WS3: PILOT NUTRITIONAL INTERVENTION FOR THE PREVENTION OF COGNITIVE DECLINE IN MALAYSIA

Outline

- Intervention (Mario)
- Rationale (Mario)
- SEACO and Proposed Protocol (Devi)
- Interventions and Outcomes (Mario)
- Feedback from SAC
- Discussion

Study

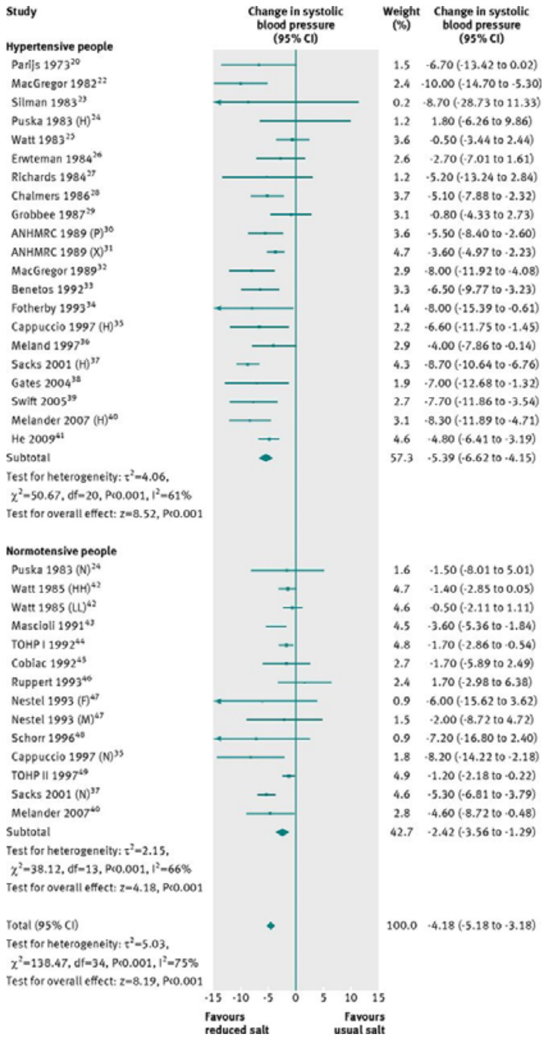
DePEC-Nutrition - A 2x2 factorial, randomised controlled trial investigating the feasibility of a nutritional intervention to increase high-nitrate vegetable consumption and reduce salt intake in middle-aged and older Malaysian adults with raised BP

Settings: SEACO Cohort, Malaysia

Rationale

- Dementia is a rising trend and global burden from LMICs and strong link with nutrition transition trends
- Diet-related chronic diseases as risk factors for dementia
- Raised blood pressure (BP) – one of the biggest worldwide health problem and strong association with nutritional factors
- Raised BP is an independent risk factor for dementia
- High salt intake key component of nutrition transition trends, strongly linked to raised BP and interventions focussed on salt reduction showing promising results
- Inorganic nitrate is a key nutrient in various vegetables and increased intake associated with reduced BP and cardiovascular risk. Associated with improved cognition via increased nitric oxide formation.
- SEACO cohort as a platform for facilitating recruitment and delivery of complex nutritional interventions
- Objective biomarkers to monitor compliance

Fig 2 Change in systolic blood pressure and corresponding 95% confidence interval in individual trials included in meta-analysis and mean effect size.



Feng J He et al. BMJ 2013;346:bmj.f1325

Salt and Cognition

ARTICLES
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nature neuroscience

Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17 response

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A diet rich in salt is linked to an increased risk of cerebrovascular diseases and dementia, but it remains unclear how dietary salt harms the brain. We report that, in mice, excess dietary salt suppresses resting cerebral blood flow and endothelial function, leading to cognitive impairment. The effect depends on expansion of TH17 cells in the small intestine, resulting in a marked increase in plasma interleukin-17 (IL-17). Circulating IL-17, in turn, promotes endothelial dysfunction and cognitive impairment by the Rho kinase-dependent inhibitory phosphorylation of endothelial nitric oxide synthase and reduced nitric oxide production in cerebral endothelial cells. The findings reveal a new gut–brain axis linking dietary habits to cognitive impairment through a gut-initiated adaptive immune response compromising brain function via circulating IL-17. Thus, the TH17 cell–IL-17 pathway is a putative target to counter the deleterious brain effects induced by dietary salt and other diseases associated with TH17 polarization.

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Neurobiology of Aging 33 (2012) 829.e21–829.e28
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Sodium intake and physical activity impact cognitive maintenance in older adults: the NuAge Study

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Association between Dietary Sodium Intake and Cognitive Function in Older Adults

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Nitrate-rich vegetables and CVD risk

Association of Vegetable Nitrate Intake With Carotid Atherosclerosis and Ischemic Cerebrovascular Disease in Older Women

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Background and Purpose—A short-term increase in dietary nitrate (NO_3^-) improves markers of vascular health via formation of nitric oxide and other bioactive nitrogen oxides. Whether this translates into long-term vascular disease risk reduction has yet to be examined. We investigated the association of vegetable-derived nitrate intake with common carotid artery intima-media thickness (CCA-IMT), plaque severity, and ischemic cerebrovascular disease events in elderly women (n=1226).

Methods—Vegetable nitrate intake, lifestyle factors, and cardiovascular disease risk factors were determined at baseline (1998). CCA-IMT and plaque severity were measured using B-mode carotid ultrasound (2001). Complete ischemic cerebrovascular disease hospitalizations or deaths (events) over 14.5 years (15 032 person-years of follow-up) were obtained from the West Australian Data Linkage System.

Results—Higher vegetable nitrate intake was associated with a lower maximum CCA-IMT (B=−0.015, *P*=0.002) and lower mean CCA-IMT (B=−0.012, *P*=0.006). This relationship remained significant after adjustment for lifestyle and cardiovascular risk factors (*P*≤0.01). Vegetable nitrate intake was not a predictor of plaque severity. In total 186 (15%) women experienced an ischemic cerebrovascular disease event. For every 1 SD (29 mg/d) higher intake of vegetable nitrate, there was an associated 17% lower risk of 14.5-year ischemic cerebrovascular disease events in both unadjusted and fully adjusted models (*P*=0.02).

Conclusions—Independent of other risk factors, higher vegetable nitrate was associated with a lower CCA-IMT and a lower risk of an ischemic cerebrovascular disease event. (*Stroke*. **2017;48:1724-1729. DOI: 10.1161/STROKEAHA.117.016844.**)

Part 2

Outcomes and Interventions

Primary Outcomes

Behavioural change in response to the interventions, evaluated by participant recruitment and retention on the trial, and changes in dietary adherence to the interventions evaluates with self-reported (dietary questionnaires) and objective biomarkers (urinary nitrate and salt excretion).

Secondary Outcomes

The following outcomes will also be evaluated during the trial:

- - Cognitive test performance (assessed on measures of global and domain specific function, including memory and non-memory performance)
- - Resting clinic blood pressure
- - Body composition: height, weight, waist circumference
- - Physical performance: hand-grip strength, walking speed and time up and go, activities of daily living
- - Adherence to nutritional interventions measured by dietary methods (multiple-pass 24-hr recall) and urinary biomarkers (24-hr sodium and nitrate excretion). Saliva samples and salivary strips will be also collected to measure changes in nitrite concentrations during the intervention.
- - Plasma biochemical outcomes monitored including routine biomarkers of cardio-vascular risk (C-reactive protein, glycated haemoglobin, interleukin-6, homo-cysteine, 3-nitrotyrosine) and more direct brain measures such as plasma brain-derived neurotrophic factor and plasma amyloid β42 and amyloid β40.

Interventions: Salt Reduction

- Inform on health risk of salt intake
- Inform on salt content of food
- Establish optimal consumption and identify high-salt food sources
- Provide examples and tools to develop tailored salt reduction strategies (i.e., reading food labels, use salt reduction spoons, etc)
- Reduce portion sizes (less food=less salt), eat fresh food and not pre-prepared and cut or reduce use of MSG or flavour-enhancers.

Interventions: Nitrate-rich vegetables

- Identify key vegetables with high nitrate content (i.e., lettuce, cabbage, beets, carrots, green beans, spinach, parsley, radishes, celery, Chinese cabbage, turnip).
- Inform on health benefits of vegetables and explain content of nitrate and its benefits
- Establish target intake in terms of amount and frequency
- Provide examples on recipes and cooking methods to preserve nitrate content.

Feedback from SAC

- <u>Sample size:</u> some members of the committee (but not all) felt that sample size is possibly too large for a feasibility and consider reducing it. My personal view is to keep it but would like to have your opinion on this as well.
- <u>Cognition:</u> MOCA was seen as limited in detecting change. I explained the rationale in terms of MOCA being applied in previous pilot study and also limited time for the visit to enhance compliance and recruitment. I think this point will come at the workshop and we can discuss additional cognitive tests with rest of the group
- <u>Behavioural intervention:</u> to have qualitative measures within the study for assessing compliance but this is part of the protocol
- Genotyping of APOE status.
- Smoking status
- Ramadan – strategy for recruitment

Cognitive tools applied in trials in Malaysia from our SR

har, 2008	Yes	Attention, processing speed and working memory	Digit span
		Attention, processing speed and working memory	Letter-number sequencing
		Conception formation and reasoning	Mental arithmetic test
har, 2013	No	Attention, processing speed and working memory	Digit span
		Attention, processing speed and working memory	Letter-number sequencing
		Memory	RAVLT
in, 2003	Yes	Attention, processing speed and working memory	Digit span
		Memory	3-minute memory test
		Memory	Mental comprehension test
		Construction and motor performance	Figures construction test
		Conception formation and reasoning	Mental arithmetic test
ari, 2014	Yes	Global cognition	MMSE: Total score
		Attention, processing speed and working memory	Digit span
		Attention, processing speed and working memory	Digit symbol
		Attention, processing speed and working memory	Visual reproduction I: Immediate recall
		Memory	Visual reproduction II: 30-min delayed recal
		Memory	RAVLT
		Construction and motor performance	Block design
		Construction and motor performance	Clock drawing test
		Conception formation and reasoning	Matrix reasoning
e, 2013	Yes	Global cognition	MMSE
		Attention, processing speed and working memory	Digit span
		Attention, processing speed and working memory	Digit symbol
		Attention, processing speed and working memory	RAVLT: immediate recall
		Attention, processing speed and working memory	Visual reproduction I
		Memory	RAVLT: delayed recall
		Memory	Visual reproduction II
		Construction and motor performance	Block design
		Construction and motor performance	Clock drawing test
		Conception formation and reasoning	Matrix reasoning

Key Steps for April – October 2018

- Staff recruitment and training (September 2018 – December 2018)
- Finalise protocol (October 2018)
- Ethics application (November 2018 – January 2019)
- Training and pilot testing (November – February 2019)
- Start of study (March 2019)
- Projected end of study (March 2020)

Discussion