

Fish, Mercury and Child Development



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NECOEM Annual Conference
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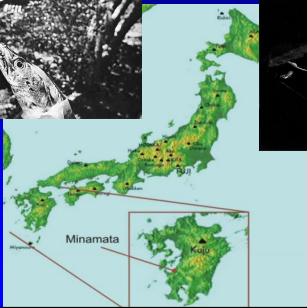
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Goals today

- Understand data underlying fish consumption advisories
- Recognize potential for risk and benefit from fish consumption during pregnancy

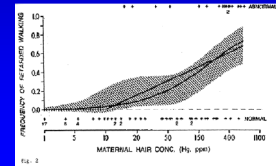
Minamata disease



William Eugene Smith, *Minamata*.

Data from Iraq allowed dose estimation

- Hair collected from 81 mothers
- Dose-response calculated based on age at walking and talking (multiples of 6 months) or from clinical neurological examination



Looking for other evidence of mercury toxicity

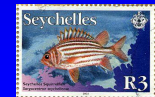
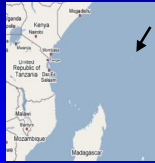
- Most people are not exposed to a catastrophic poisoning episode
- Primary source of non-occupational exposure is fish intake

Does moderate mercury exposure from frequent fish intake cause harm?

- New Zealand cohort
 - 10,000 hair samples
 - Exposure matching
- Faroe Islands
 - 1022 births 1987-88
 - Hair Hg 4.2 ppm
 - Prenatal MeHg exposure associated with detriments in motor, attention, and verbal tests



Does moderate mercury exposure from frequent fish intake cause harm?



- Seychelles Child Development Study - 1989
- 779 mother-child pairs
- Maternal hair Hg 6.9 ppm, 12 fish meals per week
- No overall association of prenatal marine fish intake with child neurodevelopment



NAS - 2000

- National Academy of Sciences convened a committee to review evidence from New Zealand, Faroes, and Seychelles
- Assumptions included:
 - Use most sensitive indicator (from Faroes study)
 - Calculations from cord MeHg to maternal blood and hair MeHg to maternal fish intake
 - 10-fold uncertainty factor (inter-individual variation in metabolism, susceptibility)



Benchmark dose

- BMD = lowest dose at which 'abnormal' result is seen, defined as doubling of kids < 5th %ile. BMDL = lower 95% CI of the BMD.
 - Based upon Boston naming test from Faroes study
- BMDL = 58 ppb cord blood or 12 ppm maternal hair
- Applying 10x uncertainty factor, **BMDL = 5.8 ppb cord blood or 1.2 ppm maternal hair**
- RfD calculated to be **0.1 mcg/kg/day**

UN and WHO 2003

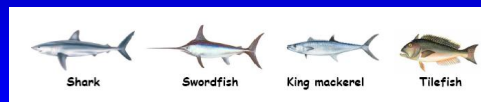
- Joint Expert Committee on Food Additives and Contaminants (JECFA)
- Provisional Tolerable Weekly Intake set at 1.6 mcg/kg/week = **0.23 mcg/kg/day** "level sufficient to protect the developing fetus"

Maternal Hair Hg levels in US

Study	Hair Hg measures	
NHANES (non-preg) N=702	Median 0.2 ppm	90 th % 1.4
Lake Ontario N=247	Median 0.5 ppm	25 th % 0.4, 75 th % 0.7
NJ N=189	Mean 0.53 ppm	range <0.2-9.1, 97 th % 2.0
Project Viva N=135	Mean 0.54 ppm	10% > 1.2

US Federal Mercury Advisory January 2001

- Women who are pregnant, nursing mothers, and children < 12 years should:
 - Avoid shark, swordfish, king mackerel, tilefish



- Consume ≤12 oz per week of all other commercially caught fish

Did the 2001 federal mercury advisory influence pregnant women's diets?



Oken E, Kleinman KP, Berland WE, Simon SR, Rich-Edwards JW, Gillman MW.

Decline in fish consumption among pregnant women after a national mercury advisory.

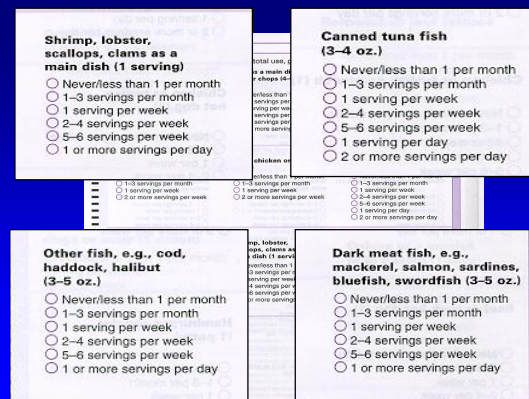
Obstet Gynecol. 2003;102(2):346-51.



- Prospective longitudinal cohort of 2100+ women
- Prenatal diet, maternal and offspring health
- Enrollment at first obstetric visit
- 8 urban and suburban obstetric practices in eastern MA
- Recruitment 4/1999 - 7/2002
- Ongoing follow-up through age 7 years

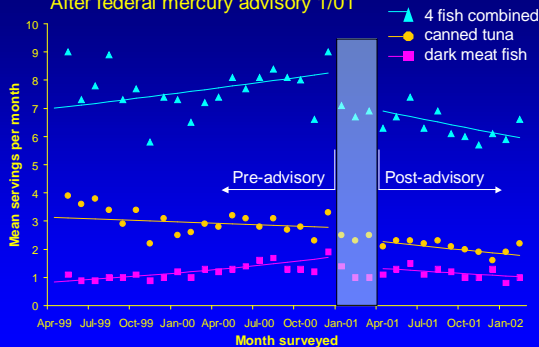
Dietary assessment

- Assessment of diet at 3 time points during pregnancy
 - First study visit (~10 weeks gestation): "since LMP"
 - 26-28 weeks: "past 3 months"
 - In hospital following delivery: "past month"
- Self-administered, optically-scanned semi-quantitative food frequency questionnaire (FFQ)



Decline in fish consumption

After federal mercury advisory 1/01



Conclusions

- Fish consumption declined after a federal Hg advisory
 - Including fish types not specifically named in the advisory
- Such an advisor can change the behavior of pregnant women
- Is this a good thing?

Fish & seafood are a primary source of elongated n-3 FA

- Contain high amounts of elongated n-3 FA (EPA and DHA)
- Higher levels of EPA and DHA among those who eat more fish
- Also higher levels in cord blood and breast milk from mothers who eat more fish

N-3 FA and pregnancy

- Pregnancy complications
- Gestation length
- Fetal growth
- Offspring cognition

N-3 FA and infant cognition postnatal data

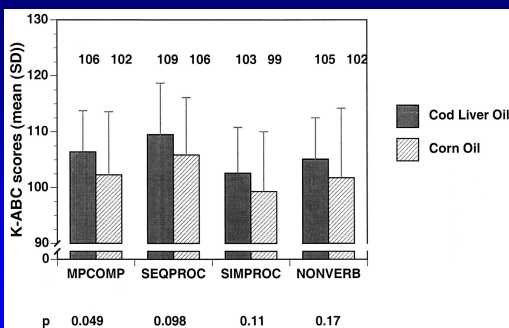
- Breastfeeding
- RCT's of infant formula supplemented with DHA
- No consistent benefit on global development
- But benefit in some specific domains, especially for preterm infants
 - Novelty preference, duration of looking, problem solving

Table 4 Association between cognitive outcomes and fatty acids in cord blood erythrocyte membranes

Test	Cognitive outcomes	Fatty acids in cord blood erythrocytes			
		20:4n-6	20:5n-3	22:6n-3	Ratio n-3:n-6†
GMDS	Isomator (n=71)	-0.123	0.228	0.233	0.201
	Social (n=71)	-0.017	0.137	0.148	0.103
	Speech and hearing (n=71)	-0.118	0.139	0.143	0.144
	Eye and hand coordination (n=71)	-0.331**	0.320**	0.308**	0.325**
	Factorial reasoning (n=71)	-0.242	0.165	0.166	0.112
Practical reasoning (n=67)		-0.004	0.034	0.030	0.014
	General quotient (n=71)	-0.170	0.209	0.215	0.202
PPVT IIIA	Mean standard score (n=71)	-0.084	0.171	0.106	0.102
CBCL	Internalizing (n=71)	0.067	-0.064	-0.131	-0.114
	Externalizing (n=71)	0.030	-0.052	-0.022	-0.038
	Total problems (n=71)	0.024	0.001	-0.022	-0.014
IDS	Average length of phrase (n=49)	-0.101	0.235	0.078	0.122
	Vocabulary score (n=57)	-0.048	0.077	0.127	0.093

CBCL, Child Behavior Checklist; GMDS, Griffiths Mental Development Scales; IDS, language development survey; PPVT, Peabody Picture Vocabulary Test.
 †Pearson's correlation is significant at the 0.05 level.
 **Pearson's correlation is significant at the 0.01 level.
 †Ratio (Sum 20:5n-3, 22:6n-3) to 20:4n-6.

J A Dunstan, et al. Arch Dis Child 2007.



Helland, I. B. et al. Pediatrics 2003;111:e39-e44

How much DHA+EPA are women getting?

- 0.12 g/day
 - Project Viva (pregnant women in MA)
- 0.1g/day
 - US women of childbearing age
- 0.22 g/day
 - pregnant women in Canada and Holland

How much DHA should pregnant women be getting?

- International Society for the Study of Fatty acids and Lipids (ISSFAL) recommendation for pregnant and lactating women
 - at least 0.65 g/day DHA+EPA
 - at least 0.3 g/day DHA

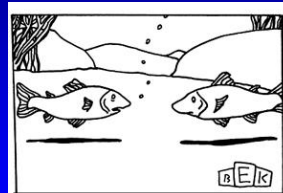
Difficulties in extrapolating from fatty acid supplementation trials to recommendations for fish intake

- Higher dose than most dietary intake
 - e.g. 2-4g/day of fish oil
- Fish may confer other benefits
 - Selenium? Iodine?
- Not possible to estimate risk/benefit balance incorporating contaminants

Fish and cognition

- Need to look at fish to incorporate risks and benefits simultaneously
- Alternatives to fish may be even less healthy (burger and fries?)

Does fish consumption harm or benefit infant cognition?



"With all these omega-3 fatty acids, you'd think I'd feel better"

Oken E, Wright RO, Kleinman KP, Bellinger D, Amarasingwardena CJ, Hu H, Rich-Edwards JW, Gillman MW.

Maternal fish consumption, hair mercury, and infant cognition in a US cohort.

Environmental Health Perspectives, October 2005.



Maternal hair collection

- Hair collection 2/2002 – 2/2003
 - ~100 strands from occiput
 - 211 consented
 - 135 with available data on maternal 2nd trimester fish intake and 6 month infant cognition
- Proximal 3cm tested
- Total Hg measured with DMA-80
 - Mean 0.54 ppm, geometric mean 0.45 ppm
 - 10% > 1.2 ppm (BMDL)

Maternal fish intake

- 2nd trimester SFFQ, administered ~28 weeks of gestation
- Used 4 fish questions combined (canned tuna + dark meat + shellfish + other) to provide an adequate range of exposure
 - Mean 1.2 servings/week, range 0-5.5
 - 7% > 2 servings/week

6 month cognitive test: VRM



6 month cognitive test: VRM



Outcome: % of time spent looking at novel stimulus
 Correlated with later IQ; relatively independent of SES
 Mean score in Viva = 60, range = 10-90

VRM score highest with high fish intake low Hg level

	Hair mercury ≤ 1.2 ppm	Hair mercury > 1.2 ppm
>2 weekly fish servings	72 (n=7)	55 (n=2)
≤ 2 weekly fish servings	60 (n=114)	53 (n=12)

Unadjusted analysis

Fish benefits infant cognition despite adverse effect of mercury

	Maternal 2 nd tri fish intake (per svg/wk)	Maternal hair mercury at delivery (per ppm)
	Change in VRM score	
Fish *	2.8 (0.2, 5.4)	---
Mercury*	---	-4.0 (-10.0, 2.0)
Fish & mercury*	4.0 (1.3, 6.7)	-7.5 (-13.7, -1.2)

*adjusted for maternal age, race, education, marital status; and infant sex, gestational age, fetal growth, breastfeeding, age at testing



Child age 3 year cognitive outcomes

- **PPVT** – language
 - Receptive vocabulary
 - Correlated with WISC-III verbal and full-scale IQ (r=0.90)
- **WRAPMA** – visual motor ability
 - Matching test (visual spatial)
 - Drawing test (visual motor)
 - Pegboard (fine motor)
 - Modestly correlated with IQ (r=0.60)
- Both standardized to have mean 100 and SD 15



Higher Hg with higher fish intake No difference in other characteristics

N=341	Fish intake		
	Never (14%)	≤2 svg/wk (74%)	>2 svg/wk (12%)
RBC mercury (ng/g)	1.9 (2.3)	3.9 (3.8)	5.6 (4.5)
RBC mercury top decile	2%	10%	23%
Hair mercury (ppm) (n=98)	0.28 (0.31)	0.56 (0.47)	0.80 (0.61)
DHA+EPA from fish (mg/d)	0 (0)	122 (97)	318 (160)
DHA+EPA total (mg/d)	22 (77)	148 (142)	301 (159)
Age (y)	31.7 (4.8)	32.8 (4.6)	32.3 (4.7)
White	85%	82%	85%
College graduate	82%	80%	83%
Breastfeeding (mos)	7.2 (4.4)	7.0 (4.5)	6.8 (4.7)



Maternal mercury and child cognition

Child test score	Age and sex	MV	MV + fish
PPVT			
Hg top decile	-5.3 (-10.1, -0.5)	-4.0 (-8.0, 0.0)	
Hg < 90 th %ile	Referent	Referent	
WRAVMA total			
Hg top decile	-3.4 (-7.0, 0.2)	-3.5 (-7.2, 0.2)	
Hg < 90 th %ile	Referent	Referent	

*MV adjustment = Child: fetal growth, gestation length, breastfeeding duration, birth order, language; Maternal: PPVT score, age, BMI, race/ethnicity, education, marital status, smoking; Paternal: education.



Maternal mercury and child cognition

Child test score	Age and sex	MV	MV + fish
PPVT			
Hg top decile	-5.3 (-10.1, -0.5)	-4.0 (-8.0, 0.0)	-4.5 (-8.5, -0.4)
Hg < 90 th %ile	Referent	Referent	Referent
WRAVMA total			
Hg top decile	-3.4 (-7.0, 0.2)	-3.5 (-7.2, 0.2)	-4.6 (-8.3, -0.9)
Hg < 90 th %ile	Referent	Referent	Referent

*MV adjustment = Child: fetal growth, gestation length, breastfeeding duration, birth order, language; Maternal: PPVT score, age, BMI, race/ethnicity, education, marital status, smoking; Paternal: education.



Maternal fish intake and child cognition

Child Test Score	Age and sex	MV	MV + Hg
PPVT			
Fish > 2x/wk	-1.5 (-7.3, 4.4)	1.2 (-3.5, 6.0)	
Fish <= 2x/wk	-2.2 (-6.5, 2.2)	-2.1 (-5.7, 1.4)	
Fish never	Referent	Referent	
WRAVMA total			
Fish > 2x/wk	3.7 (-0.7, 8.1)	5.3 (0.6, 9.6)	
Fish <= 2x/wk	0.7 (-2.5, 4.0)	1.1 (-2.2, 4.4)	
Fish never	Referent	Referent	

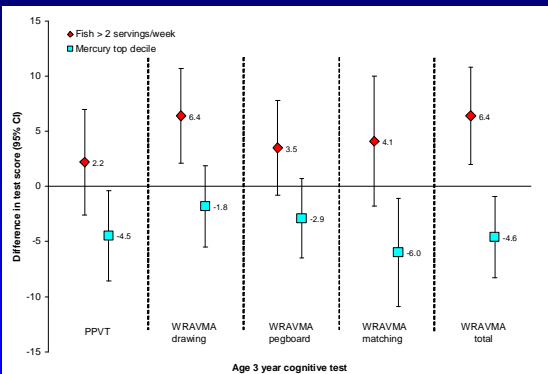
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Maternal fish intake and child cognition

Child Test Score	Age and sex	MV	MV + Hg
PPVT			
Fish > 2x/wk	-1.5 (-7.3, 4.4)	1.2 (-3.5, 6.0)	2.2 (-2.6, 7.0)
Fish <= 2x/wk	-2.2 (-6.5, 2.2)	-2.1 (-5.7, 1.4)	-1.8 (-5.4, 1.8)
Fish never	Referent	Referent	Referent
WRAVMA total			
Fish > 2x/wk	3.7 (-0.7, 8.1)	5.3 (0.6, 9.6)	6.4 (2.0, 10.8)
Fish <= 2x/wk	0.7 (-2.5, 4.0)	1.1 (-2.2, 4.4)	1.5 (-1.8, 4.7)
Fish never	Referent	Referent	Referent

*MV adjustment = Child: fetal growth, gestation length, breastfeeding duration, birth order, language; Maternal: PPVT score, age, BMI, race/ethnicity, education, marital status, smoking; Paternal: education.



Oken, et al. Submitted

Summary

- Higher 2nd trimester fish intake associated with higher Hg
- Higher Hg associated with lower cognition at age 6 months and 3 years
- But...increased fish intake associated with **higher** cognition (especially in low Hg group)
- → Moms should eat fish during pregnancy, but choose ones with low Hg (and presumably high n-3 fatty acids)

Cautions

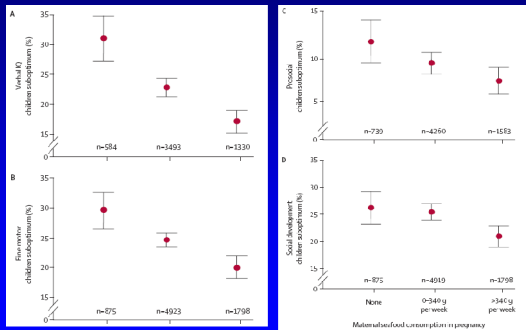
- No measure of PCB's or other toxins (e.g. lead)
- No measure of parental IQ or home stimulation
- Relatively small sample, may not be representative of other populations

Similar findings in other populations



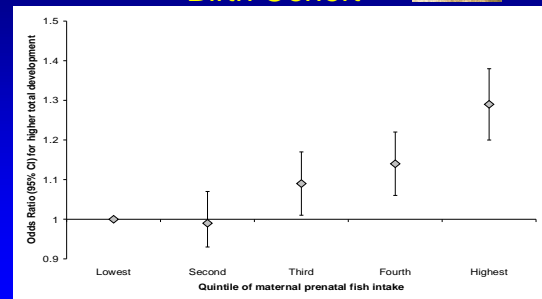
"How do we tell the kids that we're edible again?"

Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study



Hibbeln JR, et al. Lancet 2007;369:578-85.

Danish National Birth Cohort



Oken, et al. Submitted

Faroes - reanalysis

Table 1. Mercury effects on neurobehavioral tests at 7 and 14 years of age, as determined in structural equation analysis with covariate adjustment before and after addition of the frequency of maternal fish dinners during pregnancy.

Age/test group	Mercury without adjustment for fish intake		Mutual adjustment			
	Effect*	p-Value	Fish intake Effect	p-Value	Mercury Effect	p-Value
7 Years						
Motor	-9.74	0.034	25.1	0.010	-12.2	0.0092
Verbal	-10.4	0.0018	3.62	0.61	-10.9	0.0017
14 Years						
Motor	-7.41	0.033	19.9	0.006	-9.37	0.0082
Attention	-8.40	0.029	12.2	0.13	-9.54	0.016
Spatial	2.60	0.50	17.3	0.031	1.04	0.79
Verbal	-5.97	0.080	9.85	0.16	-6.87	0.049
Memory	-2.86	0.39	3.15	0.64	-3.05	0.37

*Effect of true exposure doubling expressed in percent of SD of latent response.

Budtz-Jorgensen E., et al. EHP 2007;115(3):323-7.

Limitations of fish-cognition studies

- Observational - residual confounding?
- Role of other contaminants (e.g. PCB's)
- Lack of detail about specific fish types

Summary - risk

- MeHg is a known neurotoxin, fetus is particularly susceptible
- More fish intake → higher MeHg
- Higher MeHg from maternal fish consumption during pregnancy causes subtle but measurable harm for child development
 - Effect on IQ likely minimal
 - Perhaps stronger effects on other outcomes

Summary - benefit

- Prenatal n-3 fatty acid intake likely benefits child development
 - Magnitude not certain
- Overall effect of fish intake likely beneficial
 - No randomized trials
 - Limited information available regarding fish types

Summary - message

- Message needs to be clearer to minimize confusion
- Wrong change may be harmful