RESEARCH GROUP: NICHE, Biomedical Sciences

Project Title:
Novel biomarkers of fish consumption: Implications for neurodevelopment

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Level: PhD

Background to the project:
Fish are the primary human exposure source of methylmercury (MeHg), to which the developing brain is especially sensitive. On the basis of limited data, government advisories have cautioned pregnant women to limit their consumption, especially of fish with high MeHg content. However, fish are a rich source of nutrients, including long-chain polyunsaturated fatty acids (LCPUFA), which are important for the developing brain as shown by the Seychelles Child Development Study (SCDS) (1, 2), and therefore limiting maternal fish intake could pose a threat to optimal neurodevelopment (1). The SCDS have used hair MeHg and blood LCPUFA as biomarkers of fish consumption, in addition to dietary data (3,4). However dietary data are associated with reporting error and bias (5) and often do not correlate well with physiologic biomarkers which can be further impeded by factors such as bioavailability, physiology and genetics. Uncertainties surrounding the validity of such markers warrant the investigation of alternative more robust biomarkers of fish consumption which would reflect the proportion of fish (encompassing both toxin and nutrient components), as well as the average MeHg content of fish, consumed by the individual. Stable isotope ratios could potentially fulfil these criteria and be used to improve the accuracy of risk assessment of fish consumption in relation to neurodevelopmental outcomes, with important ramifications for public health.

Objectives of the research project:
The overall objectives of the research are to explore the use of stable isotope ratios as novel biomarkers of fish consumption and to test these biomarkers in the SCDS in relation to neurodevelopmental outcomes. Furthermore, this proposal offers the opportunity to investigate the genetic factors which may influence the proposed stable isotope biomarkers, with recent work from the SCDS demonstrating that certain genotypes account for variation in hair MeHg and serum LCPUFA status (6,7).

Study-specific objectives:

STUDY 1
Aim: To evaluate the use of sulphur and nitrogen stable isotopes in conjunction with total MeHg in hair as novel biomarkers of fish consumption

1. To demonstrate that varying the amount and type (with respect to MeHg content) of fish consumed results in predictable changes in $S^{34}$ ratios and MeHg values in hair
2. To demonstrate that the MeHg/ $S^{34}$ ratio can be used as a novel biomarker for both the amount of marine fish consumed and the average MeHg content of consumed fish
3. To evaluate the potential modifying influence of genetic polymorphisms related to MeHg kinetics on the MeHg/ $S^{34}$ ratio

STUDY 2
**Aim**: To evaluate the use of nitrogen stable isotopes in hair as a more robust biomarker of LCPUFA status

4. To demonstrate that N^{15} ratios in hair reflect the red blood cell composition of LCPUFA and may therefore be an alternative marker of LCPUFA status

5. To evaluate the potential modifying influence of genetic polymorphisms related to LCPUFA metabolism on the N^{15} ratio

**STUDY 3**

**Aim**: To apply stable isotope ratios in the SCDS to assess the effects of fish consumption, as captured by above biomarkers, of mothers during pregnancy on child developmental outcomes

6. To determine if the hair MeHg/ S^{34} ratio is associated with neurodevelopmental outcomes and whether genetic variation modifies this association

7. To determine if the N^{15} ratio, as a marker of LCPUFA, modifies the association between MeHg/ δ^{34}S and neurodevelopmental outcomes

**Methods to be used**:

Objectives 1 - 5

This project will utilise samples that are currently being collected as part of the iFish study (REC 16/0077). Hair samples will be analysed for stable isotope ratios (funded by NIH grant) of S^{34} and N^{15} and for total MeHg composition by SCDS collaborators at the University of Rochester.

The student will undertake an analysis of red blood cells (RBC) collected from the iFish study for fatty acid profile using GC-MS within the Metabolomics and Proteomics Core Facility.

The genotyping of these individuals is already being completed with SCDS collaborators at the Karolinska Institute, Sweden. Single nucleotide polymorphisms will be examined in the ATP-binding cassette (ABC) transporter and Fatty Acid Desaturase (FADS) genes which we have previously shown to impact on MeHg and PUFA kinetics respectively (6,7).

The student will conduct a series of statistical analyses, with assistance of biostatisticians at the University of Rochester, in order to address Objectives 1-5.

Objectives 6 & 7

The student will have access to the large SCDS Nutrition Cohort 2 database, which will complement the analysis planned within this study.

Collected hair and blood samples from this cohort will be analysed for the stable isotope ratios above using SCDS collaborators at the University of Rochester.

The student will validate the stable isotope markers in the SCDS setting and furthermore conduct a series of statistical analyses, with assistance of biostatistical team at Rochester, in order to determine if: a) the maternal hair MeHg/ δ^{34}S ratio is associated with neurodevelopmental outcomes of the child, b) the maternal hair N^{15} ratio modifies the association between the MeHg/ δ^{34}S ratio and neurodevelopmental outcomes, c) whether genetic variation in ABC and/or FADS genes modifies the association between the MeHg/ δ^{34}S ratio and neurodevelopmental outcomes.

**Skills required of applicant**:

This project would allow the PhD student to undertake a substantial body of work through three interrelated studies.

The applicant will be required to have the following:

- Sound knowledge of nutrition, biochemistry, epidemiology or related discipline
- Excellent interpersonal skills
- Laboratory experience and willingness to acquire new laboratory skills
Good oral and written communication skills
Excellent team working skills
Ability to use his/her initiative and work under pressure
High quality level of record keeping
Ability to deal effectively with administrative tasks

References:


