

Title: Reinvigorating Brains in Adult Survivors of Severe Childhood Malnutrition

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Abstract: Severe acute malnutrition (SAM) in childhood causes impairment of brain function manifest in poorer cognition, emotional dysregulation and impulse control which persist throughout their lives into adulthood resulting in poor school performance and economic prospects. Long term consequences of childhood SAM include greater cardiometabolic risk related to elevated blood pressure, increased systemic vascular resistance and glucose intolerance which are known to accelerate cognitive decline with aging. Bench and clinical studies show that exercise and specific nutritional supplements, particularly omega 3 long chain poly-unsaturated fats (PUFA) can improve cognitive function and cardiometabolic health in adults. Mechanisms for these effects of exercise and nutritional supplementation include impacts on neurotrophic substances such as BDNF and IGF1 which affect brain structure and function to change cognition. Exercise and PUFAs also affect the gut microbiome which also has potent effects on brain function. Exercise changes the composition and function of the gut microbiome. Levels of fecal short-chain fatty acids (SCFAs), and neurotransmitters, GABA and serotonin are altered and affect brain function directly or via mediation of the vagus or both gut and systemic hormones. These observations suggest that the impact of both exercise and PUFAs on brain health may occur via several mechanistic pathways, alone or synergistic. Effects may in part be mediated through changes in neurotrophins, modulation of cardiometabolic profile as well as structure and/or function of the gut microbiome. Adult SAM survivors are generally considered beyond help and no trials of exercise and nutritional supplementation to improve their brain and cardiometabolic health have been reported. We propose to test the synergy of structured exercise + PUFAs to improve cognitive function in adult survivors of SAM and hypothesize that aerobic exercise for 60 minutes three times/week alone and with 3000mg of PUFA (DHA/EPA (ratio 55:45)) supplementation will improve neurocognitive function in adult survivors of SAM. We also predict that baseline blood inflammatory markers and gut luminal and blood neurotransmitters and SCFAs will be associated with neurocognitive function and that an exercise intervention in these study participants will be associated with changes to gut microbiome metagenomics and metatranscriptomics. Our aims are: 1a. Randomise 20 adult survivors of SAM and 20 age, sex matched community controls to supervised aerobic exercise for 60 minutes 3x/week or stretching and toning, for 6 months. 1b. Provide supplementation with 3000mg daily fish oils with DHA/EPA (ratio 55/45) or placebo (3000mg olive oil) to half of each group in a factorial design; 2. Measure neurocognition, DEXA body composition, daily physical activity via GPS enabled accelerometry, cardiovascular fitness via VO2Max, muscular strength; perform venepuncture for neurotransmitters, cardiometabolic risk factors including IL6 and hsCRP and neurotrophic factors, including BDNF and IGF-1 at baseline, and after 24 weeks intervention. 3. Microbiome studies baseline and monthly: microbiome metagenomics, metatranscriptomics and metabolomics, SCFA and neurotransmitter production. This proposal is to support the collection of pilot data and results will inform an NIH R01 proposal.