Meta-analysis of individual participant data from observational studies

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2. Epidemiological associations

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Challenges in meta-analysis of **published** observational studies

- Publication bias
  - since analysing associations is quick and easy, many probably don't get reported
- Searching for studies
  - not so much standard vocabulary (i.e. as for randomized trials)
- Variation in exposure measurement and outcome assessment
- Variation in analysis and reporting
- Dealing with adjustments for different covariates

Advantages of individual participant data (IPD) meta-analysis

- Harmonisation of exposures and outcomes
- Updated follow-up information
- Reduction of publication and reporting biases

- Consistent analyses, e.g. adjustment for confounders
- Exploration of heterogeneity, e.g. resolve controversy
- Investigation of interactions (joint effects)
- Allowance for measurement error, using serial measurements of risk factors

- Increasingly common
- Provides reliable evidence-base

Emerging Risk Factors Collaboration (ERFC)

Individual data collated from observational prospective epidemiological studies in Western populations

120 studies, 1.2m participants, 10 years average follow-up, 70,000 CVD events

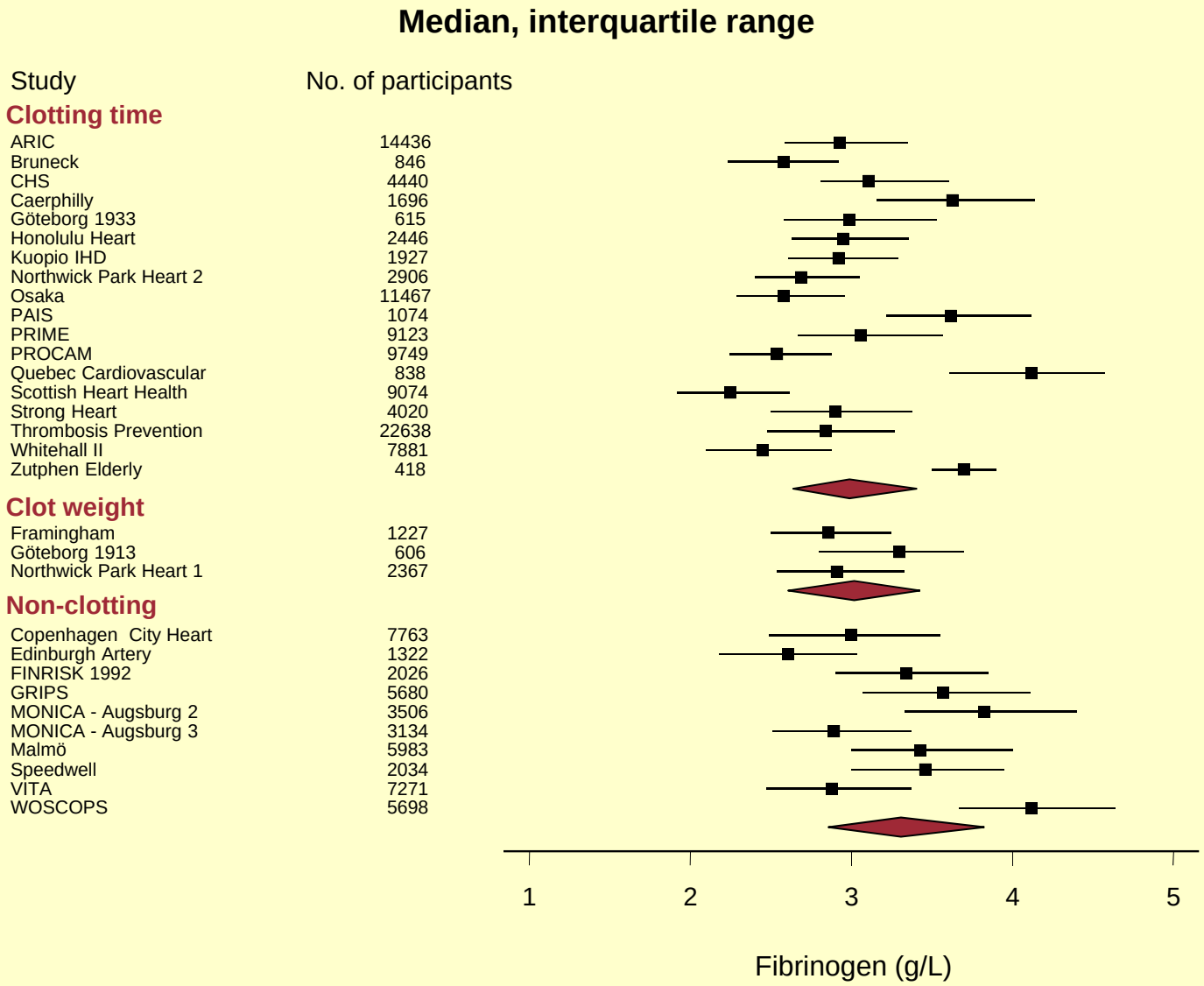
Subsets available for specific risk factors

e.g. fibrinogen, related to inflammation and blood coagulation, 31 studies, 7000 CHD events

Purpose

To provide estimates of the associations of novel (or under-investigated) risk factors with CVD, which are reliable and detailed

Heterogeneity of fibrinogen across studies



Principal method of analysis

Cox proportional hazards regression

- separately in each study
- stratified by sex
- adjusted for entry age

In each study:

$$\log(h_{ski}(t \mid E_{si}, \boldsymbol{X}_{si})) = \log(h_{0sk}(t)) + \beta_s E_{si} + \boldsymbol{\gamma}_s \boldsymbol{X}_{si}$$

for each study $s = 1,\ldots,S$, with strata $k = 1,2$, and individuals $i = 1,\ldots,n_s$ with exposure of interest E_{si} and other covariates $\boldsymbol{X}_{si}$

Random effects meta-analysis

$$\hat{\beta}_s = \beta_s + \varepsilon_s;\ \text{where}\ \ \varepsilon_s \sim N(0, v_s)$$

$$\beta_s = \beta + \eta_s;\ \text{where}\ \ \eta_s \sim N(0, \tau^2)$$

This is a 2-step method

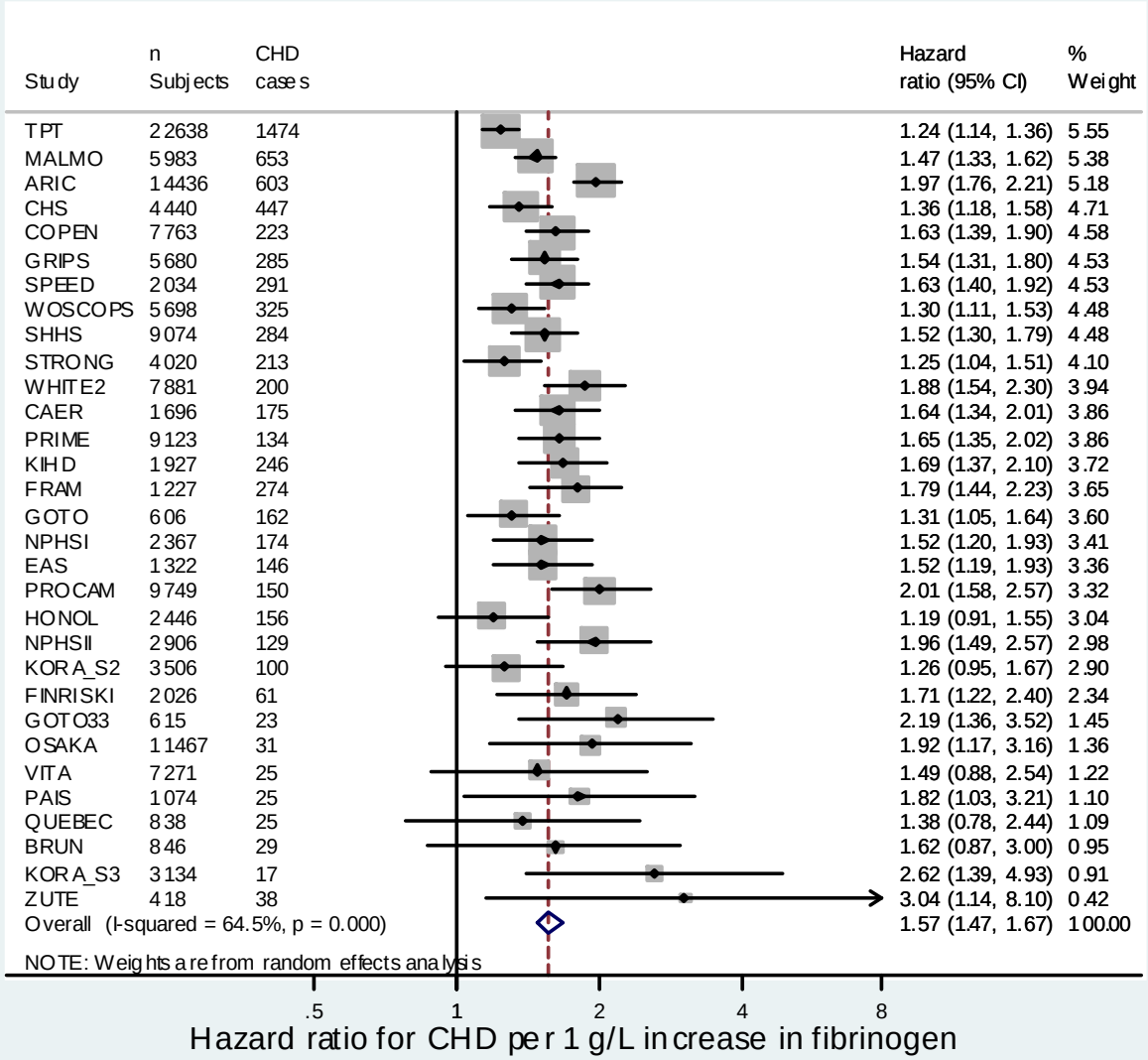
1-step method possible only in principle:

$$\log(h_{ski}(t \mid E_{si}, \boldsymbol{X}_{si})) = \log(h_{0sk}(t)) + \beta_s E_{si} + \boldsymbol{\gamma}_s \boldsymbol{X}_{si}$$

$$\beta_s = \beta + \eta_s;\ \text{where}\ \ \eta_s \sim N(0, \tau^2)$$

Provides a summary of within-study associations

Hazard ratios of CHD per 1 g/L fibrinogen increase, adjusted for age and sex



Fibrinogen Studies Collaboration, JAMA 2005

Log hazard ratios of CHD per 1 g/L increase in fibrinogen

Meta-analysis	Log hazard ratio (SE)	τ	I^2
Random effects	0.450 (0.033)	0.134	64%
Common effect	0.419 (0.018)	-	-

Hazard ratios from RE meta-analysis

Overall 1.57 (95% CI 1.47 to 1.67)

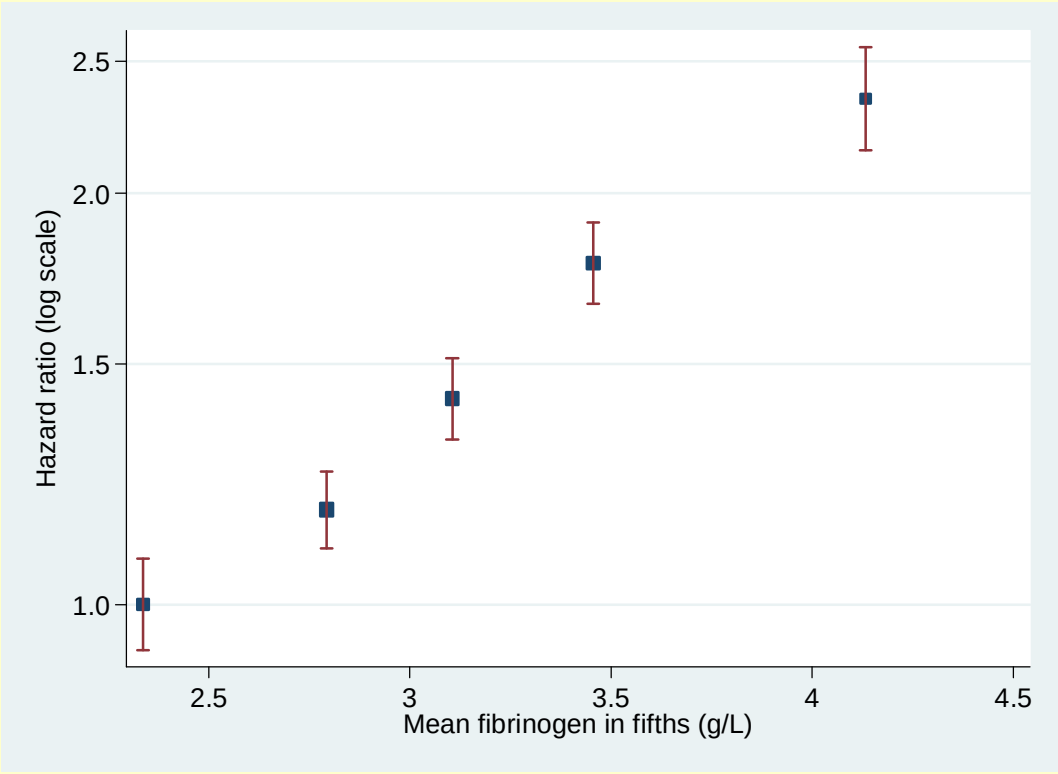
Predictive interval based on t_{S-2} distribution:

(95% range 1.18 to 2.08)

Is the risk relationship linear?

Visual approach

- Divide fibrinogen into study-specific fifths
- Estimate log hazard ratios in each fifth in each study
- Combine these using multivariate RE meta-analysis
- Plot these against the mean fibrinogen level in each fifth



Analytical options

- Quadratic term
- Fractional polynomials
- Allowance for measurement error

Choice of exposure scale

Does the log hazard ratio increase:

- Linearly with fibrinogen?
- Linearly with log fibrinogen?
- Linearly with study-specific SD score fibrinogen?

	Log hazard ratios per SD increase (SE)	I^2
Untransformed fibrinogen	0.294 (0.022)	64%
Log fibrinogen	0.325 (0.025)	65%
Study-specific SD score fibrinogen	0.292 (0.021)	63%

Covariate adjustment

$$\log(h_{ski}(t \mid E_{si}, \boldsymbol{X}_{si})) = \log(h_{0sk}(t)) + \beta_s E_{si} + \boldsymbol{\gamma}_s \boldsymbol{X}_{si}$$

The confounding effects $\boldsymbol{\gamma}_s$ are different in each study (2-step meta-analysis)

Alternatives:

$\gamma_s = \gamma$ unrealistic

$\gamma_s \sim N(\gamma, \sigma_\gamma^2)$ unnecessary

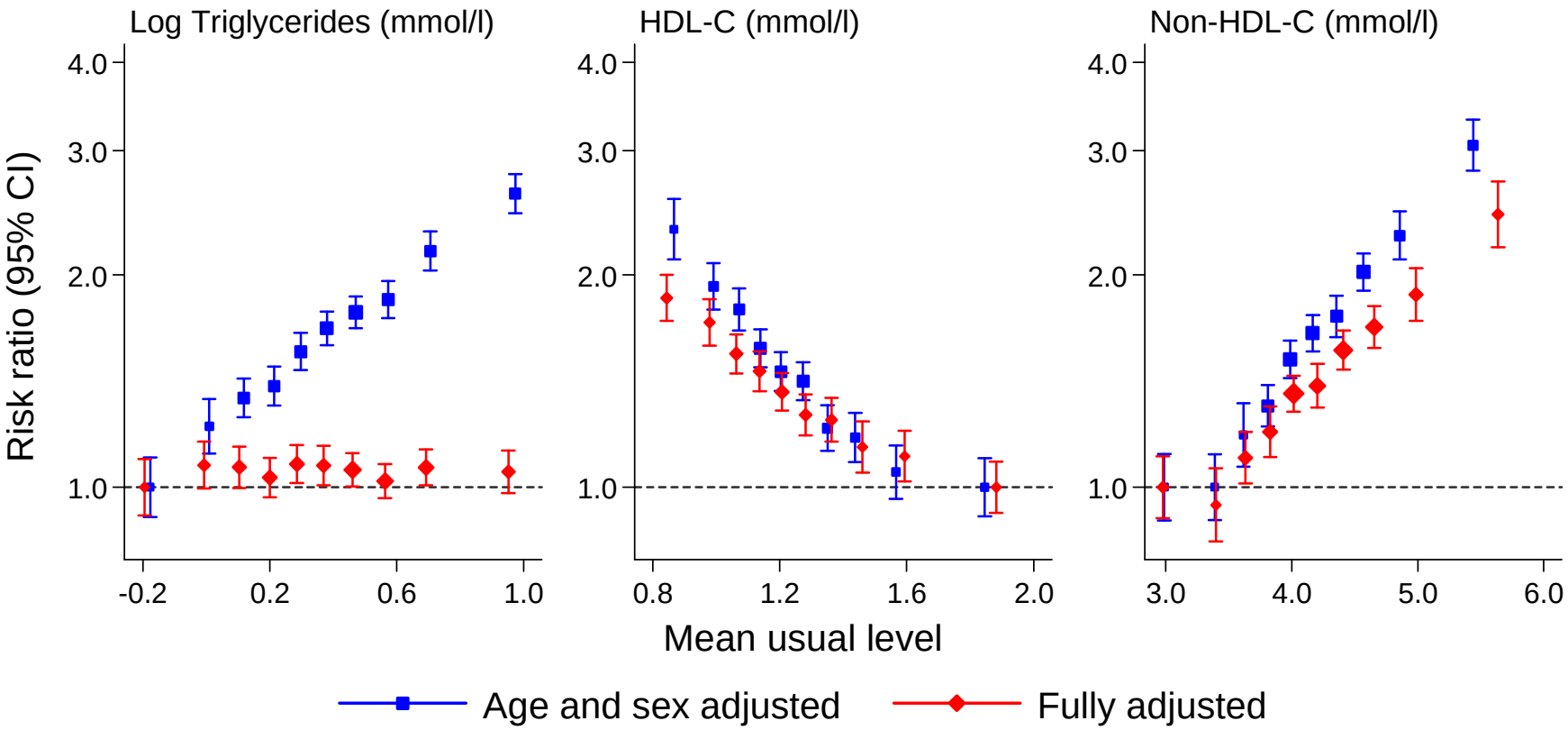
Overall log hazard ratios of CHD per 1 g/L increase in fibrinogen: **Adjusted for covariates**

	Adjustment	
	Age	Age, smoking, chol, SBP, BMI
Overall log HR	0.450	0.320
(SE)	(0.033)	(0.026)
I^2 heterogeneity	64%	35%
(95% CI)	(48 to 76%)	(0 to 58%)

BUT residual confounding from other covariates remains

Usefulness of consistent adjustment for confounders (Lipids)

Associations with CHD (68 studies, 302,430 participants, 12,785 CHD cases)



Fully adjusted: Age, sex, smoking, systolic BP, BMI, diabetes, log TG, HDL, non-HDL

Emerging Risk Factors Collab, JAMA 2009

Confounders missing in some studies

Hazard ratios of CHD per 1 g/L increase in fibrinogen

Adjustment	31 studies (n = 150,000)	14 studies (n = 72,000)
(1) Age	1.57	1.61
(2) + smok, chol, SBP, BMI	1.38	1.44
(3) + HDL, LDL, alcohol, TG, diabetes	–	1.35

Bivariate random effects MA of (2) and (3) to 'fill in the gap':

Hazard ratio 1.30 (95% CI 1.23 to 1.36)

Jackson et al, Stat Med 2009

Interactions / joint effects / subgroups

Does the relationship of fibrinogen with risk:

- vary with age or level of BMI?
- depend on how fibrinogen is measured?
- differ between men and women?

(1) Individual level variables

e.g. Does the association of fibrinogen (*E*) with risk vary with the level of BMI (*X*)?

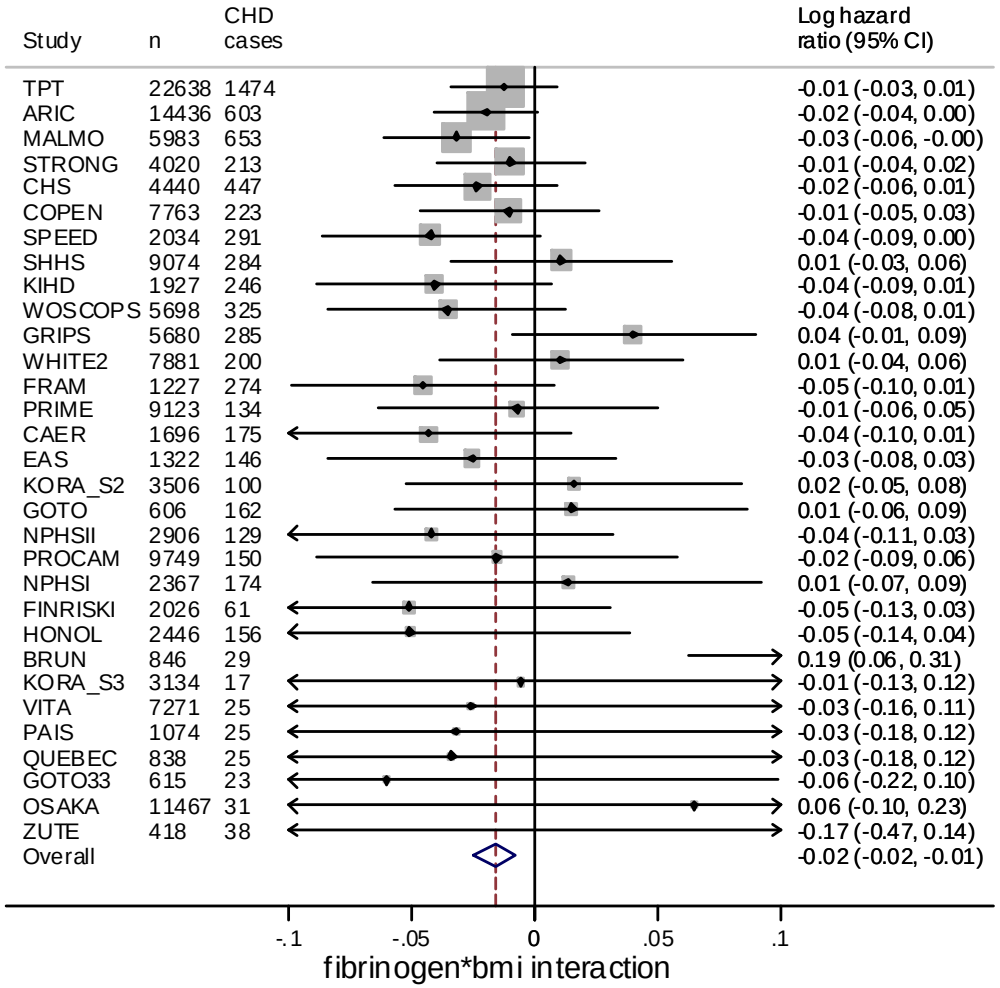
$$\log(h_{ski}(t \mid E_{si}, X_{si})) = \log(h_{0sk}(t)) + \beta_s E_{si} + \gamma_s X_{si} + \delta_s E_{si} X_{si}$$

$$\delta_s = \delta_W + \eta_s; \text{ where } \eta_s \sim N(0, \tau^2)$$

Summarises the within-study information on interaction

Expresses change in [log hazard ratio of CHD per 1 g/L increase in fibrinogen] per 1 kg/m^2 increase in BMI

Within-study fibrinogen / BMI interaction



(2) Study level variables

e.g. Does the association of fibrinogen (*E*) with risk vary with the assay method (*Z*)?

Comparison between studies

Random effects meta-regression

Limited by number of studies

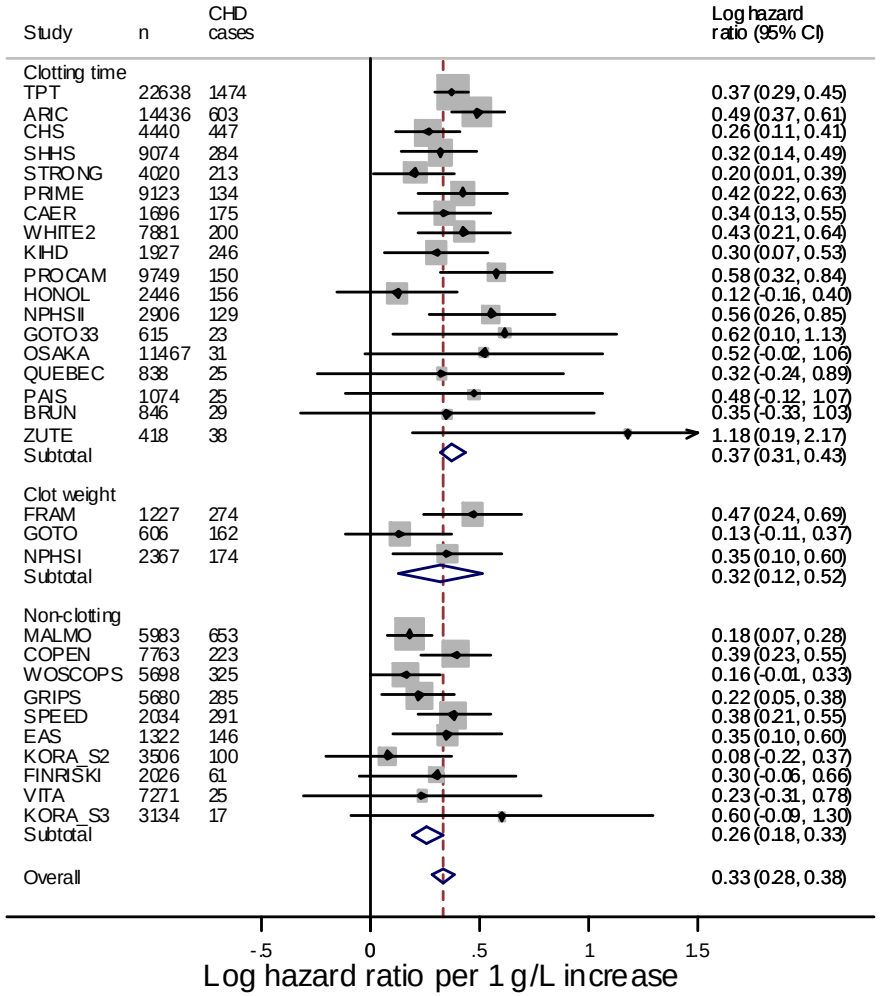
Susceptible to between-study confounding

$$\log(h_{ski}(t \mid E_{si}, \boldsymbol{X}_{si})) = \log(h_{0sk}(t)) + \beta_s E_{si} + \boldsymbol{\gamma}_s \boldsymbol{X}_{si}$$

$$\beta_s = \beta + \delta_B Z_s + \eta_s; \text{ where } \eta_s \sim N(0, \tau^2)$$

δ_B is based on between-study information only

Study-specific log hazard ratios by assay method

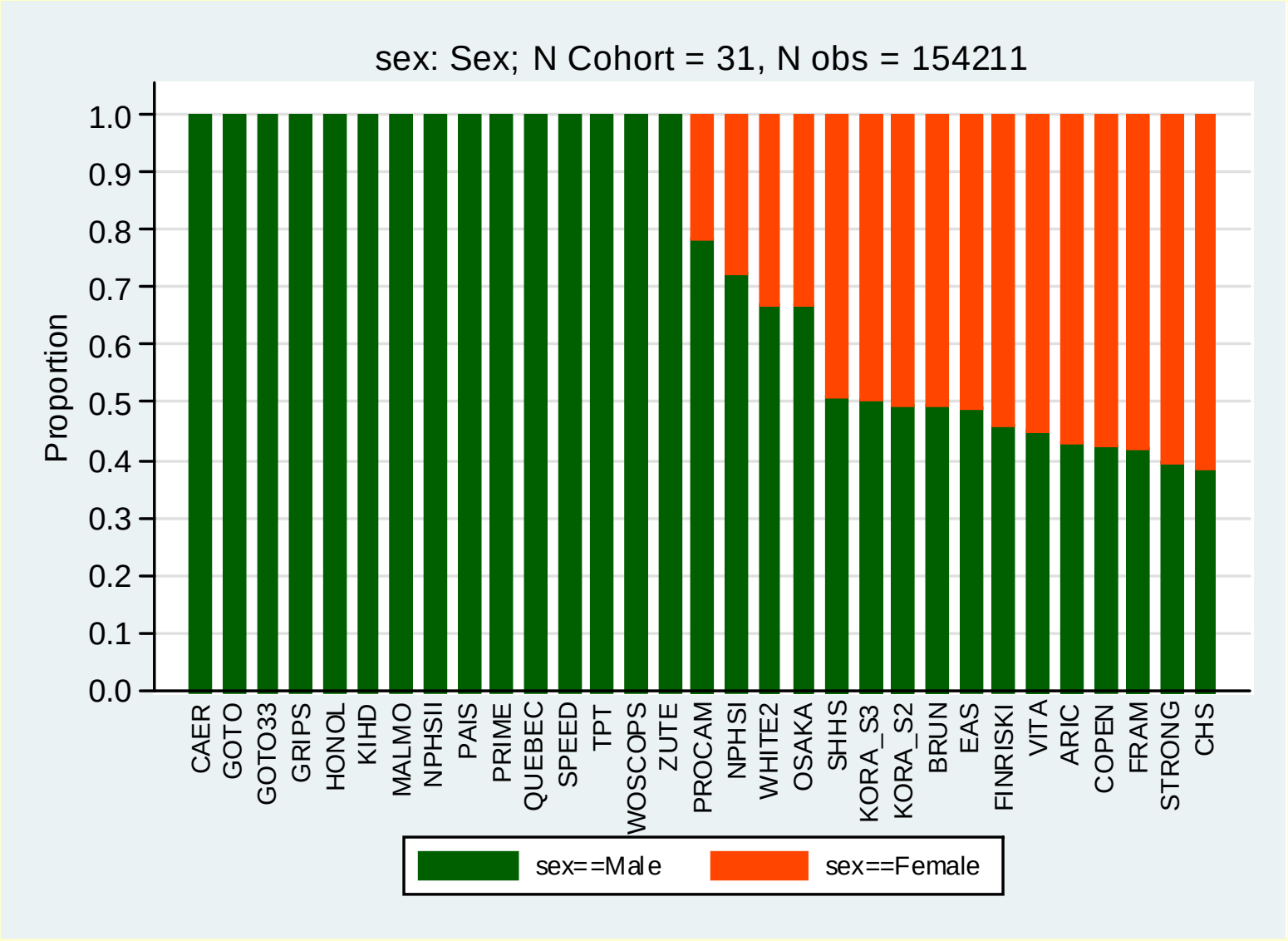


Fibrinogen – CHD association by assay method

*Potential effect modifier**	*n*	*n*	*Estimate*	χ^2 *test*	
	cohorts	*subjects*	*β (SE)*	χ^2 *(df)*	*p*
Assay methods				10 (2)	0.006
Clotting time	18	105594	0.373 (0.030)		
Clot weight	3	4200	0.319 (0.102)		
Non-clotting	10	44417	0.257 (0.037)		

*Adjusted for age, smoking, total cholesterol, systolic BP, and body mass index

(3) Mixed variables



Interaction with sex

(a) Within-study information (δ_W)

Pooling interaction terms as before

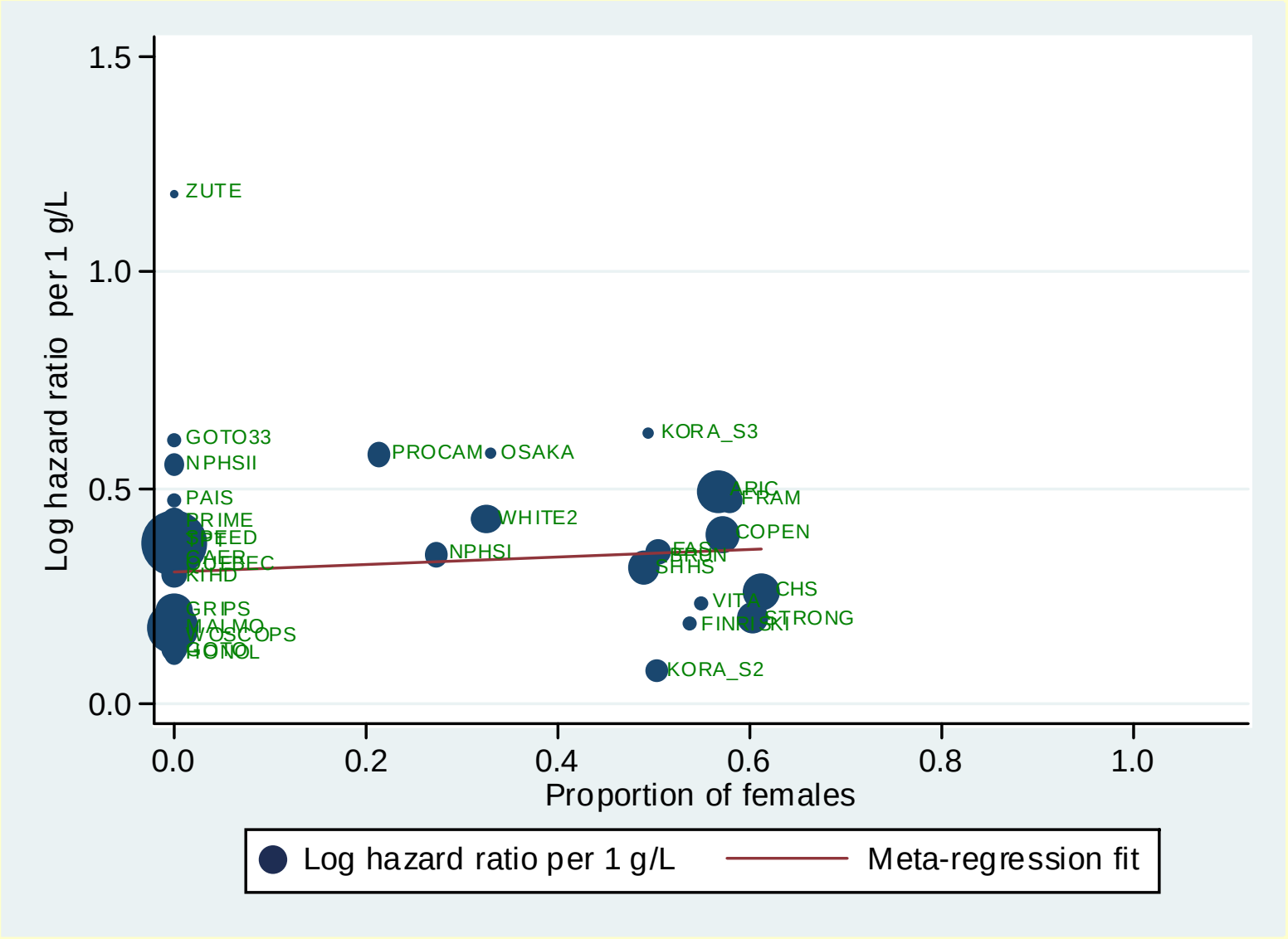
All-male / all-female studies do not contribute

(b) Between-study information (δ_B)

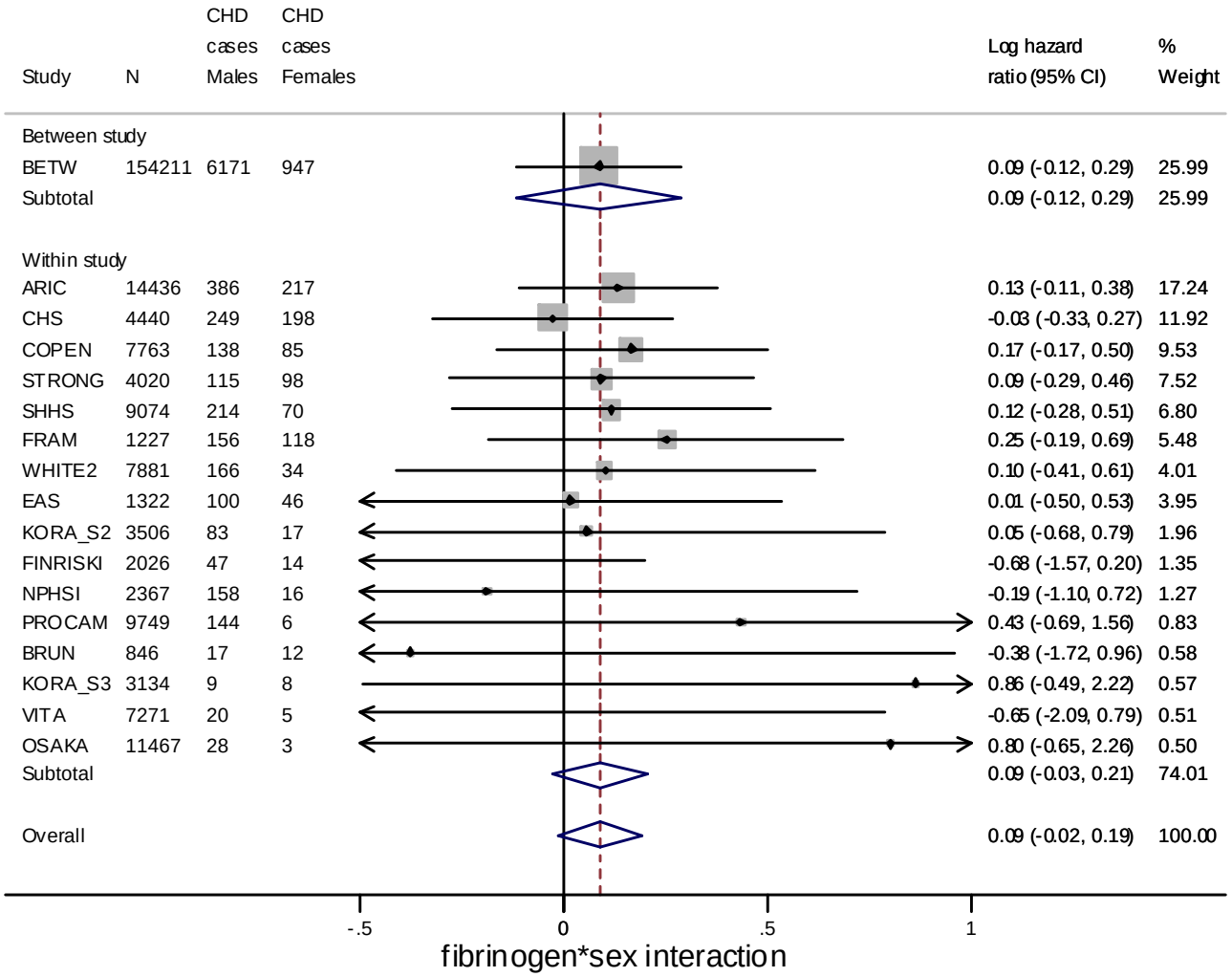
Meta-regression on proportion of women in each study

All studies contribute

Between-study fibrinogen / sex interaction



Fibrinogen / sex interaction



Some comments

Usually ignore between-study information when there is lots of within-study information (e.g. continuous variables)

Inspecting weight given to information within and between studies is useful

In principle, within and between study components of interaction can be estimated in one model, by including the terms:

$$\delta_s E_{si}(X_{si} - \overline{X}_s) + \delta_B E_{si}\overline{X}_s$$

$$\delta_s = \delta_W + \eta_s;\ \text{where}\ \eta_s \sim N(0, \tau^2)$$

Assessing proportional hazards

Non-proportional hazards can be considered simply as an interaction with time, based on within-study information alone.

Each study estimates this interaction term, a non-PH parameter:

$$\log(h_{ski}(t \mid E_{si}, X_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \xi_s t E_{si}$$

Fibrinogen and CHD risk

Summed chi-squared statistics of each non-PH parameter = 24 (df 31)

Random effects meta-analysis of study-specific non-PH parameters:
Estimate 0.0016 per year (SE 0.0045), chi-squared = 0.12 (df 1)

Related topics

Adjusting for 'measurement error' = within-person variability + laboratory error

- in exposure (Wood et al, IJE 2006)
- in confounders (Wood et al, Stat Med 2009)

How much do risk factors improve risk prediction?

- Part 3

Are risk factors associations causal?

- Part 4