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Letter to the Editor

n-3 and preterm birth: what can we learn from the heterogeneity?

Madam

Recently, Makrides et al.[1] published a thoughtful report on *n*-3 PUFA intake and preterm birth, and their findings encourage us to examine the heterogeneity in this literature. In short, they conducted a large randomized controlled trial (RCT) to evaluate the efficacy of prenatal fish oil supplement for the prevention of early preterm birth (<34 weeks of gestation). Fish oil pills were administered from ≤week 20 of gestation until week 34 of gestation, and they found no change in the risk of early preterm birth (although in their secondary outcomes, they reported a non-significant downward trend in the risk of preterm birth (<37 weeks)). These findings are somewhat incongruent with those of the 2018 Cochrane review, which concluded that higher intakes of *n*-3 PUFA are associated with lower risk of early preterm birth, preterm birth and low birth weight (<2500***g***)[2].

Makrides et al.[1] astutely noted that the baseline intakes of *n*-3 PUFA (as evidenced by blood levels of DHA) were somewhat higher in their study than in some previous investigations, and this might explain their findings. To their point, many early studies in this area did not effectively consider baseline intakes, and therefore, the presence of inconsistent findings in this literature is not surprising. Having said this, we may be able to learn by evaluating the discrepant patterns in separate studies and subgroups. While this concept has been used before[3], it is newly relevant here. For example, what internal levels of *n*-3 constitute sufficiency at specific times in gestation?[4] Which participants were above these levels and how did they achieve these levels?

The capsules used in the RCT by Makrides et al.[1] did not demonstrate efficacy with this particular dose and timing in this study population. Furthermore, although there was an interesting trend, the efficacy of these capsules did not vary significantly by baseline DHA levels. However, Table-S13 indicates that high baseline DHA levels may have protected against early preterm birth, preterm birth and low birth weight in the absence of prenatal supplementation. Among the controls, the frequencies of these three conditions decreased with increasing baseline DHA levels. Thus, habitual intake may be important, and this hypothesis should be explicitly tested in future research. If confirmed, this finding would further support the emerging conclusion that preconception health is critical for sustaining healthy pregnancies[5].

Overall, this discussion raises some fundamental questions for the research community. Are prenatal pills the most effective, equitable and safe way to address a nutrient deficiency that may be driven by cultural dietary norms, chronic food system inadequacies, toxicant contamination of fish and ecosystem constraints?[6] Are we attempting to medicalise a complex planetary health problem?.

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Timothy H. Ciesielski

Department of Population and
Quantitative Health Sciences
Case Western Reserve University
10900 Euclid Avenue
Cleveland OH 44106 USA

Ronin Institute Montclair
127 Haddon Place
Montclair, NJ 07043, USA
Email: timothyhciesielski@gmail.com

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