Evaluating Effects of Omega-3 Fatty Acids on Asthma, Eye Health, Mental Health, and Child/Maternal Health:

lessons learned
Acknowledgements

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Objectives

1. To introduce our four systematic reviews
2. To highlight the four barriers we identified, which prevented us from providing conclusive answers to most of the questions concerning clinical & biomarker outcomes
3. To highlight some future research directions, which focus primarily on design and methodology considerations.
Our four topic areas

- Asthma
- Eye health:
  - e.g., age-related macular degeneration, cataracts
- Mental health:
  - the whole spectrum, from mood disorders to schizophrenia
• Child/maternal health:
  • child development
    • term vs preterm infants
  • maternal health
    • pregnancy-related events
Types of clinical question

- Efficacy/effectiveness of omega-3 fatty acids as (primary vs supplemental) treatment
e.g., to improve visual acuity, respiratory outcomes, or psychological functioning
- Efficacy/effectiveness of omega-3 fatty acids as (primary vs secondary) prevention
  
  e.g., to prevent unwanted pregnancy outcomes (e.g., gestational hypertension; giving birth to infants small for gestational age)
  
  e.g., to alter progression of asthma or of a chronic psychological disorder
- Efficacy/effectiveness of omega-3 fatty acids in fostering “healthy” or “optimal” child development
  - i.e., growth, neurological, visual, & cognitive outcomes
- Safety of omega-3 fatty acid use (i.e., adverse effects)
Types of biomarker question

- Association of biomarker status outcomes & clinical outcomes
  e.g., between omega-3 fatty acid content in red blood cells & health/clinical status or level of (child) development
  e.g., between levels of mediators of inflammation (e.g., specific leukotrienes) & respiratory functioning
- NOT the impact of intake on biomarker status
Population requirements

- Human subjects only
- Pediatric or adult populations, where relevant
- Diagnosed vs at known risk vs no known risk, where relevant
**Intervention/exposure requirements**

- Any source, type, dose or method to deliver omega-3 fatty acids
- Intake via diet and/or supplementation (e.g., capsules of fish oil; portions of fish)
“Level of evidence” requirements

- Goal: “highest” level of evidence possible
- But,....
Barrier #1

- For many questions, which implicated both clinical & biomarker outcomes, few studies were identified as having employed the “most ideal” research design to investigate them
Question & “most ideal” design(s)

- Primary or supplemental treatment efficacy/effectiveness: RCT
  - a paucity thereof, or instead: before-after designs
Primary or secondary prevention: RCT, or prospective & controlled observational study (e.g., prospective cohort study, with prospective controls)

- instead:
  - retrospective cohort studies
  - case-control studies
  - cross-sectional studies
  - cross-national ecological analyses

- excluded descriptive studies
Association between biomarkers’ omega-3 fatty acid content & clinical outcomes: RCT, or prospective & controlled observational study (e.g., prospective cohort study, with prospective controls)

- instead: cross-sectional studies
Consequence of barrier #1

- Various questions did not receive the “most ideal” investigation design-wise
- Even when did, very often underpowered
- These are the first hints at what needs to be done in future research
Barrier #2

- Poor reporting quality
  - missing information/data
  - sketchy descriptions
  - inconsistent or contradictory descriptions
No bias shown: applied equally to descriptions concerning designs, populations, interventions/exposures, controls, outcomes, whether/how controlled for known confounding influences, etc.
Attempted solutions

- Contacted original investigators, or authors of reviews who had purportedly received additional data from the investigators
- Predictable result
Another example

- As is often observed in reports of RCTs, a dearth of information means that we were unable to determine whether or not the allocation to study groups was adequately concealed.
Consequences of barrier #2

- Complicated or precluded the appraisal of the impact of (design or analytic attempts to control for) possible threats to internal validity

- Complicated or precluded the straightforward generalizability of results
  - Equally characterized studies having employed “most ideal” design types
Second hint at what needs to be improved with respect to future research

- Reporting quality likely improving somewhat with journals & professionals adopting guidelines such as CONSORT
Barrier #3

- When enough detail was provided, we observed minor-to-major/fatal flaws in the research designs & methods
Design-related problems

- The spectre of selection bias

  e.g., asking mothers to choose how they will feed their newborn, randomizing those who solely wish to formula-feed to one of at least two study groups (e.g., DHA-present vs DHA-absent), & then comparing data from either or both of these formula-fed groups with data from those who chose to breastfeed
Failure to control for known confounding influences, observable at baseline or on-study:

- background diet, which includes the concurrent intake of omega-6 fatty acids:
  - possible significance of the omega-6/omega-3 fatty acid intake ratio =
    - dynamic interplay of omega-6 & omega-3 fatty acids in the metabolic pathway;
    - ratio may be linked to initiation or maintenance of disease, & so, for now, it likely requires analytic control in studies of the impact of omega-3 fatty acids;
Other uncontrolled variables

- on-study caloric/energy intake
- smoking
- concurrent on-study use of medications, supplements, etc.
- alcohol use

Since each has been shown to have the potential to influence both clinical & biomarker outcomes, control is required.
Population-related problems

- In a given study: source population does not reflect what the investigators wished to study
  - problematic or outdated (e.g., diagnostic) methods to identify the populations/cases
- Controls do not come from same source population as “cases”
Heterogeneous collections of diagnosed patient, defined in terms of the:

- primary diagnosis (e.g., mixture of three subtypes of AD/HD; various subtypes of cataract);
- stage or severity of the disorder (e.g., extent of treatment resistance); or,
- types & severities/stages of comorbid conditions
Intervention-related problems

- In a given study: “uncontrolled” dosing (e.g., pourable/spreadable oils; ranges of intake permitted; compliance unevaluated);

- Use of food portions, from which we could not determine the exact amounts (or amounts per type) of omega-3 fatty acid intake;
The use of “cocktails,” whereby can neither isolate the independent impact of omega-3 fatty acids on clinical outcomes nor ascertain the nature of their relationships with the other “ingredients” (e.g., synergistic; antagonistic) in affecting clinical outcomes:

e.g., infant formula studies
- Failure to establish the purity of the intervention/exposure (e.g., other agents; methylmercury);
- Failure to mask an intervention’s fishy taste or odor (defeats blinding)
Outcome-related problems

- Choice of outcomes that are not the gold standard
  
  e.g., idiosyncratic respiratory outcomes, when FEV1 is considered by many to be the gold standard
Analysis-related problems

- RCT conducted, yet only analyzed before-after data from the “exposed” study group
- No intention-to-treat analysis
- When had measured baseline or on-study data from variables with the potential to influence outcomes, did not conduct appropriate analysis
Consequences of barrier #3

- Compromised internal validity
  - Equally characterized studies having employed the “most ideal” design types
- Third set of hints at what needs to be done in future research
Barrier #4

- Even with multiple studies each employing the “most ideal” research design & sound methods (i.e., sound internal validity), which included good control of known confounders, meaningful attempts to compare & combine different study results were complicated or precluded by clinical heterogeneity….
- Population (e.g., different subtypes or severities of disorder);
- Intervention (e.g., different sources, types, doses or methods to deliver omega-3 fatty acids);
- Study group comparisons (e.g., vs placebo & vs gold standard);
- Controls (e.g., different placebo materials);
- Outcomes (e.g., clinical laboratory measures vs functional disability scores; different biomarker sources [e.g., red blood cells vs plasma phospholipids]);
- Ability to control for known confounding influences
Consequences of barrier #4

- No single answer to the question (e.g., no point estimate, with measure of precision);
- With so many bases for their noncomparability, not even specific answers to “subgroup” versions of the question were derivable (i.e., works for younger patients with asthma, but not for older patients);
- Complicated generalizability
Another hint at what future research requires: collaboration on definitions of study parameters, which might increase likelihood of the comparability & combinability of different studies.
Summing up

- Most questions across the four evidence syntheses failed to receive their “most ideal” investigation
  - result: almost no conclusive answers;
  - at best, suggestive answers (e.g., supplemental treatment for schizophrenia)
Yet, the work allowed us to identify where the research fields likely need to go next

- this was the rationale for the 2-year project in the first place
- so, selecting only studies whose clearly reported details described a “most ideal” design & sound internal validity would have left us with many fewer chances to meaningfully inform this research agenda