Measurement error and multiple responses via structural equation models

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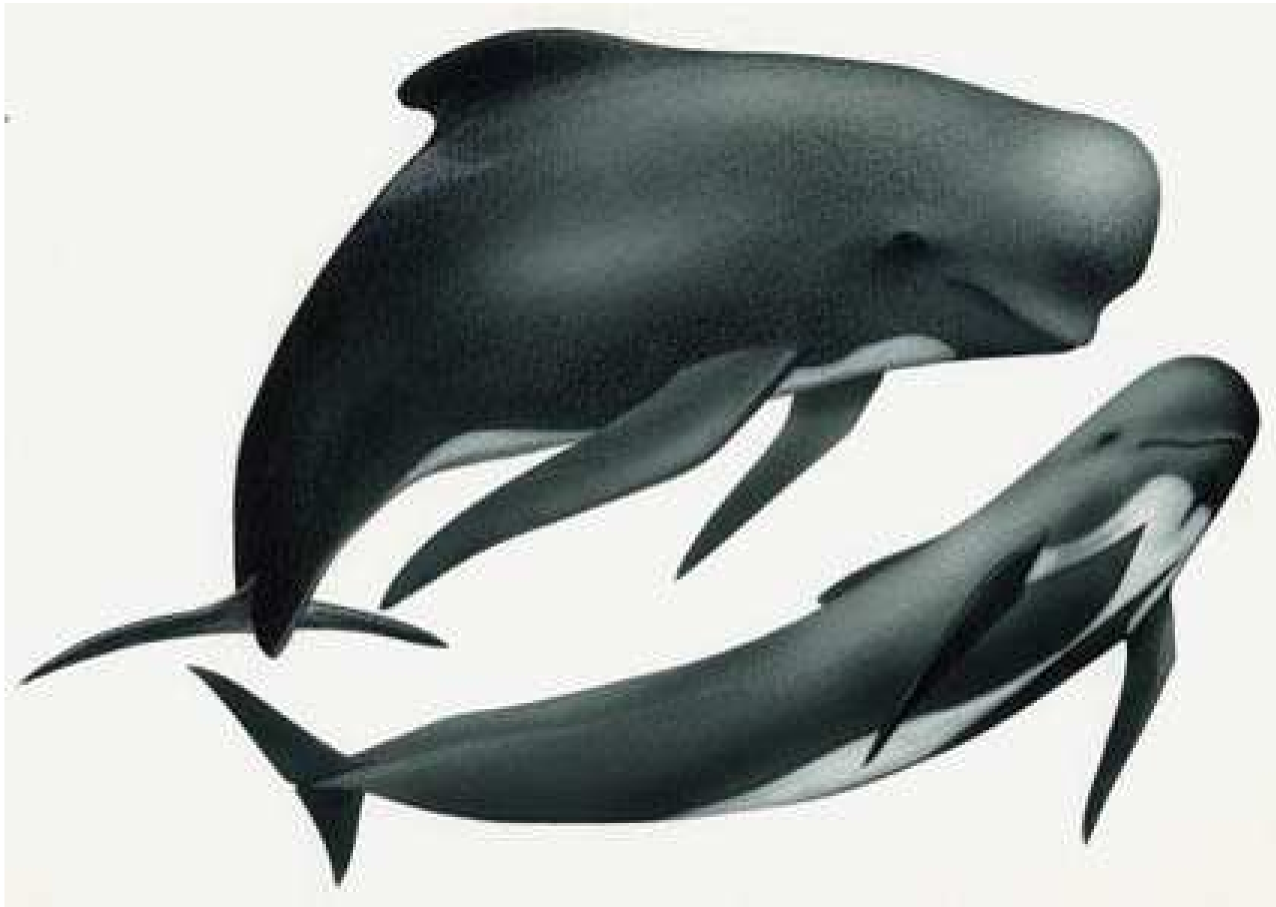
Outline

- Faroese data
- Standard analysis
- Measurement error in exposure variable
- Structural equation models (SEMs)
- Measurement error in confounders
- Effect modification in SEMs

Pilot whales



The Faroese Cohort 1

EXPOSURE:

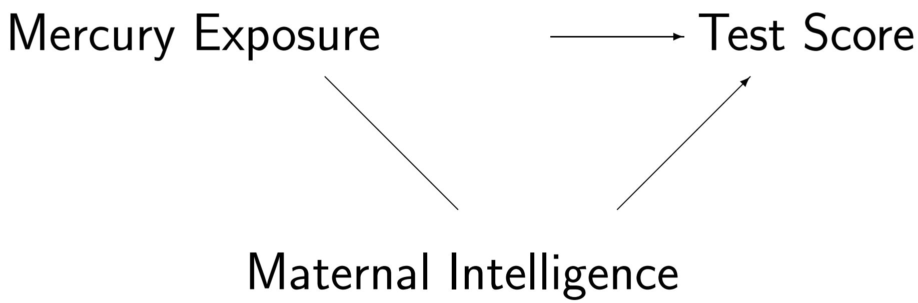
1. Cord Blood Mercury
2. Maternal Hair Mercury
3. Maternal Seafood Intake

RESPONSE:

Neuropsychological Tests

Age:	Birth	7 Years	14 Years
Calendar:	1986-87	1993-94	2000-2001
Children:	1022	917	856

Confounding



1. Intelligent mothers get intelligent children

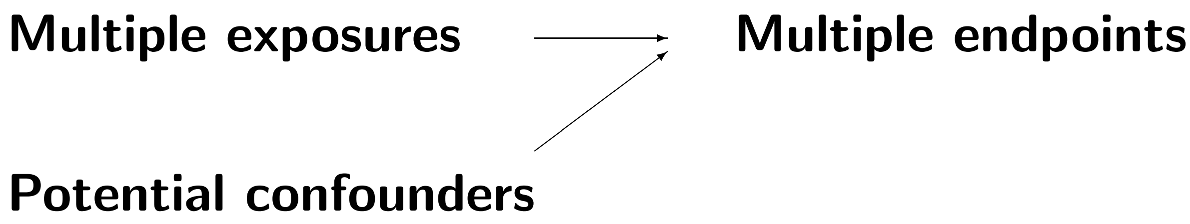
2. Children with intelligent mothers have lower prenatal mercury exposure

If we ignore the *confounder* maternal intelligence then the adverse mercury effect is overestimated. Highly exposed children are doing poorly also because their mothers are less intelligent.

Standard approach to confounder correction: *multiple regression*

Multiple Regression Results: effect of 10-fold increase in exposure

	Cord Blood		Maternal Hair	
Response	β	p	β	p
NES2 Finger tapping				
Preferred hand	−1.01	0.08	−1.03	0.08
Non preferred hand	−0.55	0.31	−0.91	0.11
Both hands	−1.90	0.10	−2.74	**0.02**
NES2 Hand-Eye Coordination				
Error score*	0.03	0.27	0.05	0.10
NES2 Continuous Performance Test				
Ln total missed*	0.22	0.07	0.08	0.52
Reaction time*	34.57	**0.002**	16.24	0.13
Wechsler Intelligence Scale				
Digit Spans	−0.21	0.14	−0.17	0.24
Similarities	−0.003	0.99	−0.23	0.57
Sqrt. Block Designs	−0.11	0.31	−0.06	0.59
Bender Visual Gestalt Test				
Errors on copying*	0.33	0.49	0.33	0.51
Reproduction	−0.10	0.54	0.07	0.68
Boston Naming Test				
No cues	−1.61	**0.002**	−1.10	**0.04**
With cues	−1.70	**0.001**	−1.12	**0.03**
California Verbal Learning Test				
Learning	−1.00	0.23	−0.97	0.27
Short-term repro.	−0.46	0.06	−0.41	0.11
Long-term repro.	−0.46	0.10	−0.42	0.15
Recognition	−0.26	0.21	−0.19	0.38



Weaknesses of the regression analysis

- result is blurred
  - multiple testing problems $\sim$ Bonferroni adjustment?
- not efficient
  - fails to borrow information from different outcomes
- exposure measurement error is ignored
  - regression coefficients become biased

Exposure error in simple linear regression

Y: response, X: true exposure, W: measured exposure

$$Y = \beta_0 + \beta_x \cdot X + \epsilon, \quad W = X + U$$

Naive Analysis: Replace X by W

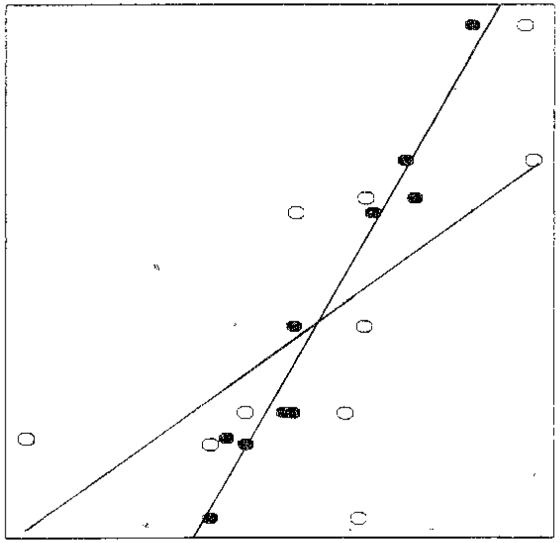


Figure 2.1. *Illustration of additive measurement error model. The filled circles are the true* $(\mathbf{Y}, \mathbf{X})$ *data and the steeper line is the least squares fit to these data. The empty circles and attenuated line are the observed* $(\mathbf{Y}, \mathbf{W})$ *data and the associated least squares regression line.*

The exposure effect is attenuated - the higher the imprecision the worse

Correlation between covariate and residual term

Y: response, X: true exposure, W: measured exposure

$Y = \beta_0 + \beta_x \cdot X + \epsilon, \quad W = X + U,\ U \sim N(0, var(U))$

Naive analysis:

$$Y = \beta_0 + \beta_x \cdot (W - U) + \epsilon = \beta_0 + \beta_x \cdot W - \beta_x \cdot U + \epsilon$$

Model violation: $cov(W, U) \neq 0$

$$\widehat{\beta}_x \rightarrow \lambda\beta_x, \quad \lambda = \frac{var(X)}{var(X) + var(U)}$$

Strong bias when imprecision is high and true exposure variation is low

Exposure error in multiple regression

Y: response, X: true exposure, W: measured exposure, Z: confounder

$$Y = \beta_0 + \beta_x \cdot X + \beta_z \cdot Z + \epsilon, \quad W = X + U$$

Naive analysis:

$$\widehat{\beta}_x \to \lambda \cdot \beta_x, \quad \lambda = \frac{var(X|Z)}{var(X|Z) + var(U)}$$

$var(X|Z)$: variance in the true exposure not explained by the confounders

Strong bias when imprecision is high and true exposure variation *for fixed level of confounders* is low

Correction for exposure error

Naive analysis:

$$\widehat{\beta}_x \rightarrow \lambda \cdot \beta_x, \quad \lambda = \frac{var(X|Z)}{var(X|Z) + var(U)}$$

If λ known: $\tilde{\beta}_x = \widehat{\beta}_x/\lambda$, $var(\tilde{\beta}_x) = var(\widehat{\beta}_x)/\lambda^2$

corrected estimate has increased variance

Alternative methods

- *Regression calibration:* Regress Y on Z and an estimate of $E(X|W, Z)$ (based on validation data including X)
- *SIMEX:* add more noise and extrapolate (var(U) known)
- *Instrumental variables:* exposure surrogate associated to X, but not to U
- *Structural equation models*

Structural equation models

Consist of two parts

<u>The measurement part:</u>

Observed variables considered manifestations of a limited number of underlying (latent) variables. Obtained through *factor analytic models*.

<u>The structural part:</u>

Latent variables related to each other and to observed covariates. Obtained through *multiple linear regression models.*

The measurement part - confirmatory factor analysis

Dependent variables $y_i = (y_{i1}, ..., y_{ip})^t$ in subject i considered manifestations of

latent variables $\eta_i = (\eta_{i1}, ..., \eta_{im})^t$

with measurement error $\epsilon_i = (\epsilon_{i1}, ..., \epsilon_{ip})^t \quad (i = 1, ..., n)$

$$
\begin{aligned}
y_{i1} &= \nu_1 + \lambda_{11} \cdot \eta_{i1} + ... + \lambda_{1m} \cdot \eta_{im} + \epsilon_{i1} \\
. & \\
. & \\
. & \\
y_{ip} &= \nu_p + \lambda_{p1} \cdot \eta_{i1} + ... + \lambda_{pm} \cdot \eta_{im} + \epsilon_{ip}
\end{aligned}
$$

In matrix form: $y_i = \nu + \Lambda \eta_i + \epsilon_i$

$\epsilon_i \sim N(0, \Omega)$

The structural part

Linear relations between latent variables $\eta_i = (\eta_{i1}, ..., \eta_{im})^t$

and independent variables $z_i = (z_{i1}, ..., z_{iq})^t$

with residuals $\zeta_i = (\zeta_{i1}, ..., \zeta_{im})^t$

$$
\begin{aligned}
\eta_{i1} &= \alpha_1 + \Sigma_{j \neq 1}\, \beta_{1j}\, \eta_{ij} + \Sigma_j\; \gamma_{1j}\, z_{ij} + \zeta_{i1} \\
&. \\
&. \\
&. \\
\eta_{im} &= \alpha_m + \Sigma_{j \neq m}\, \beta_{mj}\, \eta_{ij} + \Sigma_j\; \gamma_{mj}\, z_{ij} + \zeta_{im}
\end{aligned}
$$

In matrix form: $\eta_i = \alpha + B\eta_i + \Gamma z_i + \zeta_i$

$\zeta_i \sim N(0, \Psi)$

Neurobehavioural test scores included

Neurobehavioural Examination System (NES) Finger Tapping: First the child tapped a (computer) key for 15 seconds twice with the preferred hand, then twice with the non-preferred hand and finally two keys were tapped with both hands twice. Scores ($FT1, FT2$ and $FT3$) are the maximum number of taps under each condition.

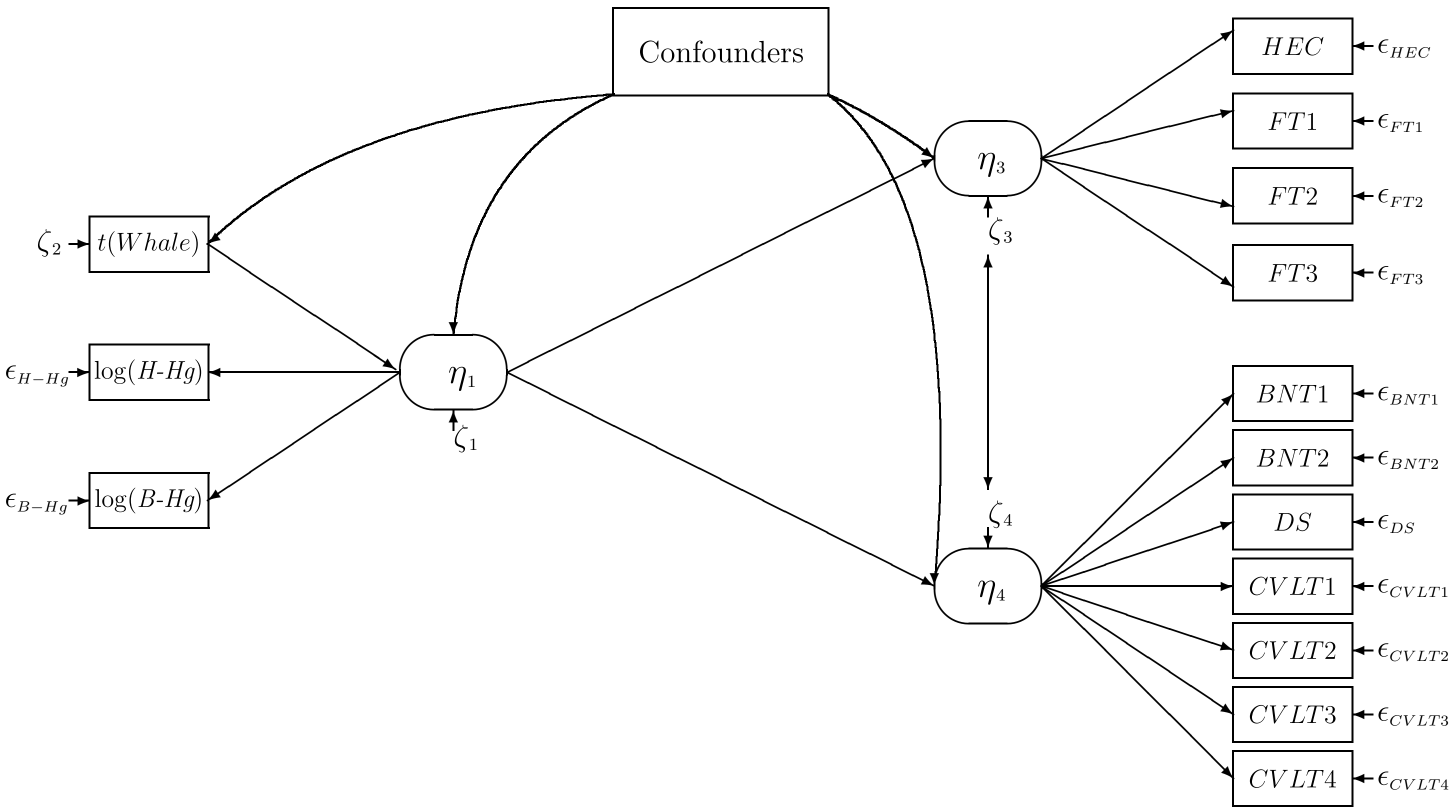
NES Hand Eye Coordination: The child had to follow a sine-wave curve on the computer screen using a joy-stick. The score (HEC) is the average deviation from the stimulus in the best two trails.

Wechsler Intelligence Scale for Children - Revised Digit Spans: Digit spans of increasing length were presented until the child failed. The score (DS) is the total number of correct trials.

California Verbal Learning Test (children): A list of 12 words that can be clustered into categories was given over five learning trails, followed by a presentation of an interference list. The child was twice requested to recall the initial list, first immediately after the presentation of the interference list and again 20 minutes later after completing some other tests. Finally, a recognition test was administered. Scores are the total number of correct responses on the learning trials ($CVLT1$), on immediate and delayed recall conditions ($CVLT2, CVLT3$) and on recognition ($CVLT4$).

Boston Naming Test: The child was presented with drawings of objects and asked to name the object. If no correct response was produced in 20 seconds a semantic cue was provided describing the type of object represented. If a correct response still was not given, a phonemic cue was presented. The scores are total correct without cues ($BNT1$) and total correct after cues ($BNT2$).

Path diagram for indicators of mercury exposure and childhood cognitive function



Selected equations

Measurement part (on the form)

$$
\begin{array}{rcccccc}
\log(B\text{-}Hg) & = & 0 & + & 1 & \cdot\eta_1 & +\epsilon_{B\text{-}Hg} \\
\log(H\text{-}Hg) & = & \nu_{H\text{-}Hg} & + & \lambda_{H\text{-}Hg} & \cdot\eta_1 & +\epsilon_{H\text{-}Hg} \\
 & & & & & & \\
FT1 & = & 0 & + & 1 & \cdot\eta_3 & +\epsilon_{FT1} \\
FT2 & = & \nu_{FT2} & + & \lambda_{FT2} & \cdot\eta_3 & +\epsilon_{FT2} \\
FT3 & = & \nu_{FT3} & + & \lambda_{FT3} & \cdot\eta_3 & +\epsilon_{FT3} \\
HEC & = & \nu_{HEC} & + & \lambda_{HEC} & \cdot\eta_3 & +\epsilon_{HEC}
\end{array}
$$

Reference indicators Hg: cord blood, Motor: FT1

Structural part

$$\eta_3 = \alpha_3 + \beta_{31} \cdot \eta_1 + \gamma_{31} \cdot z_1 + ... + \gamma_{39} \cdot z_9 + \zeta_3$$

$$\eta_4 = \alpha_4 + \beta_{41} \cdot \eta_1 + \gamma_{41} \cdot z_1 + ... + \gamma_{49} \cdot z_9 + \zeta_4$$

Distribution of observed variables

Structural part: $\eta_i = \alpha + B\eta_i + \Gamma z_i + \zeta_i$

gives: $\eta_i = (I - B)^{-1}\alpha + (I - B)^{-1}\Gamma z_i + (I - B)^{-1}\zeta_i$

Measurement part: $y_i = \nu + \Lambda\eta_i + \epsilon_i$

gives: $y_i = \nu + \Lambda(I - B)^{-1}\alpha + \Lambda(I - B)^{-1}\Gamma z_i + \Lambda(I - B)^{-1}\zeta_i + \epsilon_i$

Distribution of y_i given z_i is multivariate regression model.

Estimation and assessment of model fit

$y_i|z_i \sim N_p\{\mu(\theta) + \Pi(\theta)z_i, \Sigma(\theta)\}$, with $\theta{=}(\nu, \Lambda, \Omega, \alpha, B, \Gamma, \Psi)$

- $\mu(\theta) = \nu + \Lambda(I - B)^{-1}\alpha$
- $\Pi(\theta) = \Lambda(I - B)^{-1}\Gamma$
- $\Sigma(\theta) = \Lambda(I - B)^{-1}\Psi(I - B)^{-1^t}\Lambda^t + \Omega$

$$L(y, z, \theta) = \prod_{i=1}^{n} \phi\{y_i|\mu(\theta) + \Pi(\theta)z_i, \Sigma(\theta)\}$$

ϕ: normal distribution density. ML estimator maximizes $L(y, z, \theta)$ as a function of θ.

Unrestricted model: Let μ, Π, Σ vary freely.

Overall fit of proposed model is often assessed through:

-2 log-likelihood ratio test of proposed model against unrestricted model

Normality assumption for independent variables

$y|z \sim N_p\{\mu(\theta) + \Pi(\theta)z, \Sigma(\theta)\}$, θ=$(\nu, \Lambda, \Omega, \alpha, B, \Gamma, \Psi)$

Assume $z \sim N(\mu_z, \Sigma_z)$, then $v = (y, z)$ has normal distribution

$$E(v) = \begin{pmatrix} \nu(\theta) + \Pi(\theta)\mu_z \\ \mu_z \end{pmatrix}, \quad var(v) = \begin{pmatrix} \Pi(\theta)\Sigma_z\Pi(\theta)^t + \Sigma(\theta) & . \\ \Sigma_z\Pi(\theta)^t & \Sigma_z \end{pmatrix}$$

Maximum likelihood inference in this model and original model conditioning on z is equivalent.

Likelihood function factorization:

$$\log[L(y, z|\theta, \kappa)] = \log[L(y|z, \theta)] + \log[L(z|\kappa)]$$

Model modification

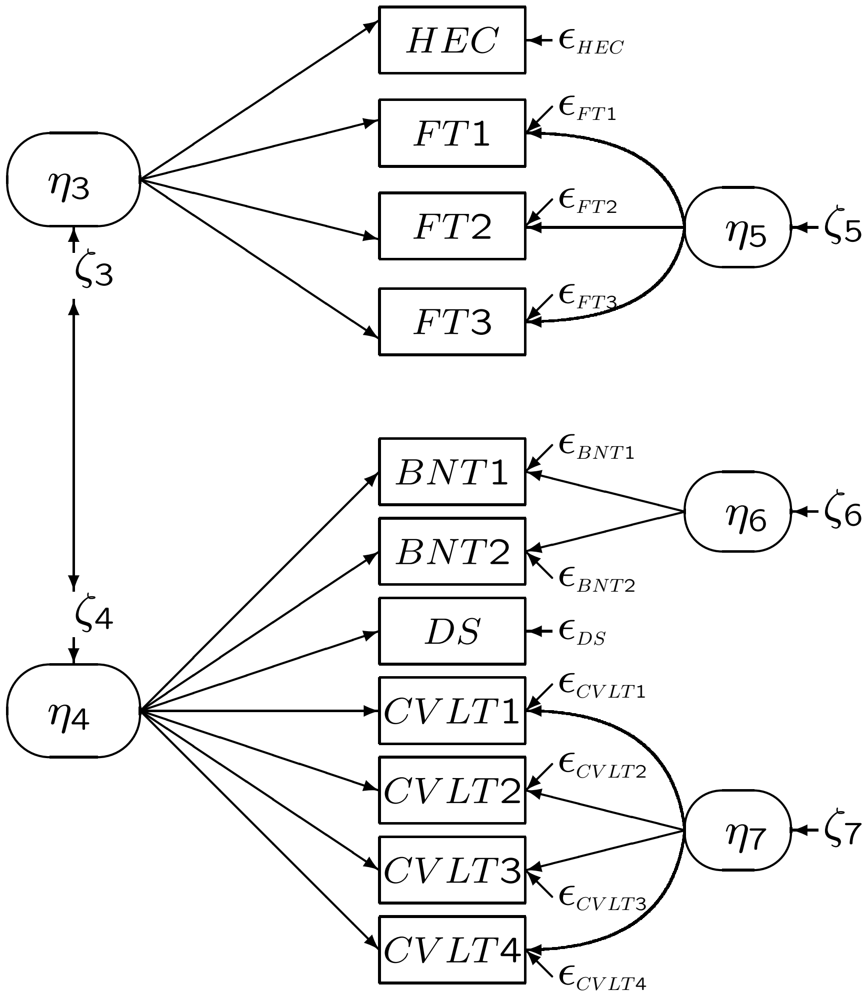
Look at path diagram. What arrows are missing?

Re-specifications should be based on substantive expertise.

Automatic model selection procedures available in most SEM software - but uncritical applications will likely yield misleading results.

Piecewise model fitting: Divide model into smaller parts. Fit each part separately. Evaluate the fit of each part. Modify model parts with poor fit.

Local dependence



Path diagram illustrating how local dependence between test scores is taken into account

Effect of a 10-fold increase in mercury exposure

	β	p
Motor Function	-1.03	0.034
Verbal Function	-1.62	0.002

Reference indicators Hg: cord blood, Motor: FT1, Verbal: BNT2.

Effect of a 10-fold increase in mercury exposure

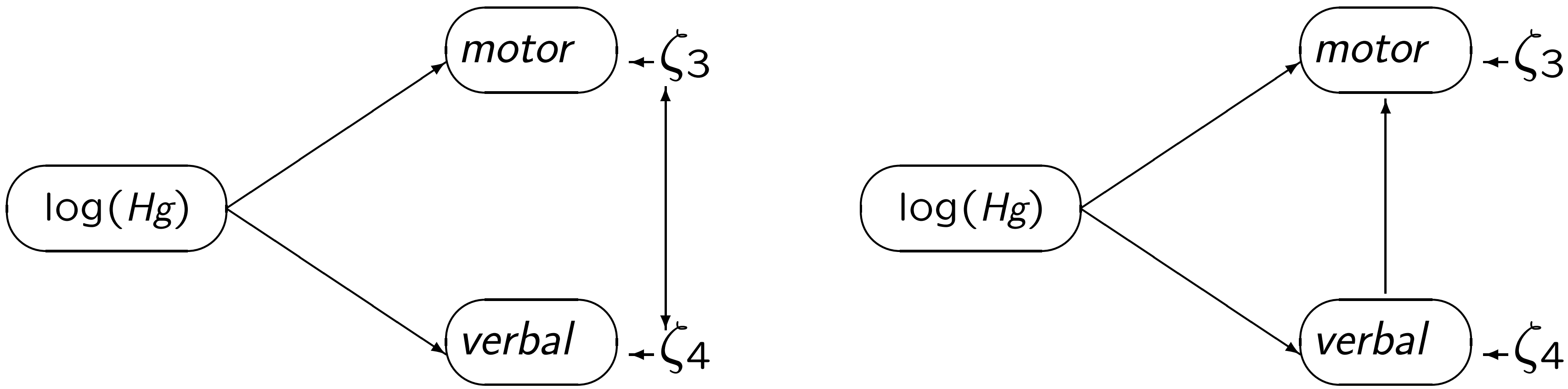
	β	p
Motor Function	-1.03	0.034
Verbal Function	-1.62	0.002

Reference indicators Hg: cord blood, Motor: FT1, Verbal: BNT2.

Selected multiple regression results

	Cord Blood Hg	
Response	β	p
NES2 Finger tapping		
Preferred hand (FT1)	-1.01	0.08
Boston Naming Test		
With cues (BNT2)	-1.70	0.001

Models for multiple outcomes



$$\textit{motor} = \alpha_3 + \beta_{31}\log(Hg) + \gamma_3^t Z + \zeta_3$$
$$\textit{verbal} = \alpha_4 + \beta_{41}\log(Hg) + \gamma_4^t Z + \zeta_4$$

β_{31} : mercury effect given covariates

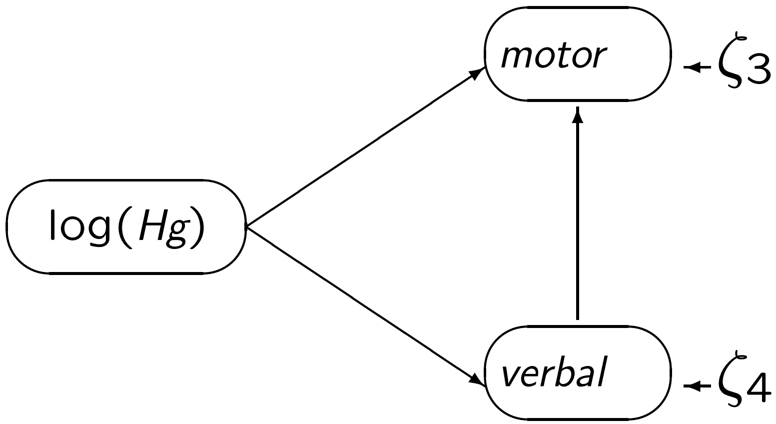
$\widehat{\beta}_{31} = -1.032$, $p < 5\%$

$$\textit{motor} = \alpha_3 + \beta_{31}\log(Hg) + \beta_{34}\textit{verbal} + \gamma_3^t Z + \zeta_3$$
$$\textit{verbal} = \alpha_4 + \beta_{41}\log(Hg) + \gamma_4^t Z + \zeta_4$$
$$cov(\zeta_3, \zeta_4) = 0$$

β_{31} : mercury effect given covariates AND verbal level

$\widehat{\beta}_{31} = -0.765$, $p > 5\%$

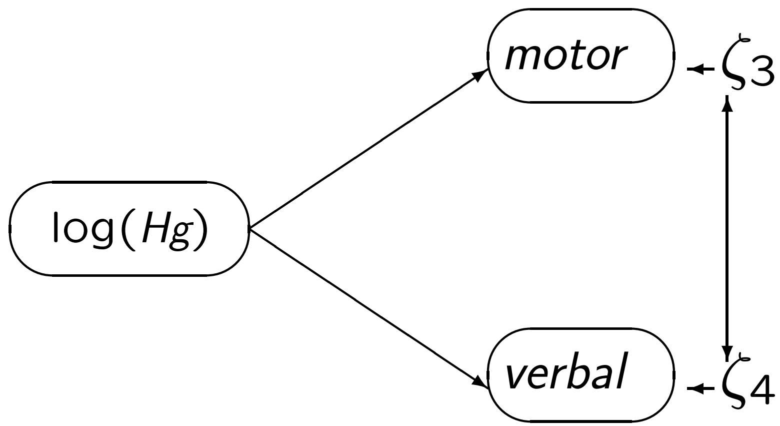
Direct and indirect effects



$$\textit{motor} = \alpha_3 + \beta_{31}\log(Hg) + \beta_{34}\textit{verbal} + \gamma_3^t Z + \zeta_3$$
$$\textit{verbal} = \alpha_4 + \beta_{41}\log(Hg) + \gamma_4^t Z + \zeta_4$$

Direct effect of log(Hg) on motor	=	β_{31}	=	-0.765
Indirect effect of log(Hg) on motor	=	$\beta_{34}\beta_{41}$	=	-0.267
Total effect of log(Hg) on motor	=	$\beta_{31} + \beta_{34}\beta_{41}$	=	-1.03

Modeling strategy



Mercury effects can be estimated in a 'verbal' and a 'motor' model respectively. Why should I build a joint model?

Effect estimation may be improved especially if some variables have missing values.

Missing data analysis

Complete case analysis: not efficient but consistent if data are missing completely at random.

Missing data indicator: $r_{i,j} = 1$ if $y_{i,j}$ observed, $r_{i,j} = 0$ otherwise

Dependent variables y_i separated into $y_i = (y_i^{obs}, y_i^{mis})$

Missing completely at random: $r_i \perp (y_i, z_i)$

Missing at random (MAR): $r_i \perp y_i^{mis} | y_i^{obs}, z_i$

Non ignorable missingness: r_i and y_i^{mis} dependent given y_i^{obs}, z_i

Missing data analysis, Likelihood methods

Observed data (r, y^{obs}, z)

Likelihood function under MAR ($r \perp y^{mis} | y^{obs}, z$):

$$\begin{aligned} L(r, y^{obs}|z, \theta, \psi) &= \int p_{\psi,\theta}(r, y^{obs}, y^{miss}|z)\, dy^{mis} \\ &= \int p_{\psi}(r|y^{obs}, y^{mis}, z)\, p_{\theta}(y^{obs}, y^{miss}|z)\, dy^{mis} \\ &= p_{\psi}(r|y^{obs}, z) \int p_{\theta}(y^{obs}, y^{mis}|z)\, dy^{mis} \end{aligned}$$

ML inference for θ can be based solely on

$$\int p_{\theta}(y^{obs}, y^{mis}|z)\, dy^{mis}$$

Consequences of confounder error

Regression model: $Y = \beta_0 + \beta_x X + \beta_z Z + \epsilon$, Error model: $V = Z + U$

Naive analysis: replace Z by V

$$\widehat{\beta}_x \rightarrow \beta_x + \beta_z \, \alpha_x \, var(U)/[var(U) + \{1 - corr(X,Z)^2\}var(Z)]$$

where $\alpha_x = cov(X,Z)/var(X)$

Sign of bias depends on the effect of Z and X-Z relationship.

Bias is stronger for increased imprecision $[var(U)]$, stronger X-Z relationship $[\alpha_x, corr(X,Z)]$ and stronger effect of confounder $[\beta_z]$.

Risks and benefits from seafood intake

Special case: X=log(Hg), Z=nutrients from fish, V=number of fish dinners

Here: $\beta_z > 0$ and $\alpha_x > 0$

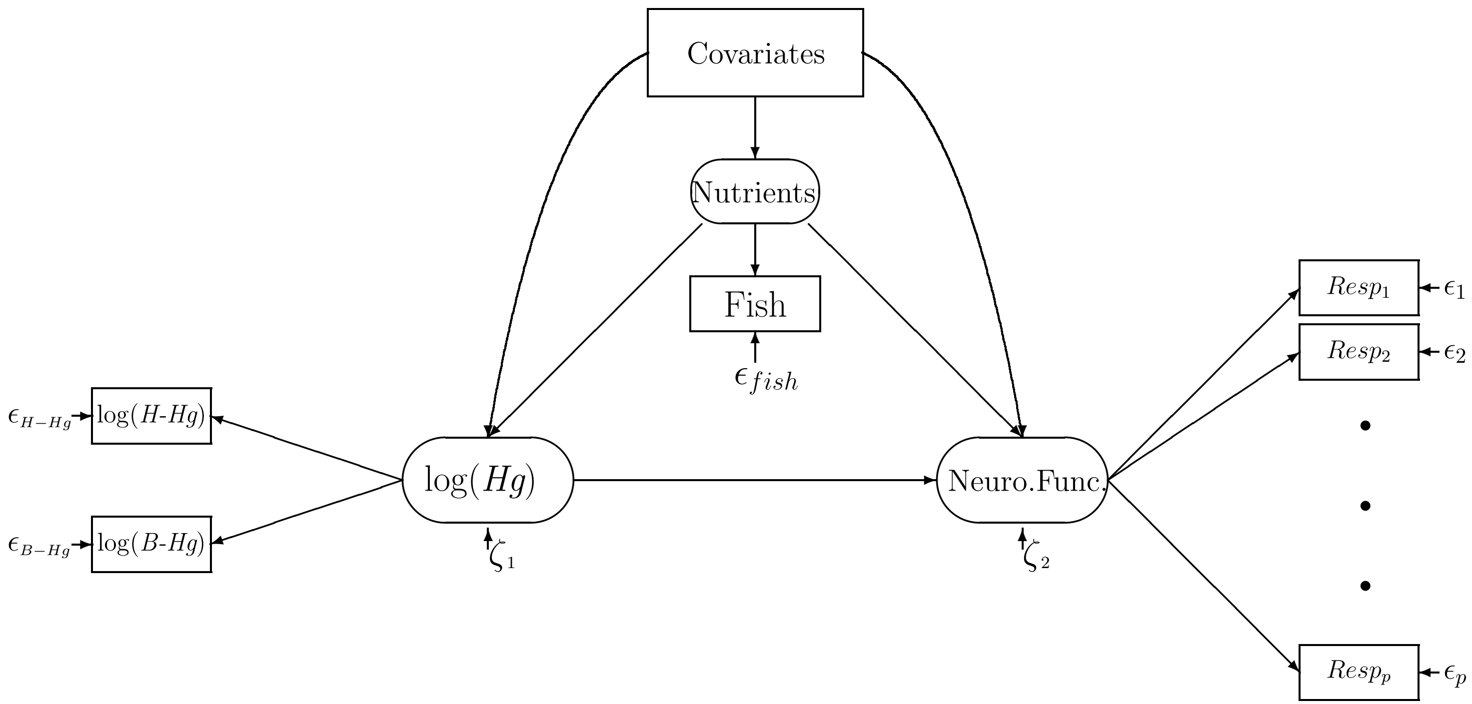
Remember: $\widehat{\beta}_x \rightarrow \beta_x + \beta_z\,\alpha_x\,var(U)/[var(U) + \{1 - corr(X,Z)^2\}var(Z)]$

Therefore: $\widehat{\beta}_x \rightarrow \beta_x^* > \beta_x$

Failure to adjust for fish error introduces bias in estimated mercury effect. *Adverse mercury effect is underestimated.*

Error variance unknown. Multiple indicators not available. Instead the error variance was fixed at a wide range of values.

SEM: mercury and nutrients from seafood intake



Results

Table 2. Mercury effects on neurobehavioral tests at ages 7 and 14 years, as determined in structural equation analysis with covariate adjustment that includes maternal fish intake during pregnancy at different levels of precision (indicated by the reliability ratio).

Precision of fish nutrient intake	Age 7 years		Age 14 years			
	Motor function		Motor function		Spatial function	
	Mercury effect[a]	*P*	Mercury effect	*P*	Mercury effect	*P*
100%	-12.2	0.0092	-9.37	0.0082	1.04	0.78
68%	-13.7	0.0048	-10.7	0.0036	0.088	0.96
43%	-17.0	0.0017	-13.6	0.0009	-1.57	0.73
27%	-23.7	0.0006	-20.1	0.0003	-4.18	0.51

[a] Effect of true exposure doubling expressed in % of s.d. of latent response

Interactions in SEMs

- *Between covariates:* Include product terms between covariates

- *Between latent variables:*

  $$\eta_3 = \beta_1 \cdot \eta_1 + \beta_2 \cdot \eta_2 + \beta_3 \cdot \eta_1 \cdot \eta_2 + \zeta_3$$

  Model is not linear in variables. Non-linear SEMs not available in standard software.

- *Between categorical covariates and latent variables:*

  Special case of *multiple group analysis*.

Extensions: Multiple group analysis

$z_i = (z_{i1}, \ldots, z_{iq})^t$: independent variables of subject i.
$y_i = (y_{i1}, \ldots, y_{ip})^t$: dependent variables of subject i.

Parameters may depend on a group variable $g = 1, ..., G$

<u>The measurement part:</u>

$$y_i = \nu^g + \Lambda^g \eta_i + K^g z_i + \epsilon_i$$

$\epsilon_i \sim N(0, \Omega^g)$

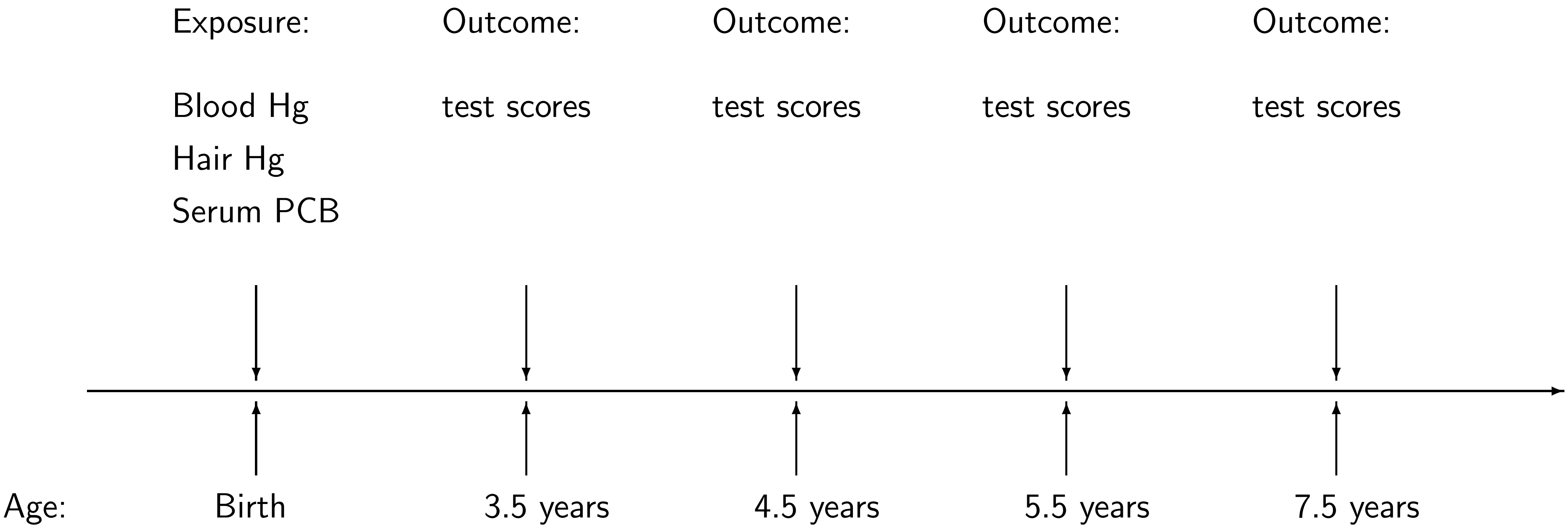
<u>The structural part:</u>

$$\eta_i = \alpha^g + B^g \eta_i + \Gamma^g z_i + \zeta_i$$

$\zeta_i \sim N(0, \Psi^g)$

Muthén, 1984

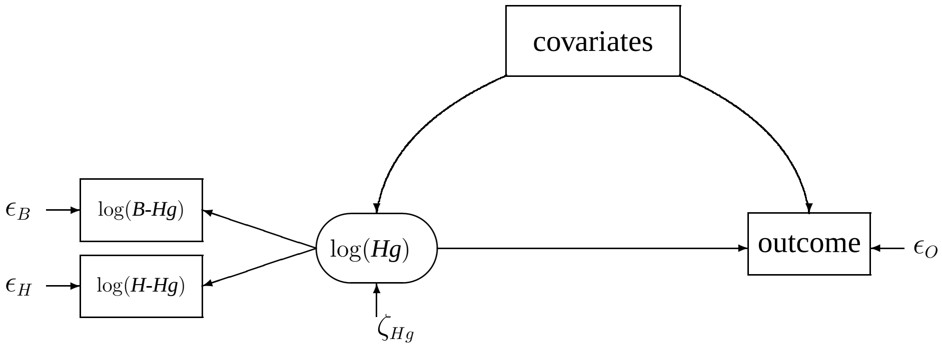
The Faroese Cohort 2



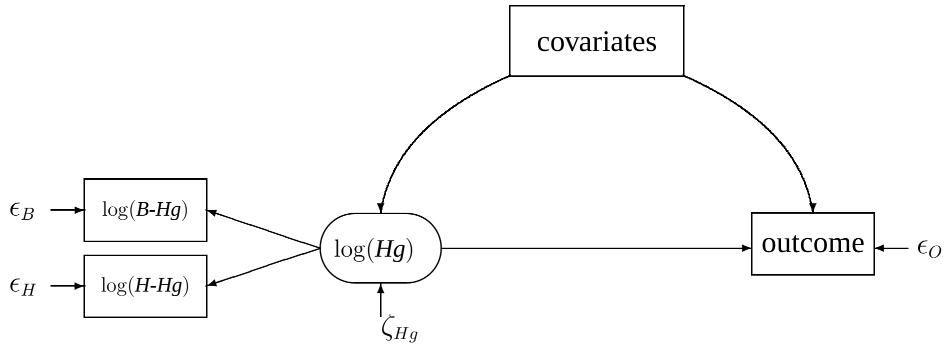
Number of children: 182

Multiple group: Faroese data

Cohort 1



Cohort 2



Path diagram showing the model fitted in each cohort. Mercury concentrations in cord blood (*B-Hg*) and hair (*H-Hg*) are indicators of true exposure (*Hg*). The outcome may be affected by the true exposure and covariates.

Effects of mercury exposure in two cohorts

	Cohort 1		Cohort 2		Test for	Cohort 1 & 2	
Outcome	β	95%-conf.	β	95%-conf.	equality	β	p
Boston Naming Test							
No cues	-2.06	-3.12; -0.99	-1.89	-4.32; 0.53	0.91	-2.03	$<$0.001
Cues	-2.18	-3.23; -1.12	-1.88	-4.26; 0.49	0.82	-2.13	$<$0.001
Wechsler Int. Scale							
Similarities	0.087	-0.75; 0.93	-0.568	-1.71; 0.57	0.37	-0.143	0.68
California Verb. Learn.							
Learning	-1.30	-3.10; 0.502	1.12	-3.15; 5.39	0.31	-0.935	0.27
Short-term repro.	-0.573	-1.10; -0.04	-0.241	-1.62; 1.14	0.66	-0.530	0.036
Long-term repro.	-0.613	-1.21; -0.02	-0.011	-1.31 ; 1.29	0.41	-0.509	0.066
Recognition	-0.234	-0.68; 0.21	0.765	-0.27; 1.80	0.083	-0.083	0.69

Estimated effect of 10 fold increase in prenatal exposure to mercury

Categorical response variables

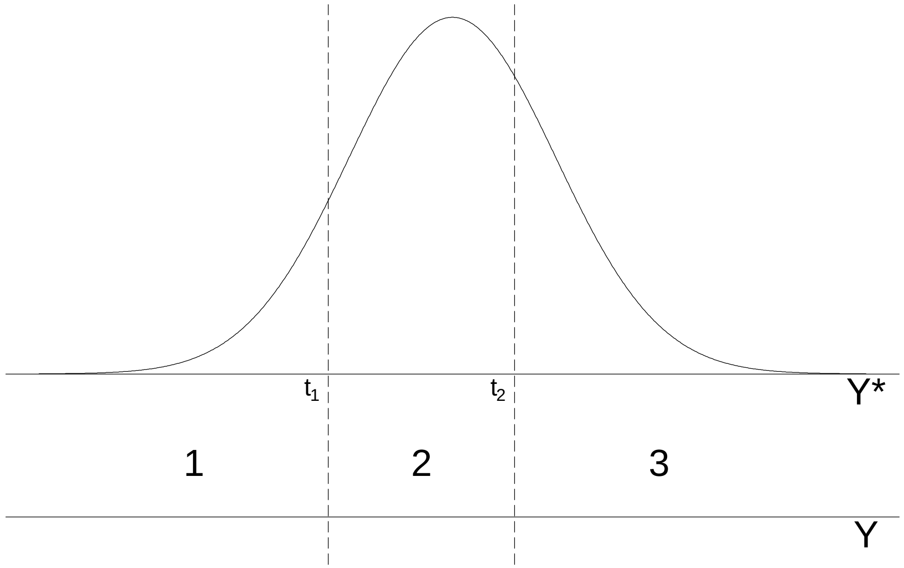
- Dichotomous — two categories:
  - live / dead

- Nominal — more categories:
  - blue / brown / gray / green

- Ordinal — ordered categories:
  - low $<$ medium $<$ high

Threshold model

Ordinal response: assume an underlying continuous variable



$$y = k \Leftrightarrow t_{k-1} < y^* < t_k$$

Thresholds (t): unknown parameters.

Extended model: inclusion of ordinal responses

$z_i = (z_{i1}, \ldots, z_{iq})^t$: covariates, $y_i = (y_{i1}, \ldots, y_{ip})^t$: responses

$y_i^* = (y_{i1}^*, \ldots, y_{ip}^*)^t$: (latent) continuous responses of subject i

- y_{ij} continuous: $y_{ij}^* = y_{ij}$
- y_{ij} ordinal: threshold model for $y_{ij}^* - y_{ij}$ relation

The measurement part:

$$y_i^* = \nu + \Lambda\eta_i + \epsilon_i$$

$\epsilon_i \sim N(0, \Omega)$

The structural part:

$$\eta_i = \alpha + B\eta_i + \Gamma z_i + \zeta_i$$

$\zeta_i \sim N(0, \Psi)$

Muthén, 1984

Software

Many possibilities!

- *Easy programming, sophisticated models, expensive software*

  Mplus and LISREL

- *Complex programming, un-sophisticated models, inexpensive software*

  R (sem)

- *Complex programming, un-sophisticated models, expensive software*

  SAS (proc calis)

Structural equation models in epidemiology

- allow effect parameters to be interpreted as regression coefficients
- allow for measurement error
  - in exposure
  - in confounders
- reduce dimensionality
- gain power
- allow missing data ML analysis

Important extensions

- **Assumption of conditional multivariate normality:** robust estimation methods that require only mean and variance to be correctly specified are available.

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- **Non-linear SEMs:** e.g. $\eta_2 = \alpha + \beta \cdot \exp(\eta_1) + \zeta$
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- **Generalized latent variable modeling**: Multilevel, Longitudinal and structural equation models.

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