Design Paper Food2Learn: Randomised controlled trial investigating the effect of increasing Omega-3 index with krill oil supplementation on learning, cognition, behaviour and visual processing in typically developing adolescents. Study design, rationale, and recruitment.

Comment: I commend the authors for a number of strengths of their work including the important role played by the long-chain (LC) omega-3 PUFA in cognitive performance throughout all life stages and the additional physiological and cognitive benefits of krill oil compared to other omega-3 supplementations. Further, consumption of LC omega-3 PUFA, particularly DHA, enhances cognitive performance relating to learning, cognitive development, memory and speed of performing cognitive tasks. Those who habitually consume diets low in DHA, children with low literacy ability seem to benefit most. Current guidelines recommend supplementation studies with at least 16 weeks in duration, account for potential interaction effects of gender, age and apolipoprotein E genotype, include vegan/vegetarian populations, and include measures of speed of cognitive performance. I therefore think that this protocol is methodologically and scientifically credible. I would like to recommend few minor revisions to clarify the design and the outcome measures of this study.

-Could you please provide a better rationale for the daily supplementation dose, e.g. age-related? based on EPA to DHA ratio? Based on national food guidelines?

-Could you please explain how you plan to control for gender-related differences in metabolism/development?

-Did you monitor participants’ diet during the trials? Fish consumption was monitored using a short questionnaire but I wonder whether sources of omega-6 such as meat, cheese etc. were controlled for. High omega-6 levels are indeed known to undermine the beneficial effects of omega-3s.

-I would consider including correlational analyses between EPA and DHA blood levels and other outcome measures such as cognition and mood. There is a fair bit of literature linking DHA to brain performance, but some studies have linked EPA to visual functioning and brain efficiency (Bauer et al. 2011/2014). Since the authors want to include eye tracking measures this could be of interest.

-Please list the ingredients included in the placebo treatment.

-How did the authors cope with minor side effects of krill/fish oil supplementation such as acid reflux which may “unblind” the study. In other words the participants may quickly find out they are taking an omega-3 supplementation.

-Were participants aware that they may be taking a placebo treatment

-Was the participants’ psychiatric and medical history thoroughly assessed? Did you have specific exclusion criteria?

-Please provide some rationale for the use of ApoE4 analyses.

-Could the authors explain why the plan to collct eye tracking measures,e.g. retinal cells being rich in DHA? Or estimate of brain activity?

-Were participants reimbursed for the participation in the study?