A Quantitative Approach to Methylmercury-Omega-3 Risk-Benefit Analysis Based on Joint Regression in Population-Based Studies

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The Problem

- How can we derive fish consumption advice that balances the risk from methylmercury (MeHg) against the benefit from omega-3s?
  - MeHg and omega-3 operate on many (some?) of the same endpoints
  - Therefore, data on risk from consumption of fish is likely to be confounded by benefit from omega-3s in the same fish
  - Vice-versa for data on benefit from fish consumption

- Some advice is easy
  - High omega-3, low MeHg - **GOOD**
    - anchovy
    - sardines
    - herring
    - salmon
  - High MeHg, low omega-3 **BAD**
    - swordfish
    - shark

- The difficulty comes when we think about advice for fish with medium levels of both MeHg and omega-3s
  - tuna
  - snapper
  - bluefish
  - sea bass
  - freshwater bass, pike, walleye????

Why not use studies that evaluate outcomes against fish consumption

- For example, Daniels et al.(2004) (ALSPAC study data)
- This was largely the approach taken by FDA in its recent proposal
- There are two arguments against using such an approach

- 1. In almost any population there will be a variety of patterns of fish consumption, but regression analyses of fish consumption vs. outcome assume that all consumers are eating the same mean diet

- 2. Data from such a study only apply to a different population if it is assumed that the second population has the same fish diet
    - i.e., that both populations eat fish with the same balance of MeHg and omega-3s

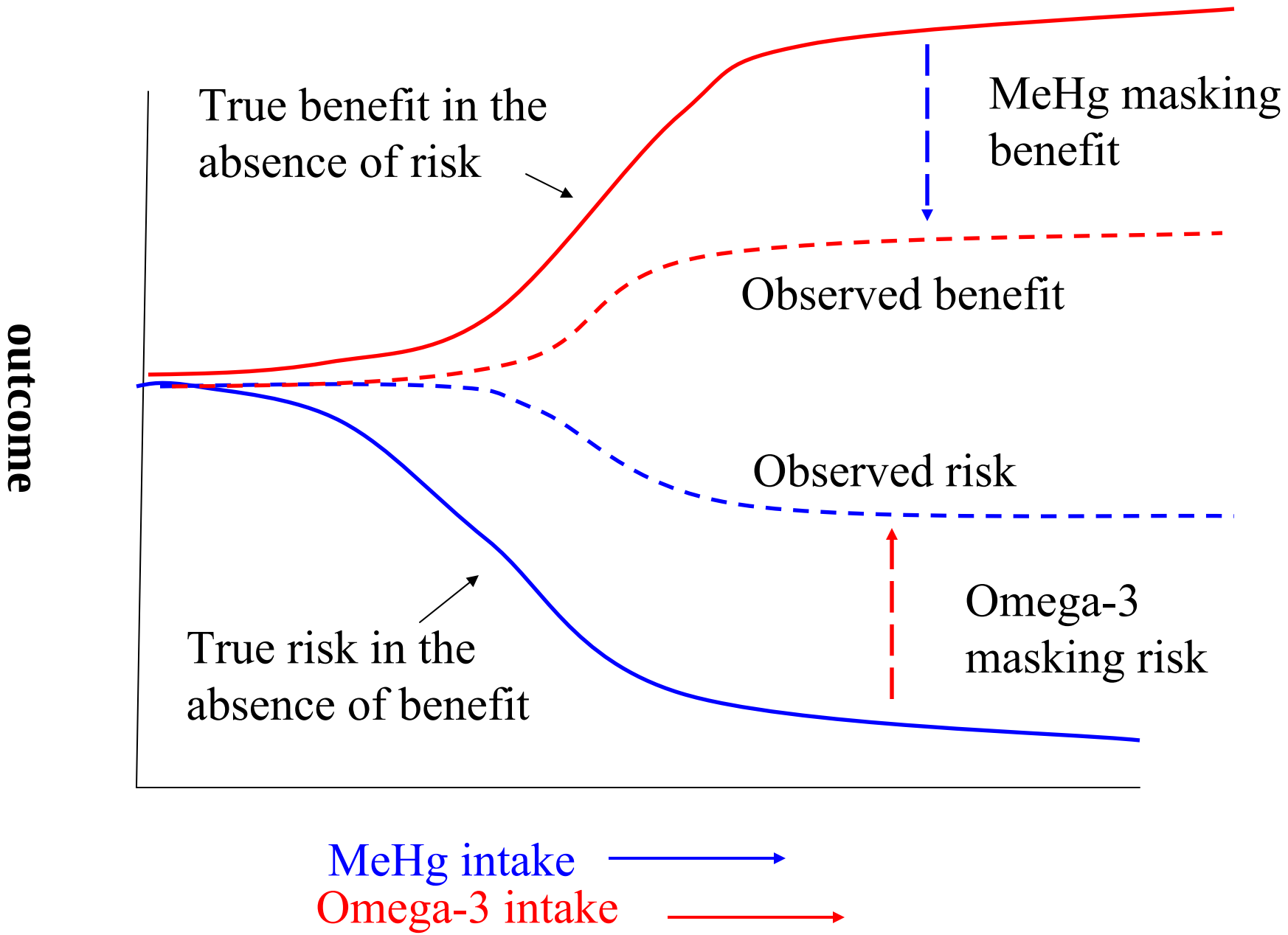
What about studies that quantify MeHg or omega-3s?

- If we at least have MeHg vs. outcome data or omega-3s vs. outcome data, can't we get risk information from one study and benefit information from another?
  - The original Faroes and Seychelles results supplied MeHg risk-only data
  - Other studies (e.g., ALSPAC) supply fish benefit-only data

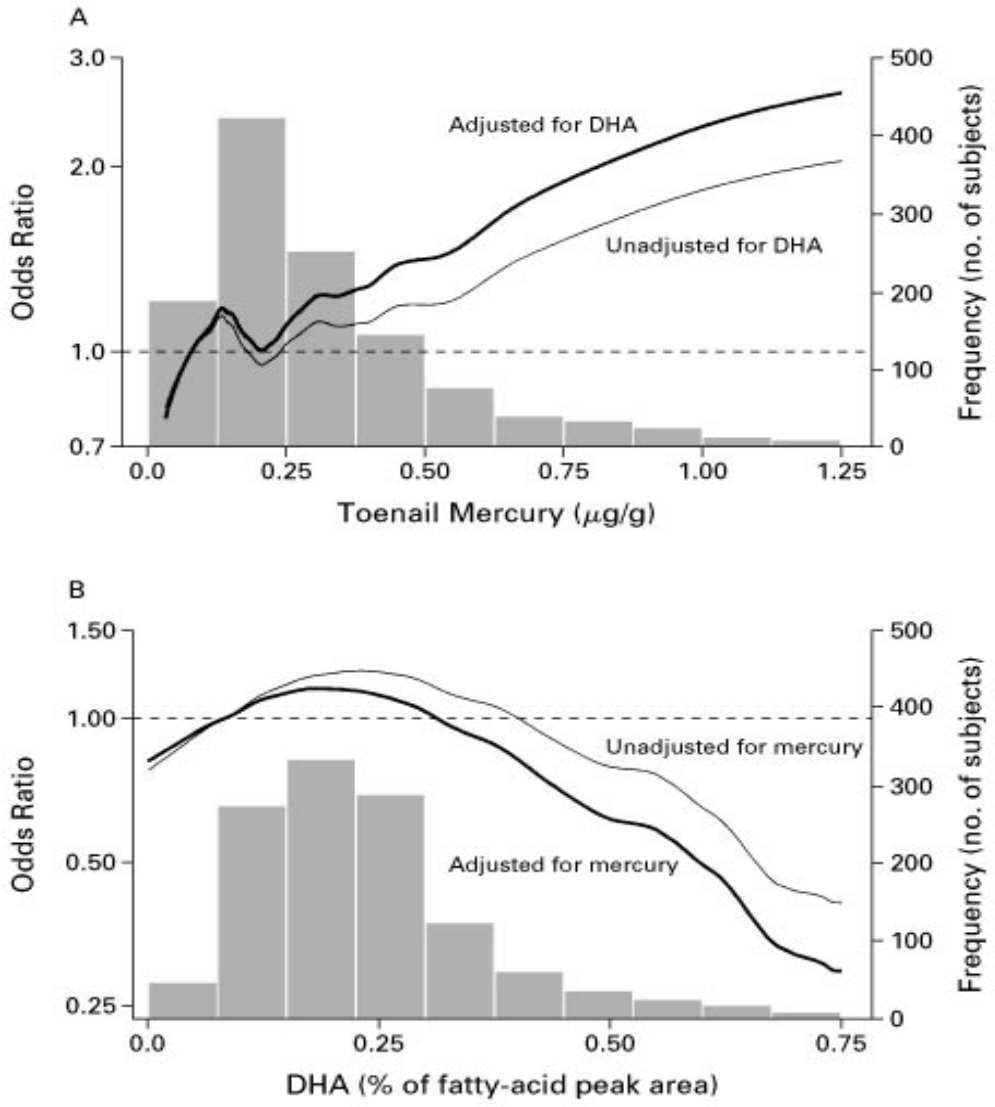
- **No.**
  - remember that MeHg and omega-3s largely operate on the same endpoints
  - therefore, if we look at each separately, the risk from MeHg is likely to be partially obscured by the benefit from the omega-3s

  and

  - the benefit from the omega-3s is likely to be partially obscured by the risk from the MeHg


outcome
True benefit in the absence of risk
MeHg masking benefit
Observed benefit
Observed risk
Omega-3 masking risk
True risk in the absence of benefit
MeHg intake
Omega-3 intake

An example from Guallar et al. (2002)



The naked truth

- What are needed are "naked" risk and benefit data
  - that is, data on MeHg risk not obscured by omega-3 benefit

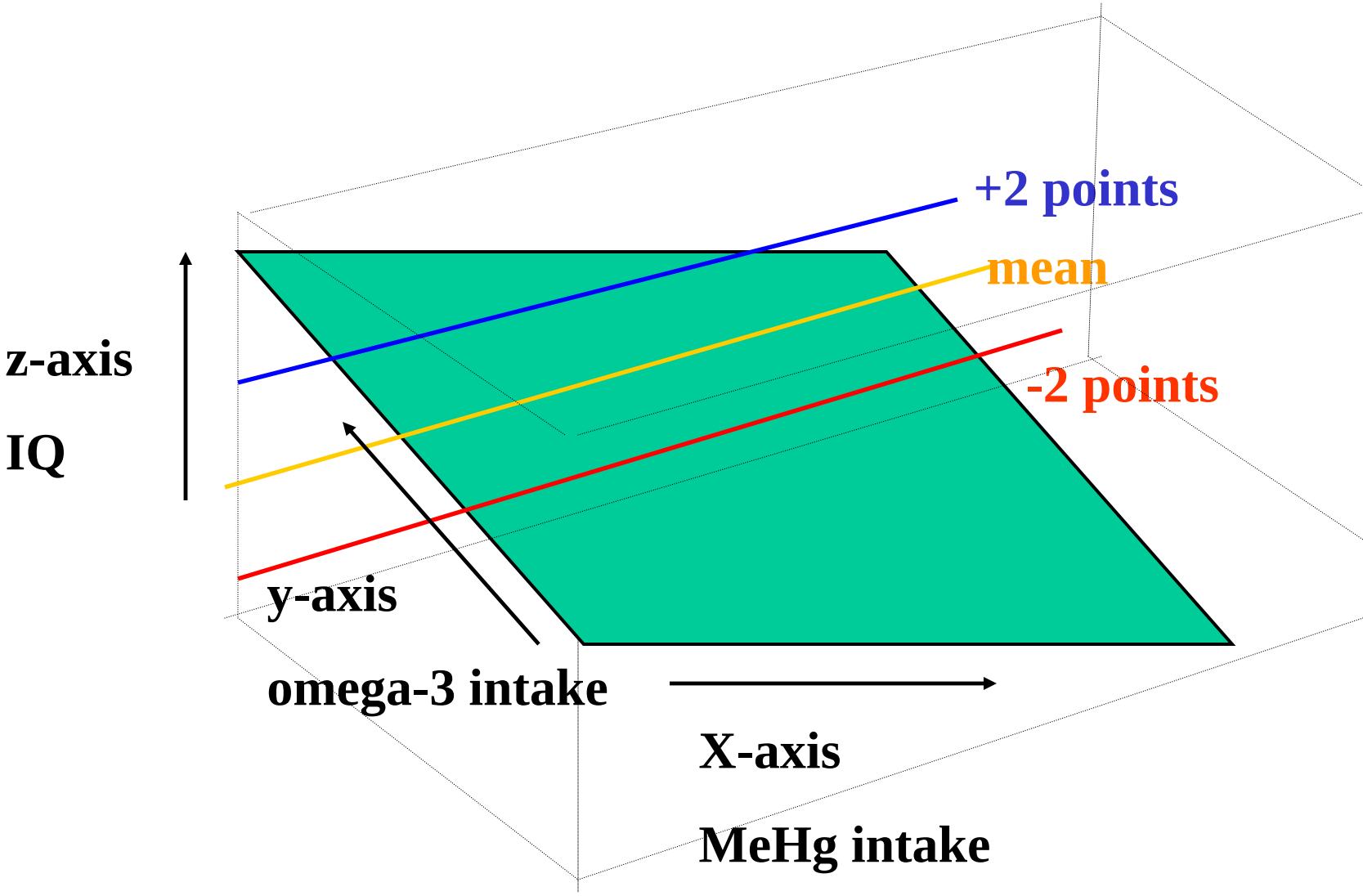
  and

  - data on omega-3 benefit not obscured by MeHg risk

So, how do we get this information?

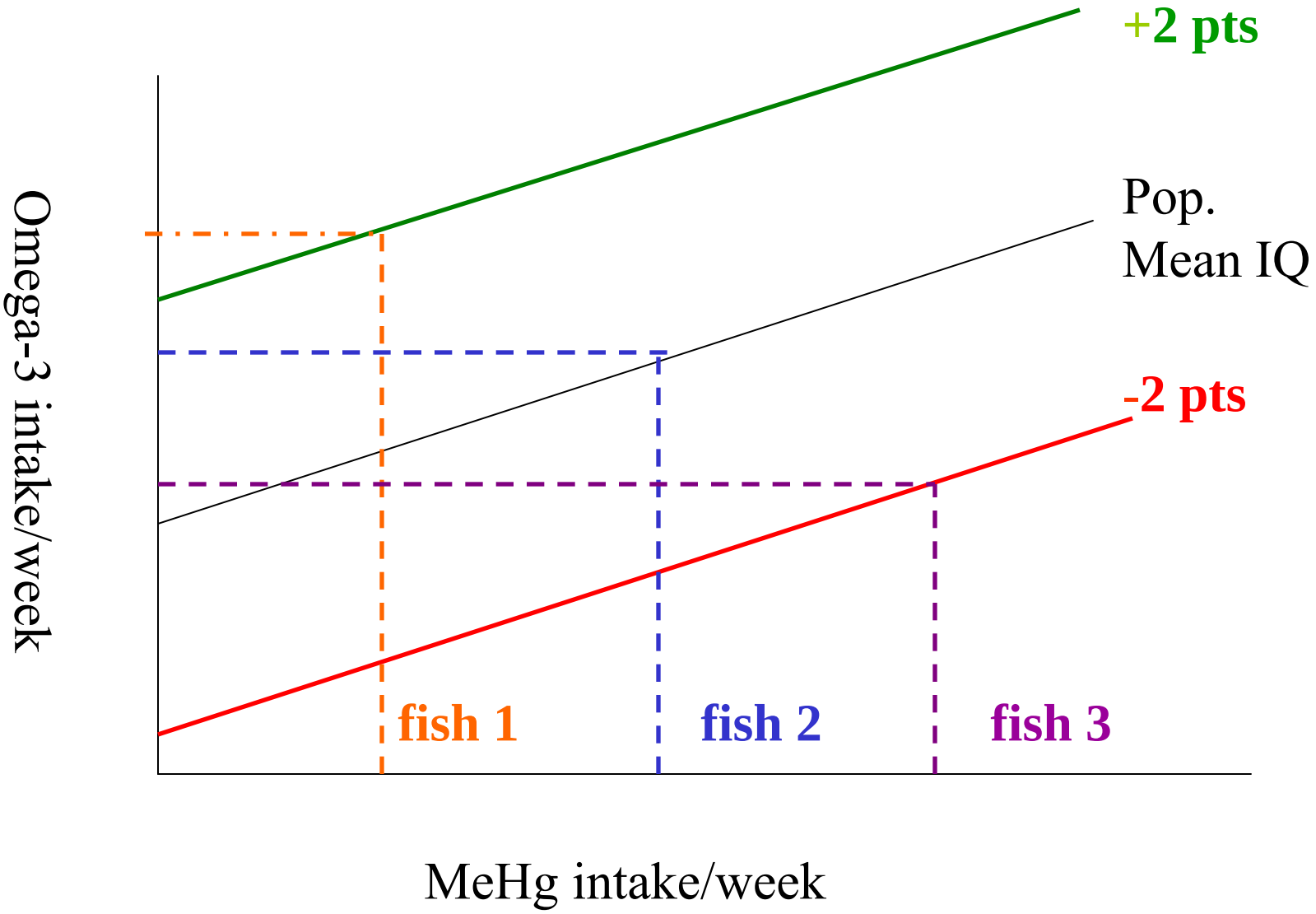
- By creating multiple regression (or structural equation) models that contain both omega-3 and MeHg exposure information
  - recall that in multiple regression, the coefficient (β) of each independent variable reflects the "slope" of that variable when the slopes of the other variables are held constant
    - this is what is meant be "controlling" for a variable

- So, if we have a regression model (for e.g., IQ) with both omega-3 and MeHg in the model, the β for each reflects the "naked" effect of each
  - the same reasoning applies to cardiovascular endpoints
- The relationship among the three variables (outcome, MeHg and omega-3) is described by a plane in three-dimensions
  - Things become more complicated if there is interaction


+2 points
mean
-2 points
z-axis
IQ
y-axis
omega-3 intake
X-axis
MeHg intake

- We can then derive the value for that particular endpoint that would result from independent values of MeHg and omega-3 intake
  - each independent combination of MeHg and omega-3 intake can represent (e.g.) 1- 8 oz portion of a particular fish per week
- For example

Hypothetical relationship of the effect of one 8 oz meal per week of different fish during pregnancy on IQ

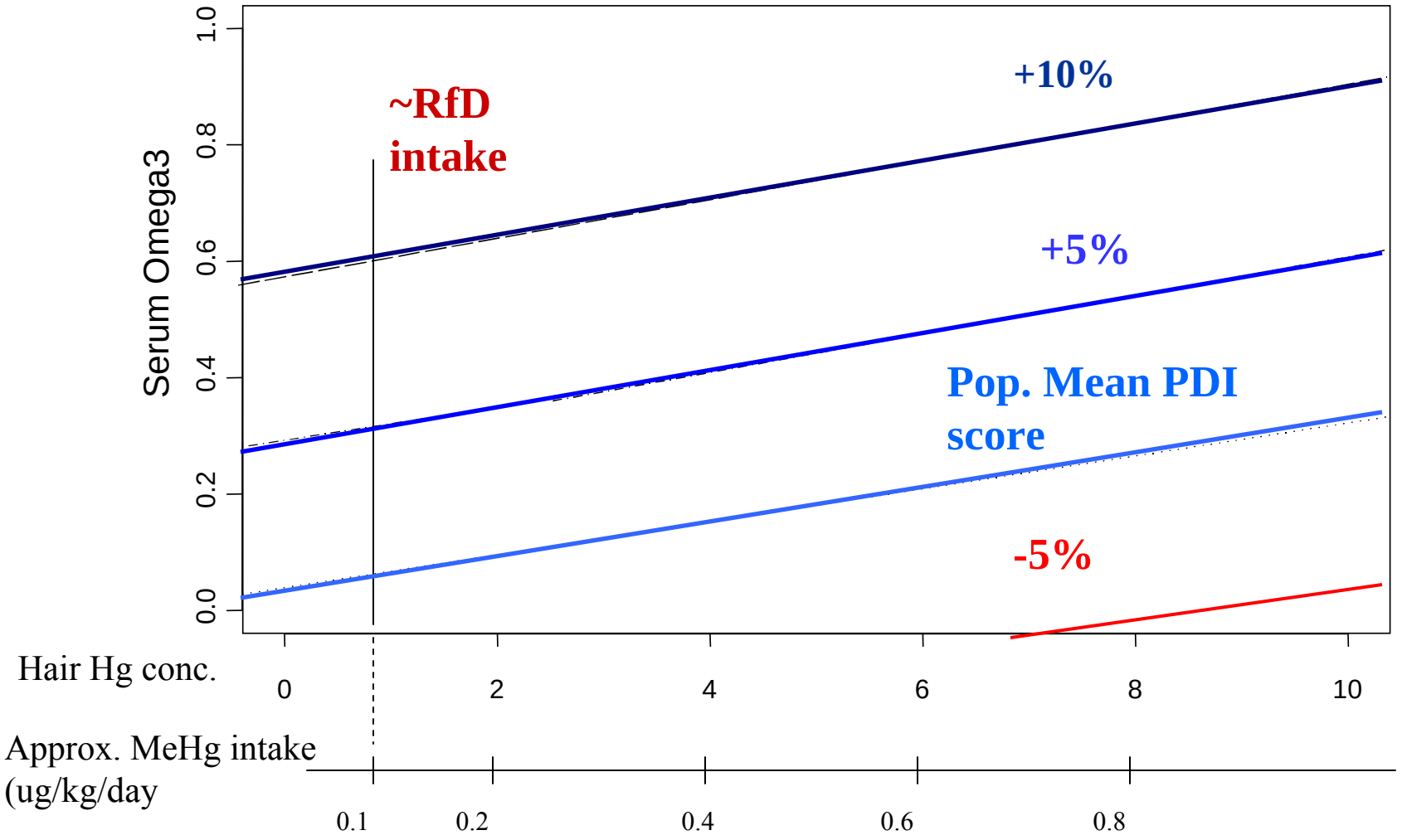


- In theory, these data can be combined in any combination to reflect the combination of MeHg and omega-3s from different fish and different fish diets to arrive at an overall beneficial outcome.

A real-world example

- Unfortunately, there is currently only one developmental study that provides data that is somewhat appropriate for such an analysis.
- Strain et al. (2008) - Seychelles data for MDI and PDI at 9 and 30 months of age.
  - MeHg is only significant for PDI-30 months
  - omega-3 is not significant for any endpoint
    - intake may be saturated
- Therefore, just an example and not a basis for advisories

Strain et al. (2008) - PDI at 30 months



Many endpoints, many possible combinations of MeHg and omega-3 influences

- Even if we confine ourselves to developmental endpoints, many endpoints have been identified that are sensitive to MeHg risk

- Will the MeHg-risk, omega-3 benefit derived for one endpoint hold for other endpoints?

- We can get an idea of the answer from looking at studies in which MeHg intake and **fish consumption** (not omega-3 intake) were both controlled in a regression model

- Choi et al (2008); Budtz-Jorgensen et al. (2007)
- For motor endpoints both fish consumption and MeHg exposure are significant in the structural equation model.
- e.g.,
  - motor performance at 7 yrs

	Fish intake	Hg biomarker
coefficient	25.1 (p - 0.0 1)	-12.2 (p - 0.009)

- However, for some endpoints there was MeHg risk, but no significant evidence of benefit for fish consumption
- e.g.,

	Fish intake	Hg biomarker
verbal performance at 7 yrs		
coefficient	3.62 **(p = 0.61)**	-10.8 (p = 0.002)
attention at 14 yrs		
coefficient	12.2 **(p = 0.13)**	-9.54 (p = 0.016)

- Lederman et al. (2008) - NYC
- both fish consumption during pregnancy (yes/no) and ln cord blood Hg were significant in some of the models

.	Fish intake	ln cord blood Hg
PDI-36 months		
coefficient	8.73 (p = 0.006)	- 4.16 (p = 0.007)
Full IQ		
coefficient	5.64 (p = 0.015)	- 3.76 (p = 0.002)

- But, for some endpoints MeHg, but not fish consumption was significant

	Fish intake	ln cord blood Hg
performance IQ		
coefficient	4.26 **(p = 0.138)**	- 4.16 (p = 0.007)
MDI-24 months		
coefficient	2.44 **(p = 0.325)**	- 2.76 (p = 0.035)

- Thus, it appears that different endpoints have different responses to fish consumption/omega-3 (and MeHg)
- Some may be susceptible to MeHg risk, but not omega-3 benefit.
- This means that MeHg risk and omega-3 benefit need to be defined for a wide variety of endpoints
  - otherwise advice could result in significant benefit for some outcomes, but significant risk for others.

Conclusion

- There is a conceptual way forward for providing fish consumption advice that balances risk and benefit
- BUT, we are not there yet
  - except for the all-benefit and all-risk cases
  - need to consider:
    - risk and benefit data not confounded by each other
    - variable response to MeHg and omega-3 across the various sensitive outcomes