to enhance the translation of therapeutics to clinical settings.

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A systematic review on sleep duration and Alzheimer's disease fluid biomarkers: Preliminary findings

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OBJECTIVES/GOALS: This review examined if sleep duration is associated with established Alzheimer's disease (AD) fluid biomarkers, such as amyloid-β peptides (Aβ40 and Aβ42), total-tau (t-tau), phosphorylated tau (p-tau181 and p-tau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP).

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METHODS/STUDY POPULATION: We searched PubMed, CINAHL, and SCOPUS through September 15, 2024, using keywords and appropriate subject headings related to AD, fluid biomarkers, and sleep. The search was developed and conducted in collaboration with a medical librarian. We also searched Google Scholar and screened the reference lists of relevant reviews. Two independent reviewers screened 1,657 peer-reviewed articles, of which 21 met the inclusion criteria (14 with biomarkers measured in cerebrospinal fluid [CSF] and 7 in blood). Two review authors independently extracted study details from included articles using a standardized data extraction template. RESULTS/ANTICIPATED RESULTS: Sample sizes ranged from 18 to 4,712 participants. Sleep duration was assessed using self-reported measures in 8 studies and objective measures in 13. For the 14 studies using CSF biomarkers, lower Aβ42 (3/14), Aβ40 (1/14), or the ratio (1/14) were associated with either short or long sleep duration; t-tau (3/14) and p-tau181 (4/14) levels were mostly associated with short sleep. For the 7 blood-based biomarker studies, Aβ42 (2/7), Aβ40 (2/7), and the ratio (3/7) had mixed results with either short or long sleep. T-tau (1/7) and p-tau181 (1/7) levels were associated with long sleep; NfL (2/7) was associated with both short and long sleep. Six studies reported nonlinear relationships, with both short and long sleep associated with unfavorable biomarker profiles. None of the studies investigated p-tau 217 or GFAP. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results suggest that the relationship between sleep duration and AD fluid biomarkers is very complex, and it highlights the importance of sleep in AD risk assessment and prevention. The inconsistency in findings stresses the need for standardized study design and measurement methods to clarify causality and inform clinical guidelines.

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Targeting negative-self-referential processing with transcranial magnetic stimulation: Feasibility studies

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OBJECTIVES/GOALS: Neuromodulation strategies like transcranial magnetic stimulation (TMS) can target specific neural circuits underlying particular psychiatric symptoms, potentially 1) enhancing understanding of mechanisms of illness and recovery and 2) acting as novel therapeutics. These feasibility studies lay foundation for a study of major depression. METHODS/STUDY POPULATION: Four healthy volunteers completed structural and functional MRI (fMRI). fMRI included a trait-adjective task, a negative self-referential processing task known to activate VMPFC, which is known to be abnormal in major depression. During the task, participants respond on a task pad whether they feel that each of a series of displayed adjectives (positive, negative, or neutral) applies to them. Three participants then participated in a simulated image-guided TMS session using their MRI data to target their VMPFC. Three-dimensional tracking of the participant's head and the TMS coil was used to position the coil for peak stimulation of the targeted brain region. RESULTS/ANTICIPATED RESULTS: Our team collected quality neural and behavioral data on the fMRI task; participants reported a tolerable experience. Simulated neuronavigated TMS showed feasibility and tolerability of positioning the device to stimulate VMPFC. The fMRI task activated the VMPFC as predicted. The MRI and TMS protocols were replicable and tolerable. These procedures can now be used experimentally by our team with confidence to test our hypothesis that targeting the VMPFC within the brain's default-mode network may normalize aberrant VMPFC activity seen in major depression, thereby improving excessive negative self-referential processing. DISCUSSION/SIGNIFICANCE OF IMPACT: This project lays essential groundwork for my K12 project, "Targeting Negative-Self Referential Processing in Depression with TMS," a longitudinal neuroimaging and behavioral study using these methods in the study population of people with major depression.

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Follicle-stimulating hormone is reduced following a novel nutritional therapeutic in postmenopausal women with obesity

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OBJECTIVES/GOALS: Increased follicle-stimulating hormone (FSH) is linked to declines in ovarian and metabolic function in older women. Obesity is both a manifestation and a driver of aging pathologies. In animal models, FSH and insulin resistance (IR) were reduced after 6 mos. of a nutritional therapeutic (GLYLO). Our goal was to translate preclinical evidence to humans. METHODS/STUDY POPULATION: An integrated, precision medicine approach identified a unique phenotype of aging-related debility relative to older females. A non-comparer pilot study was conducted to translate GLYLO preclinical findings to postmenopausal women with obesity (n = 85; >55 years; body mass index [BMI] = 35.0 ±4.35; range: 30.3–42.8). Participants meeting the inclusion and exclusion criteria (n = 13) were enrolled and received two capsules of GLYLO (vitamins and natural products) daily for 6 mos. Assessments for FSH, estradiol (E2), IR (homeostatic model [HOMA-IR]), total cholesterol (TC), low- (LDL), high-density lipoproteins (HDL), safety biomarkers (e.g., red cell distribution width [RDW%], mean corpuscular volume [MCV]), and depression (Center for Epidemiologic Studies Depression Scale) were conducted prior to and after 6 mos. RESULTS/ANTICIPATED RESULTS: Mixed-effect models with intent-to-treat analysis were applied to compare outcomes prior to (n = 13) and following (n = 7) the intervention. Significant reductions in FSH were observed (-13.1 [2.47] Δ/SD; p = 0.002)) following the 6-month intervention. Interestingly, BMI, E2 (p = 0.412), HOMA-IR (p = 0.885), TC (p = 0.363), and LDL (p = 0.145) were unchanged, while HDL

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