Large-scale meta-analysis of individual participant data: methods and challenges.

The Emerging Risk Factors Collaboration (ERFC)

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Outline

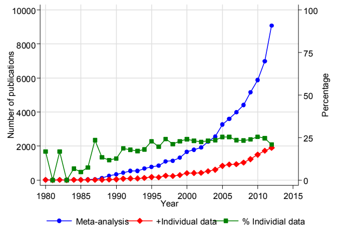
- Meta-analysis
  - What, why, and how in general?
- Overview of IPD methods.
  - The Emerging Risk Factors Collaboration (ERFC).
- Examples of approaches to meta-analysis of:
  - Shape of dose-response relationships and specificity.
  - Adjusted main effects with correction for regression dilution.
  - Interactions (separating within vs between-study components).
  - Potential public health impact.
  - Risk prediction measures.
- Remarks
  - Stata programs made available for IPD meta-analysis.

Background

- An increasing number of molecular and genetic markers are being proposed as important predictors and/or causes of chronic diseases such as cardiovascular disease (CVD).
- Trend accelerated by the advent of technologies that enable rapid measurement of large numbers of blood proteins or genes.
- Reliable demonstration that a particular marker is relevant to CVD may have important implications for prediction and prevention (e.g. blood cholesterol).
- Meta-analysis i.e. "use of statistical methods to combine results from individual studies" should help improve statistical power to detect important associations and other features.

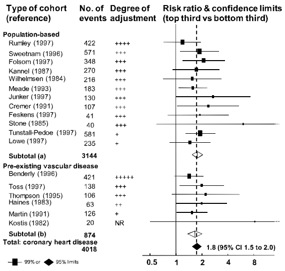
Meta-analysis

- Use of meta-analysis has been growing in recent decades.
  - Literature-based meta-analysis.
  - Individual participant data (IPD) meta-analysis.



Literature-based meta-analysis

Prospective studies of fibrinogen and coronary heart disease by 1998



Danesh et al, JAMA 1998

Limitations:

- Heterogeneity
  - Non-standardized definition of outcomes.
  - Inconsistent adjustment for confounding.
- Inability to assess shape of association.
- Impossible to assess effect modification by individual level characteristics.
- Associations not corrected for measurement error.

Solution:

- Large-scale meta-analysis using individual participant data (IPD).

Why IPD meta-analysis?

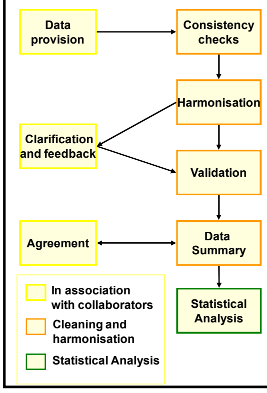
- Enables better standardised and more detailed analysis.
  - Standardised definition of outcomes and coding of variables.
- Improved power to assess dose-response relationships.
- Consistent adjustment for confounding across studies.
- Ability to correct estimates for regression dilution bias.
- Improved power to consistently assess subgroup effects.
- Evaluation of the utility of markers for risk prediction.

The Emerging Risk Factors Collaboration (ERFC)

- A collation of IPD from 2.2 million participants in 143 prospective studies of cardiovascular disease (CVD) outcomes and cause-specific mortality.

- Aim: To quantify in detail the associations between established and emerging risk factors with CVD outcomes and cause-specific mortality, and to assess improvements in risk prediction.
  - Lipids and lipid-related markers (triglycerides, cholesterol, lipoprotein(a), apolipoproteins). JAMA 2009, JAMA 2012.
  - Inflammation markers (C-reactive protein, fibrinogen, leukocyte count, albumin). JAMA 2005, Lancet 2010, NEJM 2012.
  - Glycaemia markers (glucose, HbA1c) Lancet 2010.
  - Adiposity (BMI, waist, hip, waist:hip ratio). Lancet 2011.

ERFC data collation process



- Population-based prospective studies identified by literature searches/ discussion with investigators.
- Invited to contribute IPD data on vascular/non-vascular outcomes and key exposure/confounding variables.
- Data checked for consistency and queries referred back to investigators.
- Harmonised data merged into one dataset for analysis.

Study designs and methods in general

- Majority (>90%) are prospective cohort studies; a few clinical trials (mostly placebo arms); a few nested case-control studies for some novel markers; and one or two case-cohort studies.

- Principal analysis by 2-stage approach, first deriving study-specific estimates and then pooling by random effect meta-analysis.
  - Cox regression stratified by sex for cohort and clinical trials.
  - Conditional logistic regression for nested case-control studies.
  - Weighted Cox regression for case-cohort studies.

- Sensitivity analysis using fixed effect meta-analysis or 1-stage approach (i.e. stratified Cox model).e.g. for rare outcomes.

Univariate meta-analysis (stage 1)

- In cohort studies, Cox-proportional hazards models fitted to each study.

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

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

- For most studies $K_s = 1$ *or* 2, representing sex and in a few $K_s > 2$ in the presence of trial arm.

Univariate meta-analysis (stage 2)

- β_s = log hazard ratio per unit higher exposure in study *s*, adjusted for the confounding effects of the covariates $\boldsymbol{X}_{si.}$

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

- β = average log hazard ratio, combining the within-study associations, while allowing for heterogeneity between studies (i.e. $\tau^2>0$).
  - DerSimonian & Laird moment estimator of τ^2 is used, and the impact of heterogeneity is quantified using I^2 statistic.

- Stata program --metan-- for univariate meta-analysis.

Multivariate meta-analysis

- At times interest is on meta-analysis of multiple correlated parameters, such as contrasts for categorical exposures, in which case multivariate meta-analysis is appropriate.

- Where now, $\boldsymbol{\beta}_s$ is a vector of log hazard ratios in study *s* with known within study covariances Σ_s, adjusted for the covariates $\boldsymbol{X}_{si}$.

$$\hat{\boldsymbol{\beta}}_s = \boldsymbol{\beta}_s + \boldsymbol{\varepsilon}_s; \text{ where } \boldsymbol{\varepsilon}_s \sim MVN(\mathbf{0}, \Sigma_s)$$
$$\boldsymbol{\beta}_s = \boldsymbol{\beta} + \boldsymbol{\eta}_s; \text{ where } \boldsymbol{\eta}_s \sim MVN(\mathbf{0}, \Omega)$$

- Stata program --mvmeta-- for multivariate meta-analysis.

--mvmeta-- White IR The Stata Journal 2009(9)40-56

Regression dilution bias

- Noise in exposures and covariates (e.g. due to measurement errors or normal within person variability) often leads to regression dilution bias when using only a single baseline measurement in regression models.

$$X = Z + U;\ \text{ where Z is true value, } U \sim N(0,\sigma_u^2)$$
$$Y = \beta_{0z} + \beta_z Z + \varepsilon;\ \text{ where } \varepsilon \sim N(0,\sigma_\varepsilon^2)$$
$$Y = \beta_{0x} + \beta_x X + \varepsilon;\ \text{ where } \varepsilon \sim N(0,\sigma_\varepsilon^2)$$
$$\beta_z = \frac{\beta_x}{\lambda}\ \text{ where } \lambda = \frac{\sigma_z^2}{\sigma_z^2 + \sigma_u^2}$$

- Rarely would the true value of X (i.e. Z) be known, but repeat measures of X can provide unbiased assessments.

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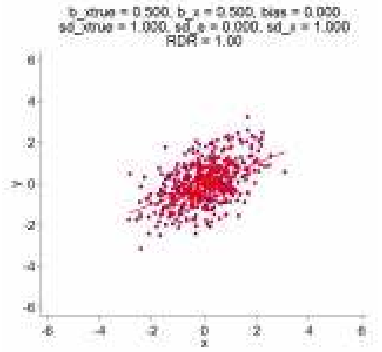
Regression dilution bias demo



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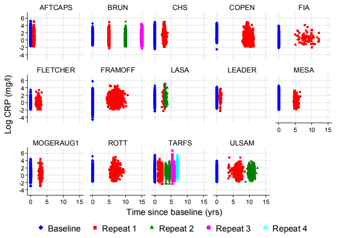
Correction for regression dilution

- Repeat measurements of exposure and other covariates allow for correction for impact of regression dilution bias simultaneously.



- Repeat measures are regressed on baseline measures to estimate regression dilution ratios (RDRs) over time.

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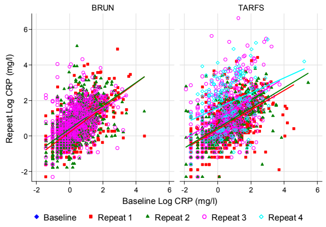
Regression dilution ratios (RDRs)

- Repeat measures are regressed on baseline measures to estimate regression dilution ratios (RDRs) over time.

RDR (95% CI)
R1: 0.63 (0.55, 0.71)
R2: 0.67 (0.61, 0.73)
R3: 0.48 (0.39, 0.57)



RDR (95% CI)
R1: 0.54 (0.47, 0.60)
R2: 0.54 (0.47, 0.60)
R3: 0.58 (0.47, 0.70)
R4: 0.42 (0.23, 0.61)

- Linear mixed modelling used to fit a joint regression calibration model to data from all cohorts allowing for random effects across studies and individuals.

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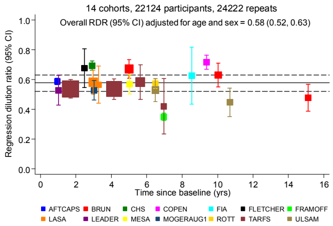
RDRs and long-term "usual" levels

- RDRs of log CRP over time in 14 cohorts.



- Long-term average ("usual") levels of exposures predicted from the linear mixed regression calibration models and used as new exposures/covariates in the regression models for association with disease outcomes.

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Shape of dose-response relationships

- Categorise exposure into deciles (or appropriate bins) and calculate study-specific RR estimates vs. an appropriate reference group, adjusted for confounders as appropriate.

- Pool the study-specific log RRs by multivariate random effects meta-analysis (--mvmeta--, White IR) and plot against pooled mean exposure values within deciles.

- Sensitivity analysis by meta-analysis of continuous shape of association based on fractional polynomial models (--metacurve--, Royston P).

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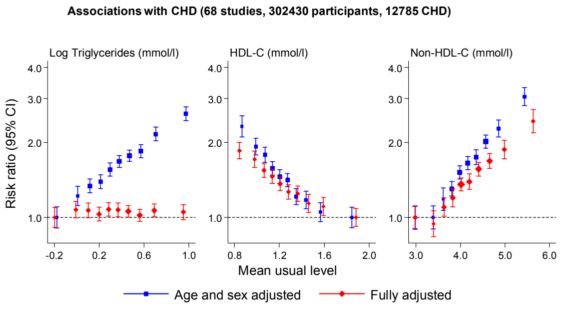
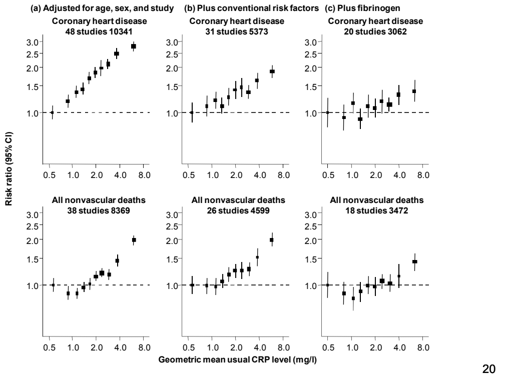
Shape of dose-response relationships (Lipids)



ERFC JAMA 2009(302)1993-2000 19

Shape of dose-response relationships (CRP)



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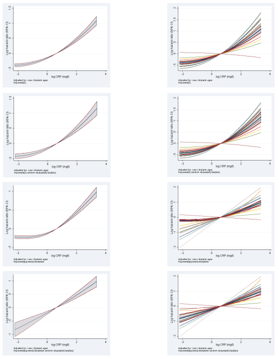
Continuous shape of dose-response relationships (CRP)

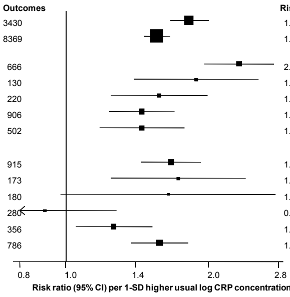
Method/Stat	(a) Overall shape	(b) Study-specific, fitted FP
(i) Overall selected FP, fixed effect meta		
(ii) Overall selected FP, random effects meta		
(iii) Studywise selected FP, fixed effect meta		
(iv) Studywise seleced FP, random effects meta		



Adjusted for sex, age

--metacurve-- Royston P Stat Med 2011(30)3341-60 21

Specificity of associations (CRP)



	Studies	N	Outcomes	Risk ratio (95% CI)
All vascular deaths	37	136912	3430	1.82 (1.66, 2.00)
All nonvascular deaths	38	138063	8369	1.55 (1.46, 1.66)
Cancer deaths				
Respiratory/intrathorasic cancer	24	61356	666	2.32 (1.96, 2.74)
Breast cancer	8	18276	130	1.88 (1.39, 2.55)
Blood related cancer	14	45806	220	1.57 (1.24, 1.99)
Digestive cancer	25	64508	906	1.44 (1.23, 1.70)
Genitourinary related cancer	17	48646	502	1.45 (1.18, 1.78)
Non-cancer non-vascular deaths				
Respiratory disease	22	73342	915	1.67 (1.44, 1.92)
Digestive system (except liver)	13	32943	173	1.72 (1.24, 2.39)
Endocrine, nutritional and metabolic	8	24505	180	1.64 (0.97, 2.77)
Nervous system disorder	11	37397	280	0.90 (0.64, 1.28)
External causes (violence/suicide)	19	74631	356	1.26 (1.05, 1.52)
Unclassified deaths	9	30455	786	1.57 (1.37, 1.81)

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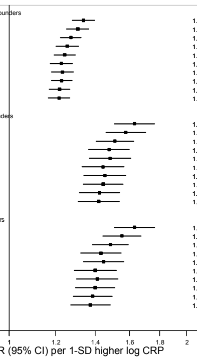
Regression dilution and confounding (CRP)



Model\Adjustments	RR (95% CI)
Baseline exposure, baseline confounders	
Cohort, sex, age	1.34 (1.28, 1.40)
. plus systolic blood pressure	1.31 (1.25, 1.37)
. plus smoking status	1.27 (1.22, 1.32)
. plus history of diabetes	1.25 (1.20, 1.31)
. plus body mass index	1.24 (1.19, 1.29)
. plus log triglycerides	1.23 (1.17, 1.28)
. plus total cholesterol	1.23 (1.18, 1.29)
. plus non-HDL cholesterol	1.23 (1.18, 1.28)
. plus HDL cholesterol	1.22 (1.17, 1.27)
. plus alcohol consumption	1.22 (1.17, 1.27)
Usual exposure, baseline confounders	
Cohort, sex, age	1.63 (1.51, 1.76)
. plus systolic blood pressure	1.58 (1.46, 1.70)
. plus smoking status	1.51 (1.40, 1.63)
. plus history of diabetes	1.48 (1.36, 1.60)
. plus body mass index	1.48 (1.37, 1.61)
. plus log triglycerides	1.44 (1.33, 1.57)
. plus total cholesterol	1.45 (1.34, 1.58)
. plus non-HDL cholesterol	1.44 (1.34, 1.56)
. plus HDL cholesterol	1.42 (1.32, 1.54)
. plus alcohol consumption	1.42 (1.31, 1.54)
Usual exposure, usual confounders	
Cohort, sex, age	1.63 (1.51, 1.76)
. plus systolic blood pressure	1.55 (1.44, 1.67)
. plus smoking status	1.48 (1.38, 1.59)
. plus history of diabetes	1.43 (1.32, 1.55)
. plus body mass index	1.45 (1.34, 1.56)
. plus log triglycerides	1.40 (1.29, 1.52)
. plus total cholesterol	1.41 (1.30, 1.53)
. plus non-HDL cholesterol	1.40 (1.30, 1.51)
. plus HDL cholesterol	1.39 (1.28, 1.49)
. plus alcohol consumption	1.37 (1.27, 1.48)

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Confounding and between-study heterogeneity

RR for CHD per 1-SD higher usual log CRP adjusted for usual levels of confounders (31 studies, 91990 participants, 5373 CHD)

	RR (95% CI)	Wald χ^2_1	I² (95% CI)
Adjusted for age, sex, and study	1.63 (1.51, 1.76)	149	51 (26, 68)
plus systolic blood pressure	1.55 (1.44, 1.67)	134	42 (12, 62)
plus smoking	1.48 (1.38, 1.59)	123	30 (0, 55)
plus history of diabetes	1.43 (1.32, 1.55)	78	42 (10, 62)
plus BMI	1.45 (1.34, 1.56)	85	31 (0, 56)
plus $\log_e$ triglycerides	1.40 (1.29, 1.52)	64	35 (0, 58)
plus total cholesterol	1.41 (1.30, 1.53)	69	33 (0, 57)
plus non-HDL cholesterol§	1.40 (1.30, 1.51)	74	26 (0, 53)
plus cholesterol§	1.39 (1.28, 1.49)	71	25 (0, 52)
plus alcohol§	1.37 (1.27, 1.48)	65	26 (0, 53)

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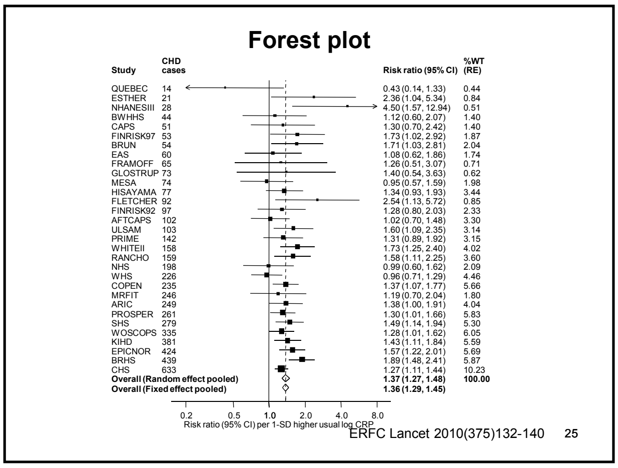

Forest plot

Study	CHD cases	Risk ratio (95% CI)	%WT (RE)
QUEBEC	14	0.43 (0.14, 1.33)	0.44
ESTHER	21	2.36 (1.04, 5.34)	0.84
NHANESIII	28	4.50 (1.57, 12.94)	0.51
BWHHS	44	1.12 (0.60, 2.07)	1.40
CAPS	51	1.30 (0.70, 2.42)	1.40
FINRISK97	53	1.73 (1.02, 2.92)	1.87
BRUN	54	1.71 (1.03, 2.81)	2.04
EAS	60	1.08 (0.62, 1.86)	1.74
FRAMOFF	65	1.26 (0.51, 3.07)	0.71
GLOSTRUP	73	1.40 (0.54, 3.63)	0.62
MESA	74	0.95 (0.57, 1.59)	1.98
HISAYAMA	77	1.34 (0.93, 1.93)	3.44
FLETCHER	92	2.54 (1.13, 5.72)	0.85
FINRISK92	97	1.28 (0.80, 2.03)	2.33
AFTCAPS	102	1.02 (0.70, 1.48)	3.30
ULSAM	103	1.60 (1.09, 2.35)	3.14
PRIME	142	1.31 (0.89, 1.92)	3.15
WHITEII	158	1.73 (1.25, 2.40)	4.02
RANCHO	159	1.58 (1.11, 2.25)	3.60
NHS	198	0.99 (0.60, 1.62)	2.09
WHS	226	0.96 (0.71, 1.29)	4.46
COPEN	235	1.37 (1.07, 1.77)	5.66
MRFIT	246	1.19 (0.70, 2.04)	1.80
ARIC	249	1.38 (1.00, 1.91)	4.04
PROSPER	261	1.30 (1.01, 1.66)	5.83
SHS	279	1.49 (1.14, 1.94)	5.30
WOSCOPS	335	1.28 (1.01, 1.62)	6.05
KIHD	381	1.43 (1.11, 1.84)	5.59
EPICNOR	424	1.57 (1.22, 2.01)	5.69
BRHS	439	1.89 (1.48, 2.41)	5.87
CHS	633	1.27 (1.11, 1.44)	10.23
Overall (Random effect pooled)		**1.37 (1.27, 1.48)**	**100.00**
Overall (Fixed effect pooled)		**1.36 (1.29, 1.45)**	

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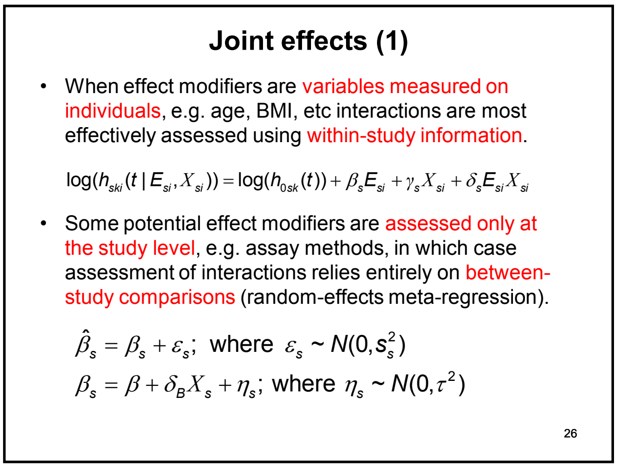


Joint effects (1)

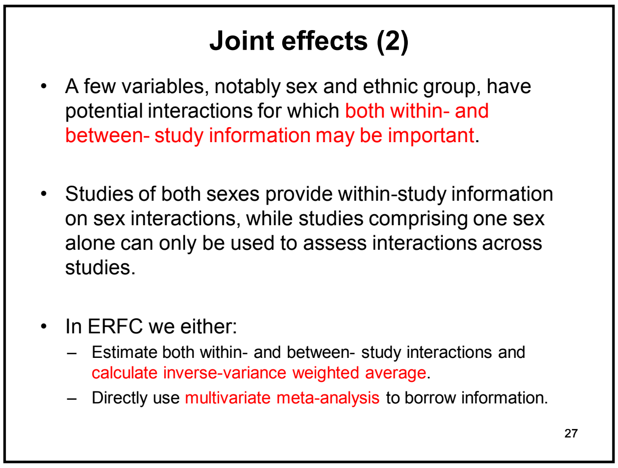
- When effect modifiers are variables measured on individuals, e.g. age, BMI, etc interactions are most effectively assessed using within-study information.

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

- Some potential effect modifiers are assessed only at the study level, e.g. assay methods, in which case assessment of interactions relies entirely on between-study comparisons (random-effects meta-regression).

$$\hat{\beta}_s = \beta_s + \varepsilon_s; \text{ where } \varepsilon_s \sim N(0, s_s^2)$$

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

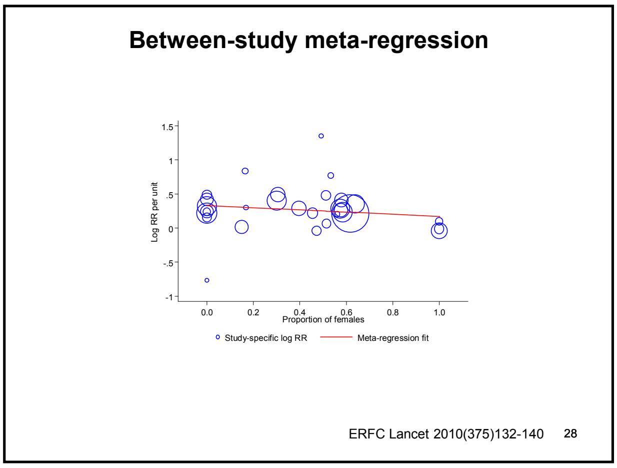


Joint effects (2)

- A few variables, notably sex and ethnic group, have potential interactions for which both within- and between- study information may be important.

- Studies of both sexes provide within-study information on sex interactions, while studies comprising one sex alone can only be used to assess interactions across studies.

- In ERFC we either:
  - Estimate both within- and between- study interactions and calculate inverse-variance weighted average.
  - Directly use multivariate meta-analysis to borrow information.



Between-study meta-regression

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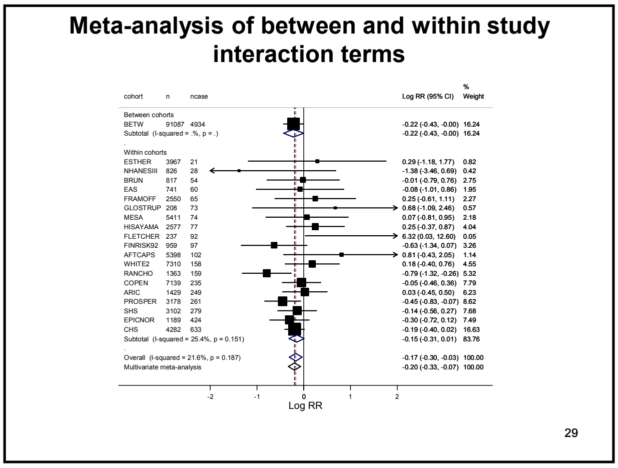
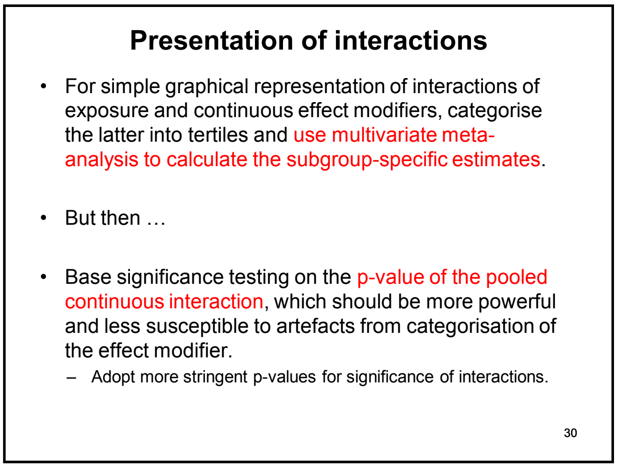


Meta-analysis of between and within study interaction terms

cohort	n	ncase	Log RR (95% CI)	% Weight
Between cohorts				
BETW	91087	4934	-0.22 (-0.43, -0.00)	16.24
Subtotal (I-squared = .%, p = .)			-0.22 (-0.43, -0.00)	16.24
.				
Within cohorts				
ESTHER	3967	21	0.29 (-1.18, 1.77)	0.82
NHANESIII	826	28	-1.38 (-3.46, 0.69)	0.42
BRUN	817	54	-0.01 (-0.79, 0.76)	2.75
EAS	741	60	-0.08 (-1.01, 0.86)	1.95
FRAMOFF	2550	65	0.25 (-0.61, 1.11)	2.27
GLOSTRUP	208	73	0.68 (-1.09, 2.46)	0.57
MESA	5411	74	0.07 (-0.81, 0.95)	2.18
HISAYAMA	2577	77	0.25 (-0.37, 0.87)	4.04
FLETCHER	237	92	6.32 (0.03, 12.60)	0.05
FINRISK92	959	97	-0.63 (-1.34, 0.07)	3.26
AFTCAPS	5398	102	0.81 (-0.43, 2.05)	1.14
WHITE2	7310	158	0.18 (-0.40, 0.76)	4.55
RANCHO	1363	159	-0.79 (-1.32, -0.26)	5.32
COPEN	7139	235	-0.05 (-0.46, 0.36)	7.79
ARIC	1429	249	0.03 (-0.45, 0.50)	6.23
PROSPER	3178	261	-0.45 (-0.83, -0.07)	8.62
SHS	3102	279	-0.14 (-0.56, 0.27)	7.68
EPICNOR	1189	424	-0.30 (-0.72, 0.12)	7.49
CHS	4282	633	-0.19 (-0.40, 0.02)	16.63
Subtotal (I-squared = 25.4%, p = 0.151)			-0.15 (-0.31, 0.01)	83.76
.				
Overall (I-squared = 21.6%, p = 0.187)			-0.17 (-0.30, -0.03)	100.00
Multivariate meta-analysis			-0.20 (-0.33, -0.07)	100.00



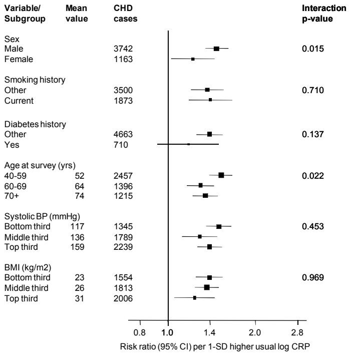
Presentation of interactions

- For simple graphical representation of interactions of exposure and continuous effect modifiers, categorise the latter into tertiles and use multivariate meta-analysis to calculate the subgroup-specific estimates.

- But then …

- Base significance testing on the p-value of the pooled continuous interaction, which should be more powerful and less susceptible to artefacts from categorisation of the effect modifier.
  - Adopt more stringent p-values for significance of interactions.

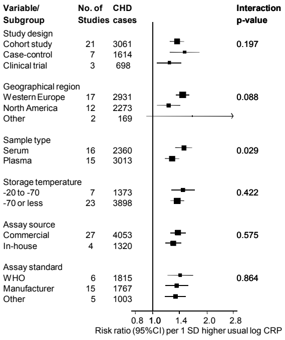
Joint effects with individual-level covariates



Variable/ Subgroup	Mean value	CHD cases	Interaction p-value
Sex			
Male		3742	0.015
Female		1163	
Smoking history			
Other		3500	0.710
Current		1873	
Diabetes history			
Other		4663	0.137
Yes		710	
Age at survey (yrs)			
40-59	52	2457	0.022
60-69	64	1396	
70+	74	1215	
Systolic BP (mmHg)			
Bottom third	117	1345	0.453
Middle third	136	1789	
Top third	159	2239	
BMI (kg/m2)			
Bottom third	23	1554	0.969
Middle third	26	1813	
Top third	31	2006	

ERFC Lancet 2010(375)132-140

Joint effects with study-level covariates



Variable/ Subgroup	No. of Studies	CHD cases	Interaction p-value
Study design			
Cohort study	21	3061	0.197
Case-control	7	1614	
Clinical trial	3	698	
Geographical region			
Western Europe	17	2931	0.088
North America	12	2273	
Other	2	169	
Sample type			
Serum	16	2360	0.029
Plasma	15	3013	
Storage temperature			
-20 to -70	7	1373	0.422
-70 or less	23	3898	
Assay source			
Commercial	27	4053	0.575
In-house	4	1320	
Assay standard			
WHO	6	1815	0.864
Manufacturer	15	1767	
Other	5	1003	

ERFC Lancet 2010(375)132-140

Proportional hazards (PH) assumption

- A key assumption in the Cox model is that of proportional hazards (PH), i.e. hazard ratios remain constant in time.
- We evaluate PH assumption in each study separately, by testing for interaction between the exposure and time.

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

- The non PH parameters ξ_s are pooled across studies by random effect meta-analysis.

PH assumption (alternative methods)

- Alternatively, can sum independent $\chi^2{}_1$ statistics from standard PH tests based on Schoenfeld residuals within each of *S* studies, yielding a $\chi^2{}_S$ statistic testing H0 that PH holds in each study.
- Compare results with a 1-stage approach fitting a single model stratified by cohort and sex.

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

- where β_s are separate fixed effects, and the focus is on the common estimate of *ξ*.
  - Can also assume that $\beta_s = \beta$, *i.e.* common effect across studies.

Potential public health impact: Estimating years of Life Lost (YLL)

Background

- Relative risks (RR) provide useful aetiological information on exposure (E) - disease (D) associations.

$$RR = \frac{p(D=1 \mid E=1, \mathbf{X}=\mathbf{x})}{p(D=1 \mid E=0, \mathbf{X}=\mathbf{x})}$$

- But alternative measures may be better suited for conveying the potential public health impact of a risk factor e.g.
  - Population attributable risk.
  - Short to medium term absolute risk (e.g. 10-year CVD risk).
  - Long term absolute risk (e.g. lifetime risk, or risk up to age 95y).
  - Years of life lost (YLL).

Population attributable risk (PAR)

- By how much could population disease burden be reduced by eliminating a certain risk factor?

$$PAR = \left(1 - \frac{1}{RR}\right) \times p(E = 1 \mid D = 1)$$

- Lacks an individual perspective or interpretation.
- Ambiguous interpretation if exposure prevalence or if RRs importantly vary over time (e.g. by age).

Short to medium term absolute risk

- What is the probability of disease (or death) occurring within t-years (e.g. 10-year CVD) given risk factor profile?

$$\begin{aligned} p(D = 1, T \leq t \mid E = 1, \mathbf{X} = \mathbf{x}) &= 1 - S(t) \\ &= 1 - S_0(t)^{\exp(\beta E + \boldsymbol{\beta}' \mathbf{x})} \end{aligned}$$

- Has some individual perspective or interpretation.
- Interpretation is subject to length of time-horizon.
- Importance can be disproportionately weighted towards older age-groups, where incidence is higher.

Long term absolute risk (e.g. lifetime risk)

- What is the probability of disease (or death) occurring over someone's lifetime conditional on survival to a certain age and risk factor profile (i.e. cumulative incidence, CI)?

$$p(D = 1 \mid age = age_{risk}, E = 1, \mathbf{X} = \mathbf{x}) = CI(age_{risk} \mid E = 1, \mathbf{X} = \mathbf{x})$$

- Individual perspective or interpretation.
- Should ideally take into account competing risks (e.g. death from non-cardiovascular disease).
- Gives more weight to events occurring at younger ages.

Years of life lost (YLL)

- Conditional on survival to a certain age, how many years of life are lost because someone's risk factor profile promotes premature death?
- Essentially a difference in area under survival curves for exposed vs. unexposed from age$_{\text{risk}}$ to age$_{\text{max}}$.

$$YLL = \int_{age_{risk}}^{age_{max}} S(t \mid E = 1, \mathbf{X} = \mathbf{x}) dt - \int_{age_{risk}}^{age_{max}} S(t \mid E = 0, \mathbf{X} = \mathbf{x}) dt$$

- Gives a more intuitive perspective for the individual since it is expressed in life-year units rather than probability or RR scale.
  - Also it is calculated over the potential life-course of an individual.

YLL estimation: Statistical inputs needed

- Age-at-risk specific hazard ratios (HRs) for exposure association with all-cause and cause-specific death (e.g. from ERFC).
- Population cause-specific and overall death rates by age and sex (e.g. EU 2000 death rates, in 5-year age groups).
  - Preferably for unexposed group (e.g. non-diabetics or non-smokers), but a work-around is possible if only available for total population.
- A computer with large memory, since estimating age-at-risk specific HRs involves expanding the dataset to obtain a record for each 5-year age-at-risk group.

YLL estimation: Method in general

- Estimate sex and age-at-risk specific HRs for association of exposure with causes of interest (e.g. using ERFC data).
- Infer the expected death rates among the exposed (e.g. diabetics) by multiplying the reference population age-specific death rates by the estimated age-specific HRs.
- Derive the expected population survival curves for the exposed and unexposed groups, assuming exponential survival within each 5-year age-at-risk group.
- Estimate remaining life-years for each group by integrating both survival curves from each age$_{\text{risk}}$ to age$_{\text{max}}$ (cubic splines approx) and then calculate YLL as the difference.

ERFC example 1: YLL lost due to diabetes

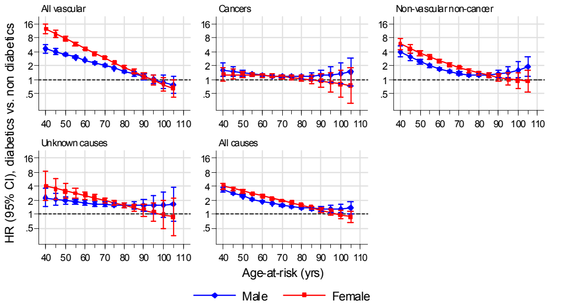
Data setup for modelling age-at-risk specific HRs …

```
+-----------------------------------------------------------------------------------------------------------------+
|   idno   sex    ages   ageout   hxdiab   duration   ep_dead   agerisk   outage   agegrp5   _d    _t0     _t   _trisk |
|-----------------------------------------------------------------------------------------------------------------|
| C000074    1   59.99     70.3        0       10.3         0     59.99       60        55    0      0   .011     .011 |
| C000074    1   59.99     70.3        0       10.3         0        60       65        60    0   .011   5.01        5 |
| C000074    1   59.99     70.3        0       10.3         0        65       70        65    0   5.01     10        5 |
| C000074    1   59.99     70.3        0       10.3         0        70     70.3        70    0     10   10.3     .297 |
|-----------------------------------------------------------------------------------------------------------------|
| C000113    1    64.2    75.86        0       11.7         1      64.2       65        60    0      0     .8       .8 |
| C000113    1    64.2    75.86        0       11.7         1        65       70        65    0     .8    5.8        5 |
| C000113    1    64.2    75.86        0       11.7         1        70       75        70    0    5.8   10.8        5 |
| C000113    1    64.2    75.86        0       11.7         1        75    75.86        75    1   10.8   11.7     .863 |
|-----------------------------------------------------------------------------------------------------------------|
| C000135    1   49.35    61.93        1       12.6         0     49.35       50        45    0      0   .648     .648 |
| C000135    1   49.35    61.93        1       12.6         0        50       55        50    0   .648   5.65        5 |
| C000135    1   49.35    61.93        1       12.6         0        55       60        55    0   5.65   10.6        5 |
| C000135    1   49.35    61.93        1       12.6         0        60    61.93        60    0   10.6   12.6     1.93 |
|-----------------------------------------------------------------------------------------------------------------|
| C000217    1   58.65    71.16        1       12.5         1     58.65       60        55    0      0   1.35     1.35 |
| C000217    1   58.65    71.16        1       12.5         1        60       65        60    0   1.35   6.35        5 |
| C000217    1   58.65    71.16        1       12.5         1        65       70        65    0   6.35   11.4        5 |
| C000217    1   58.65    71.16        1       12.5         1        70    71.16        70    1   11.4   12.5     1.16 |
+-----------------------------------------------------------------------------------------------------------------+
```

Sex-specific Cox model: *s* = study, *i* = individual, *t* = time in study

$$\log(h_{si}(t)) = \log(h_{si0}(t)) + \beta_1 diab_{si} + \beta_2 agerisk_{si} + \beta_3 agerisk_{si}^2 + \beta_4 diab_{si} \times agerisk_{si} + \beta_5 diab \times agerisk_{si}^2$$

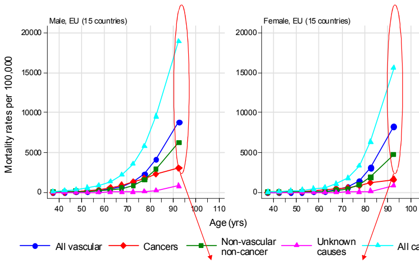
Input 1: Age specific HRs for cause-specific death (ERFC)



Graphs by cause

Inference from Cox model with diabetes status interacted with linear and quadratic terms for age-at-risk.

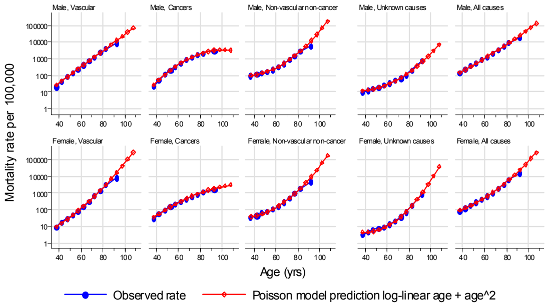
Input 2: Population death rates (EU 2000, 15 countries)



Mortality rates for year 2000

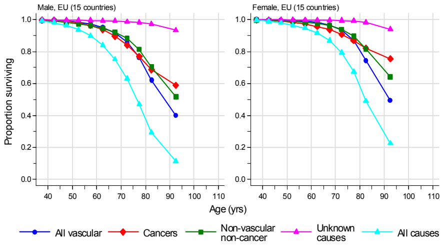
Provided as rates for age 85+, and are arbitrarily plotted at age 92.5 y

Input 2: Poisson smoothing/extrapolation of death rates



Graphs by sex and cause

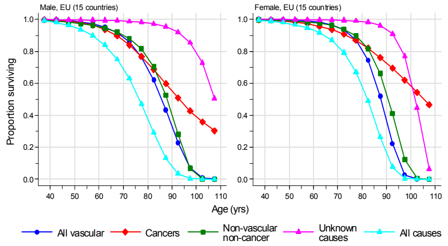
Input 3: Estimated population survival curves (1)



Survival probabilities for year 2000

$$p(survival \mid age_{risk} \geq 35) = \prod_{age_{risk}}^{age_{max}} e^{-5 \times \frac{IR_i}{100000}}$$

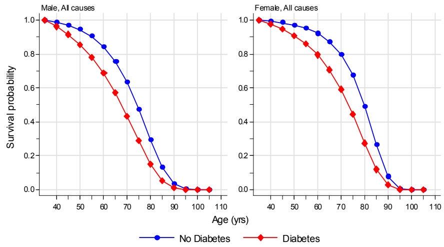
Input 3: Estimated population survival curves (2)



Survival probabilities for year 2000

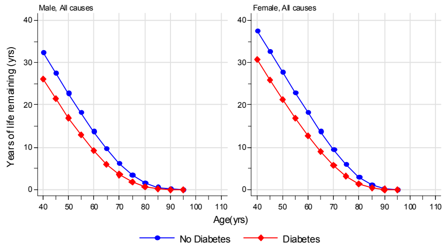
$$p(survival \mid age_{risk} \geq 35) = \prod_{age_{risk}}^{age_{max}} e^{-5\times\frac{IR_i}{100000}}$$

YLL Task 1: Survival by diabetes status



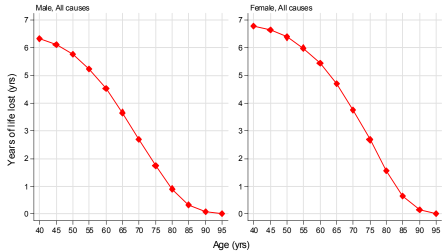
Graphs by sex and cause

YLL Task 2: Remaining life years by diabetes status …



Graphs by sex and cause

YLL Task 3: Years of life lost with diabetes …



Graphs by sex and cause

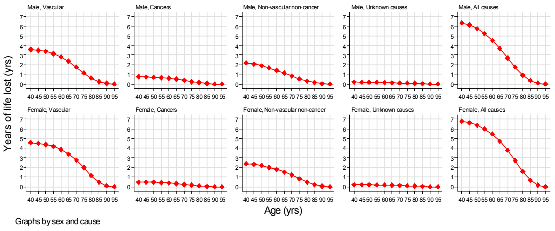
Proportioning YLL by cause of death

- Calculation of YLL by cause of death requires additional constraints on the rates of 'other causes' of death when applying the cause-specific HRs to the death rates.
  - Exposure effect on the cause of interest is calculated while maintaining the death rates for all 'other causes' of death at their original death rates.
- Ensures that the sum of cause-specific YLLs is close to the YLLs directly estimated based on the all-cause mortality endpoint.
- For each age and sex group, denote the death rates as r_A (all-cause), r_V (vascular), r_C (cancer), r_N (non-vascular, non-cancer), and r_O (other), and the hazard ratios as HR_* with the same suffices.

Proportioning YLL by cause of death

- The rates add up so that r_A = r_V + r_C + r_N + r_O.
- For YLLs due to vascular death, compare survival curves derived from (r_V + r_C + r_N + r_O) to that derived from (HR_V*r_V + r_C + r_N + r_O).
- For YLLs due to cancer death, compare survival curves derived from (r_V + r_C + r_N + r_O) to that derived from (r_V + HR_C*r_C + r_N + r_O).
- For YLLs due to non-vascular, non-cancer death, compare survival curves derived from (r_V + r_C + r_N + r_O) to that derived from (r_V + r_C + HR_C*r_N + r_O), etc.

YLL Task 4: YLL by cause and age-at-risk …



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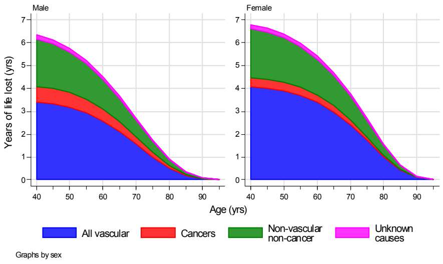
YLL Task 5: Proportionate YLL with diabetes by cause of death



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ERFC example 2: YLL lost due to smoking

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Inferring death rates for the reference group

- The population death rates would rarely be available separately for the exposure groups of interest e.g. never smokers (0) – reference group, former smokers (1), and current smokers (2).

- To get death rates for never smokers (reference group), assume the overall population age-specific incidence rate is a weighted average

  $IR = p_0{*}IR_0 + p_1{*}IR_1 + p_2{*}IR_2$

  Given relative risks versus never smokers are

  $RR_{10} = IR_1/IR_0$ and $RR_{20} = IR_2/IR_0$
- Can rewrite above equation as

  $IR = p_0{*}IR_0 + p_1{*}RR_{10}{*}IR_0 + p_2{*}RR_{20}{*}IR_0$

  from which

  $IR_0 = IR/(p_0 + p_1{*}RR_{10} + p_2{*}RR_{20})$
- Hence need age-specific prevalence of never (p_0), former (p_1), and current (p_2) smoking. Moreover, as smoking prevalence has declined over the years, period specific prevalence estimates are appropriate.

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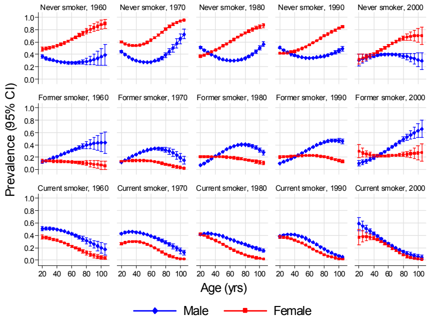
Sex- and age-specific prevalence of smoking by decade



Inference from sex-specific multinomial logit model with linear and quadratic terms for age interacted with decade of survey.

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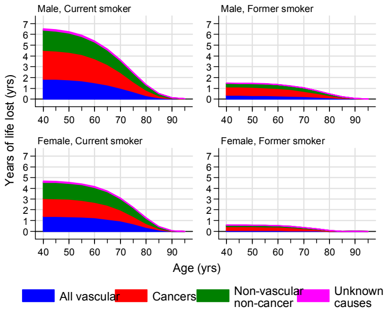
Proportionate YLL due to smoking by cause of death



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Remarks

- The outlined methods for calculation of YLL provide a useful way of combining overall population mortality rates and exposure association statistics from population-based studies to express the public health impact of risk factors.
- Future work would involve fully taking into account the impact of competing risks (e.g. cumulative incidence calculation) and finer subdivision by cause of death (e.g. lung v. other cancers for smoking).
- The results provide credible evidence that diabetes and current smoking are each associated with significantly shortened life expectancy. The impact of diabetes is greater in females than males, and the impact of smoking is greater in males.

Risk prediction methods in ERFC

(If time allows)

Risk prediction - Background

- In addition to summarising the association between a risk marker and disease, there is interest in knowing the predictive ability that can be attributed to a marker when it is included in a model to predict future risk of CVD.
- Need to assess the predictive ability of risk models with and without inclusion of the marker of interest.
- In ERFC we have assessed:
  - Discrimination
  - Calibration
  - Reclassification

The risk prediction model

$$\hat{S}_{ki}(t \mid \mathbf{x_i}, k) = \hat{S}_{0k}(t)^{\exp(\hat{\boldsymbol{\beta}}\mathbf{x}_i)}$$

- Gives the probability of surviving event free to at least time *t* given risk factors $\boldsymbol{x}_i$.
- Interested in assessing the accuracy of the predictions made for all participants, given risk factors.
- Also interested in assessing the improvements in risk predictions when a new risk marker is added to some existing set of predictors.

Discrimination

- The ability of a model to discriminate between different levels of risk.
- Assessed using:
  - Concordance statistics (C-index, AUROC)
  - The D measure or R^2_D
- The improvement in risk prediction upon addition of a new marker is quantified by assessing the change in discrimination measures e.g.

  C-index for new model – C-index for old model

C-index for survival data

- Estimates the probability that the predicted order of failure is correct for a randomly selected pair of individuals.
- Calculation of the C-index (within a single study):

Count pairs of participants for which t_i and $\hat{\beta}x_i$ are concordant (n_c), discordant (n_d) and undecided (n_u)

$$C = \frac{n_c + 0.5n_u}{n_c + n_d + n_u}$$

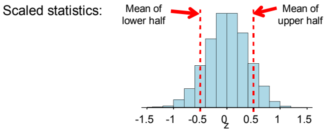
Where t_i = time in the study for participant *i*

$\hat{\beta}x_i$ = prognostic index/risk prediction for participant *i*

D-statistic

- Measures the spread of observed risk across model predictions. Expressed as log-hazard ratio equivalent to comparing risk of outcome in the upper vs. lower half of the predicted risk distribution.

- Estimation steps
  1. Fit prediction model (eg: Cox PH)
  2. Transform linear predictor (**βX**) to scaled N(0,1) statistics (z)
  3. Fit outcome model (eg: Cox PH) to the scaled statistics, from which D is the coefficient of z



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Risk prediction in ERFC

- Aim: To assess improvements in risk prediction by meta-analysis of data from observational studies.

- Measures used:
  - Discrimination: C-index, D measure, R^2_D
  - Reclassification: NRI, IDI

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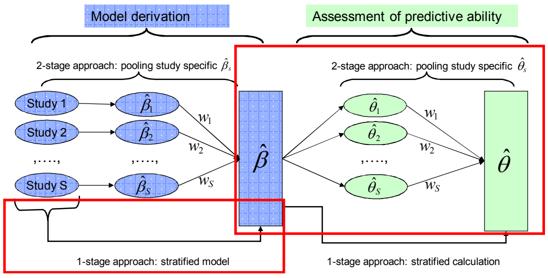
ERFC prediction methods schemata


Model derivation
Assessment of predictive ability
2-stage approach: pooling study specific $\hat{\beta}_i$
2-stage approach: pooling study specific $\hat{\theta}_i$
Study 1
Study 2
,...,
Study S
$\hat{\beta}_1$
$\hat{\beta}_2$
,...,
$\hat{\beta}_S$
w_1
w_2
w_S
$\hat{\beta}$
$\hat{\theta}_1$
$\hat{\theta}_2$
,...,
$\hat{\theta}_S$
w_1
w_2
w_S
$\hat{\theta}$
1-stage approach: stratified model
1-stage approach: stratified calculation

W_i = study-specific weights for meta-analysis

Primary ERFC prediction analyses

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ERFC CRP-CHD prediction examples
(37 studies, 165856 participants, 8806 CHD)

		Multivariable adjusted log HR (SE) per 1-SD higher value or in comparison with reference category*			Heterogeneity
	Mean (SD) or n (%)	1-stage Stratified†	2-stage FE§	2-stage RE§	I² (95% CI)
Age at survey (yrs)	64.2 (8.6)	0.567 (0.013)	0.565 (0.013)	0.529 (0.043)	76 (67, 82)
Male sex	81732 (49%)	NA	NA	NA	NA
Current smoking*	35577 (21%)	0.516 (0.024)	0.529 (0.024)	0.515 (0.050)	63 (48, 73)
SBP (mmHg)	131 (19)	0.202 (0.009)	0.203 (0.009)	0.211 (0.017)	30 (0, 53)
History of diabetes*	10790 (7%)	0.557 (0.038)	0.587 (0.037)	0.600 (0.049)	24 (0, 49)
TCHOL (mmol/l)	5.84 (1.06)	0.234 (0.010)	0.235 (0.010)	0.216 (0.018)	32 (0, 54)
HDL-C (mmol/l)	1.27 (0.38)	-0.247 (0.014)	-0.240 (0.014)	-0.232 (0.023)	52 (32, 67)
Log CRP (mg/l)	0.55 (1.09)	0.206 (0.012)	0.207 (0.012)	0.201 (0.013)	9 (0, 38)

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ERFC methods: Discrimination

- Discrimination (2-stage): C-index, D, R^2_D.
  - Stratified (1-stage) Cox model used to derive a single risk prediction model across studies.
  - Discrimination measures calculated within each study, including their changes therein.
  - Absolute values and changes combined by meta-analysis, weighting by number of events.
  - Sensitivity analyses using 2-stage derivation of the prediction model and also alternative weights for the meta-analysis of discrimination measures.

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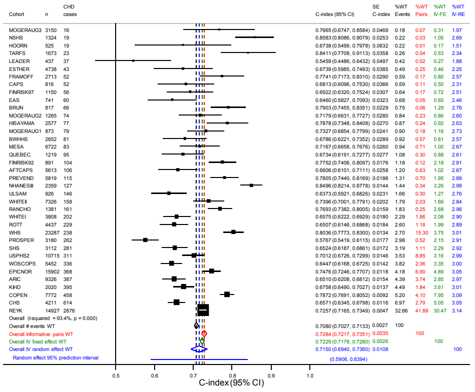
Meta-analysis of C-index



Cohort	n	CHD cases	C-index (95% CI)	SE C-index	%WT Events	%WT Pairs	%WT IV-FE	%WT IV-RE
MOGERAUG3	3150	16	0.7665 (0.6747, 0.8584)	0.0469	0.18	0.07	0.31	1.97
NSHS	1324	19	0.8583 (0.8086, 0.9079)	0.0253	0.22	0.03	1.05	2.69
HOORN	525	19	0.6738 (0.5499, 0.7978)	0.0632	0.22	0.01	0.17	1.51
TARFS	1673	23	0.8411 (0.7708, 0.9113)	0.0358	0.26	0.04	0.53	2.34
LEADER	437	37	0.5459 (0.4486, 0.6432)	0.0497	0.42	0.02	0.27	1.88
ESTHER	4738	43	0.6739 (0.5985, 0.7493)	0.0385	0.49	0.25	0.46	2.25
FRAMOFF	2713	52	0.7741 (0.7173, 0.8310)	0.0290	0.59	0.17	0.80	2.57
CAPS	816	52	0.6813 (0.6096, 0.7530)	0.0366	0.59	0.11	0.50	2.31
FINRISK97	1150	56	0.6922 (0.6320, 0.7524)	0.0307	0.64	0.17	0.72	2.51
EAS	741	60	0.6460 (0.5827, 0.7093)	0.0323	0.68	0.05	0.65	2.46
BRUN	817	66	0.7903 (0.7455, 0.8351)	0.0229	0.75	0.06	1.29	2.76
MOGERAUG2	1265	74	0.7179 (0.6631, 0.7727)	0.0280	0.84	0.23	0.86	2.60
HISAYAMA	2577	77	0.7878 (0.7348, 0.8408)	0.0270	0.87	0.24	0.92	2.63
MOGERAUG1	873	79	0.7327 (0.6854, 0.7799)	0.0241	0.90	0.18	1.16	2.73
BWHHS	2652	81	0.6786 (0.6221, 0.7352)	0.0289	0.92	0.57	0.81	2.57
MESA	6722	83	0.7167 (0.6658, 0.7676)	0.0260	0.94	0.71	1.00	2.67
QUEBEC	1219	95	0.6734 (0.6191, 0.7277)	0.0277	1.08	0.30	0.88	2.61
FINRISK92	891	104	0.7752 (0.7406, 0.8097)	0.0176	1.18	0.12	2.18	2.91
AFTCAPS	5613	106	0.6606 (0.6101, 0.7111)	0.0258	1.20	0.63	1.02	2.67
PREVEND	5819	115	0.7805 (0.7440, 0.8169)	0.0186	1.31	0.70	1.95	2.89
NHANESIII	2359	127	0.8496 (0.8214, 0.8778)	0.0144	1.44	0.34	3.26	2.99
ULSAM	926	146	0.6373 (0.5921, 0.6826)	0.0231	1.66	0.30	1.27	2.76
WHITEII	7326	158	0.7396 (0.7001, 0.7791)	0.0202	1.79	2.03	1.66	2.84
RANCHO	1381	161	0.7693 (0.7382, 0.8005)	0.0159	1.83	0.25	2.68	2.96
WHITEI	3808	202	0.6575 (0.6222, 0.6929)	0.0180	2.29	1.86	2.08	2.90
ROTT	4437	229	0.6507 (0.6146, 0.6868)	0.0184	2.60	1.18	1.99	2.89
WHS	23287	238	0.8036 (0.7773, 0.8300)	0.0134	2.70	15.30	3.75	3.01
PROSPER	3180	262	0.5767 (0.5419, 0.6115)	0.0177	2.98	0.52	2.15	2.91
SHS	3112	281	0.6524 (0.6187, 0.6861)	0.0172	3.19	1.11	2.29	2.92
USPHS2	10715	311	0.7012 (0.6726, 0.7299)	0.0146	3.53	8.85	3.16	2.99
WOSCOPS	5452	336	0.6447 (0.6168, 0.6725)	0.0142	3.82	2.36	3.35	3.00
EPICNOR	15902	368	0.7476 (0.7246, 0.7707)	0.0118	4.18	6.90	4.89	3.05
ARIC	9326	387	0.6510 (0.6208, 0.6812)	0.0154	4.39	3.74	2.85	2.97
KIHD	2020	395	0.6758 (0.6490, 0.7027)	0.0137	4.49	1.84	3.61	3.01
COPEN	7772	458	0.7872 (0.7691, 0.8052)	0.0092	5.20	4.10	7.95	3.09
CHS	4211	614	0.6571 (0.6345, 0.6798)	0.0116	6.97	2.79	5.05	3.05
REYK	14927	2876	0.7257 (0.7165, 0.7349)	0.0047	32.66	41.88	30.47	3.14
Overall (I-squared = 93.4%, p = 0.000)								
Overall # events WT			0.7080 (0.7027, 0.7133)	0.0027	100			
Overall Informative pairs WT			0.7284 (0.7217, 0.7351)	0.0035		100		
Overall IV fixed effect WT			0.7229 (0.7178, 0.7280)	0.0026			100	
Overall IV random effect WT			0.7150 (0.6940, 0.7360)	0.0108				100
Random effect 95% prediction interval			(0.5906, 0.8394)					

C-index with conventional CVD risk factors

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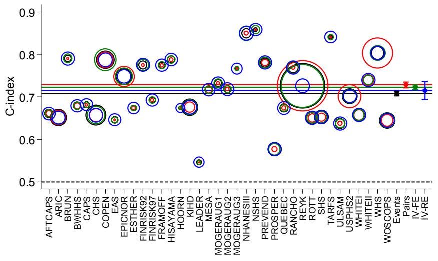
Meta-analysis of C-index

Comparison of study weights

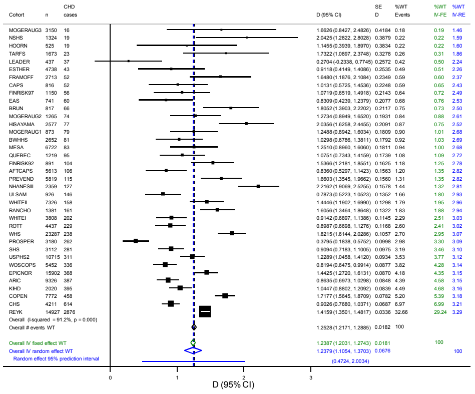


○ # events WT ○ Informative pairs WT ○ IV fixed effect WT ○ IV random effect WT

The pooled estimates for the 4 weighting methods respectively are:
0.7080 (p = 0.000), 0.7284 (p = 0.000), 0.7229 (p = 0.000), and 0.7150 (p = 0.000)

C-index with conventional CVD risk factors

Meta-analysis of D

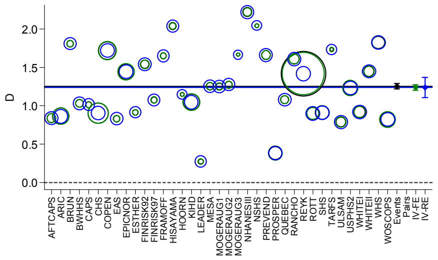


Cohort	n	CHD cases	D (95% CI)	SE D	%WT Events	%WT IV-FE	%WT IV-RE
MOGERAUG3	3150	16	1.6626 (0.8427, 2.4826)	0.4184	0.18	0.19	1.46
NSHS	1324	19	2.0425 (1.2822, 2.8028)	0.3879	0.22	0.22	1.59
HOORN	525	19	1.1455 (0.3939, 1.8970)	0.3834	0.22	0.22	1.60
TARFS	1673	23	1.7322 (1.0897, 2.3748)	0.3278	0.26	0.31	1.86
LEADER	437	37	0.2704 (-0.2338, 0.7745)	0.2572	0.42	0.50	2.24
ESTHER	4738	43	0.9118 (0.4149, 1.4086)	0.2535	0.49	0.51	2.26
FRAMOFF	2713	52	1.6480 (1.1876, 2.1084)	0.2349	0.59	0.60	2.37
CAPS	816	52	1.0131 (0.5725, 1.4536)	0.2248	0.59	0.65	2.43
FINRISK97	1150	56	1.0719 (0.6519, 1.4918)	0.2143	0.64	0.72	2.49
EAS	741	60	0.8309 (0.4239, 1.2379)	0.2077	0.68	0.76	2.53
BRUN	817	66	1.8052 (1.3903, 2.2202)	0.2117	0.75	0.73	2.50
MOGERAUG2	1265	74	1.2734 (0.8949, 1.6520)	0.1931	0.84	0.88	2.61
HISAYAMA	2577	77	2.0356 (1.6258, 2.4455)	0.2091	0.87	0.75	2.52
MOGERAUG1	873	79	1.2488 (0.8942, 1.6034)	0.1809	0.90	1.01	2.68
BWHHS	2652	81	1.0298 (0.6786, 1.3811)	0.1792	0.92	1.03	2.69
MESA	6722	83	1.2510 (0.8960, 1.6060)	0.1811	0.94	1.00	2.68
QUEBEC	1219	95	1.0751 (0.7343, 1.4159)	0.1739	1.08	1.09	2.72
FINRISK92	891	104	1.5366 (1.2181, 1.8551)	0.1625	1.18	1.25	2.78
AFTCAPS	5613	106	0.8360 (0.5297, 1.1423)	0.1563	1.20	1.35	2.82
PREVEND	5819	115	1.6603 (1.3545, 1.9662)	0.1560	1.31	1.35	2.82
NHANESIII	2359	127	2.2162 (1.9069, 2.5255)	0.1578	1.44	1.32	2.81
ULSAM	926	146	0.7873 (0.5223, 1.0523)	0.1352	1.66	1.80	2.93
WHITEII	7326	158	1.4446 (1.1902, 1.6990)	0.1298	1.79	1.95	2.96
RANCHO	1381	161	1.6056 (1.3464, 1.8648)	0.1322	1.83	1.88	2.94
WHITEI	3808	202	0.9142 (0.6897, 1.1386)	0.1145	2.29	2.51	3.03
ROTT	4437	229	0.8987 (0.6698, 1.1276)	0.1168	2.60	2.41	3.02
WHS	23287	238	1.8215 (1.6144, 2.0286)	0.1057	2.70	2.95	3.07
PROSPER	3180	262	0.3795 (0.1838, 0.5752)	0.0998	2.98	3.30	3.09
SHS	3112	281	0.9094 (0.7183, 1.1005)	0.0975	3.19	3.46	3.10
USPHS2	10715	311	1.2289 (1.0458, 1.4120)	0.0934	3.53	3.77	3.12
WOSCOPS	5452	336	0.8194 (0.6475, 0.9914)	0.0877	3.82	4.28	3.14
EPICNOR	15902	368	1.4425 (1.2720, 1.6131)	0.0870	4.18	4.35	3.15
ARIC	9326	387	0.8635 (0.6973, 1.0298)	0.0848	4.39	4.58	3.15
KIHD	2020	395	1.0447 (0.8802, 1.2092)	0.0839	4.49	4.68	3.16
COPEN	7772	458	1.7177 (1.5645, 1.8709)	0.0782	5.20	5.39	3.18
CHS	4211	614	0.9026 (0.7680, 1.0371)	0.0687	6.97	6.99	3.21
REYK	14927	2876	1.4159 (1.3501, 1.4817)	0.0336	32.66	29.24	3.29
Overall (I-squared = 91.2%, p = 0.000)							
Overall # events WT			1.2528 (1.2171, 1.2885)	0.0182	100		
Overall IV fixed effect WT			1.2387 (1.2031, 1.2743)	0.0181		100	
Overall IV random effect WT			1.2379 (1.1054, 1.3703)	0.0676			100
Random effect 95% prediction interval			(0.4724, 2.0034)				

D with conventional CVD risk factors

Meta-analysis of D

Comparison of study weights

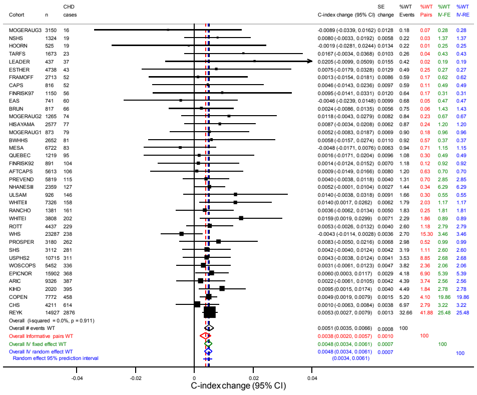


○ # events WT ○ IV fixed effect WT ○ IV random effect WT

The pooled estimates for the 4 weighting methods respectively are:
1.2528 (p = 0.000), 1.3881 (p = 0.000), 1.2387 (p = 0.000), and 1.2379 (p = 0.000)

D with conventional CVD risk factors

Meta-analysis of C-index change

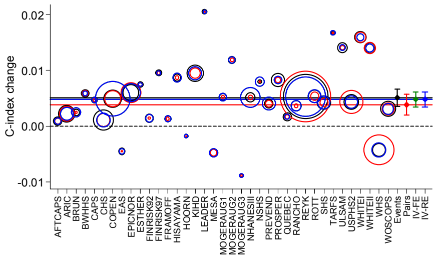


Cohort	n	CHD cases	C-index change (95% CI)	SE change	%WT Events	%WT Pairs	%WT IV-FE	%WT IV-RE
MOGERAUG3	3150	16	-0.0089 (-0.0339, 0.0162)	0.0128	0.18	0.07	0.28	0.28
NSHS	1324	19	0.0080 (-0.0033, 0.0192)	0.0058	0.22	0.03	1.37	1.37
HOORN	525	19	-0.0019 (-0.0281, 0.0244)	0.0134	0.22	0.01	0.25	0.25
TARFS	1673	23	0.0167 (-0.0034, 0.0368)	0.0103	0.26	0.04	0.43	0.43
LEADER	437	37	0.0205 (-0.0099, 0.0509)	0.0155	0.42	0.02	0.19	0.19
ESTHER	4738	43	0.0075 (-0.0179, 0.0328)	0.0129	0.49	0.25	0.27	0.27
FRAMOFF	2713	52	0.0013 (-0.0154, 0.0181)	0.0086	0.59	0.17	0.62	0.62
CAPS	816	52	0.0046 (-0.0143, 0.0236)	0.0097	0.59	0.11	0.49	0.49
FINRISK97	1150	56	0.0095 (-0.0141, 0.0331)	0.0120	0.64	0.17	0.31	0.31
EAS	741	60	-0.0046 (-0.0239, 0.0148)	0.0099	0.68	0.05	0.47	0.47
BRUN	817	66	0.0024 (-0.0086, 0.0135)	0.0056	0.75	0.06	1.43	1.43
MOGERAUG2	1265	74	0.0118 (-0.0043, 0.0279)	0.0082	0.84	0.23	0.67	0.67
HISAYAMA	2577	77	0.0087 (-0.0034, 0.0208)	0.0062	0.87	0.24	1.20	1.20
MOGERAUG1	873	79	0.0052 (-0.0083, 0.0187)	0.0069	0.90	0.18	0.96	0.96
BWHHS	2652	81	0.0058 (-0.0157, 0.0274)	0.0110	0.92	0.57	0.37	0.37
MESA	6722	83	-0.0048 (-0.0171, 0.0076)	0.0063	0.94	0.71	1.15	1.15
QUEBEC	1219	95	0.0016 (-0.0171, 0.0204)	0.0096	1.08	0.30	0.49	0.49
FINRISK92	891	104	0.0014 (-0.0124, 0.0152)	0.0070	1.18	0.12	0.92	0.92
AFTCAPS	5613	106	0.0009 (-0.0149, 0.0166)	0.0080	1.20	0.63	0.70	0.70
PREVEND	5819	115	0.0040 (-0.0038, 0.0118)	0.0040	1.31	0.70	2.85	2.85
NHANESIII	2359	127	0.0052 (-0.0001, 0.0104)	0.0027	1.44	0.34	6.29	6.29
ULSAM	926	146	0.0140 (-0.0038, 0.0318)	0.0091	1.66	0.30	0.55	0.55
WHITEII	7326	158	0.0140 (0.0017, 0.0262)	0.0062	1.79	2.03	1.17	1.17
RANCHO	1381	161	0.0036 (-0.0062, 0.0134)	0.0050	1.83	0.25	1.81	1.81
WHITEI	3808	202	0.0159 (0.0019, 0.0299)	0.0071	2.29	1.86	0.89	0.89
ROTT	4437	229	0.0053 (-0.0026, 0.0132)	0.0040	2.60	1.18	2.79	2.79
WHS	23287	238	-0.0043 (-0.0114, 0.0028)	0.0036	2.70	15.30	3.46	3.46
PROSPER	3180	262	0.0083 (-0.0050, 0.0216)	0.0068	2.98	0.52	0.99	0.99
SHS	3112	281	0.0042 (-0.0040, 0.0124)	0.0042	3.19	1.11	2.60	2.60
USPHS2	10715	311	0.0043 (-0.0038, 0.0124)	0.0041	3.53	8.85	2.68	2.68
WOSCOPS	5452	336	0.0031 (-0.0061, 0.0123)	0.0047	3.82	2.36	2.06	2.06
EPICNOR	15902	368	0.0060 (0.0003, 0.0117)	0.0029	4.18	6.90	5.39	5.39
ARIC	9326	387	0.0022 (-0.0061, 0.0105)	0.0042	4.39	3.74	2.56	2.56
KIHD	2020	395	0.0095 (0.0015, 0.0174)	0.0040	4.49	1.84	2.78	2.78
COPEN	7772	458	0.0049 (0.0019, 0.0079)	0.0015	5.20	4.10	19.86	19.86
CHS	4211	614	0.0010 (-0.0063, 0.0084)	0.0038	6.97	2.79	3.22	3.22
REYK	14927	2876	0.0053 (0.0027, 0.0079)	0.0013	32.66	41.88	25.48	25.48
Overall (I-squared = 0.0%, p = 0.911)								
Overall # events WT			0.0051 (0.0035, 0.0066)	0.0008	100			
Overall Informative pairs WT			0.0038 (0.0020, 0.0057)	0.0010		100		
Overall IV fixed effect WT			0.0048 (0.0034, 0.0061)	0.0007			100	
Overall IV random effect WT			0.0048 (0.0034, 0.0061)	0.0007				100
Random effect 95% prediction interval			(0.0034, 0.0061)					

C-index change with addition of log CRP

Meta-analysis of C-index change

Comparison of study weights

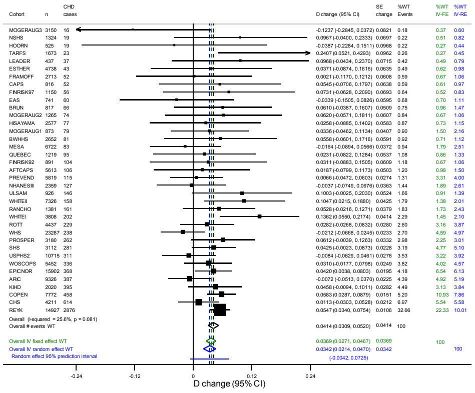


○ # events WT ○ Informative pairs WT ○ IV fixed effect WT ○ IV random effect WT

The pooled estimates for the 4 weighting methods respectively are:
0.0051 (p = 0.000), 0.0038 (p = 0.000), 0.0048 (p = 0.000), and 0.0048 (p = 0.000)

C-index change with addition of log CRP

Meta-analysis of D change

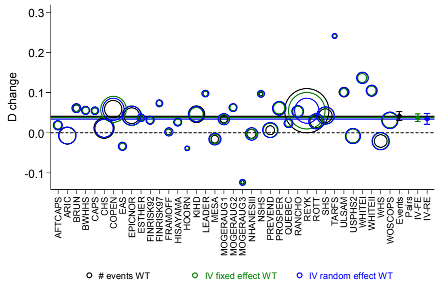


Cohort	n	CHD cases	D change (95% CI)	SE change	%WT Events	%WT IV-FE	%WT IV-RE
MOGERAUG3	3150	16	-0.1237 (-0.2845, 0.0372)	0.0821	0.18	0.37	0.60
NSHS	1324	19	0.0967 (-0.0400, 0.2333)	0.0697	0.22	0.51	0.82
HOORN	525	19	-0.0387 (-0.2284, 0.1511)	0.0968	0.22	0.27	0.44
TARFS	1673	23	0.2407 (0.0521, 0.4293)	0.0962	0.26	0.27	0.45
LEADER	437	37	0.0968 (-0.0434, 0.2370)	0.0715	0.42	0.49	0.79
ESTHER	4738	43	0.0371 (-0.0874, 0.1616)	0.0635	0.49	0.62	0.98
FRAMOFF	2713	52	0.0021 (-0.1170, 0.1212)	0.0608	0.59	0.67	1.06
CAPS	816	52	0.0545 (-0.0706, 0.1797)	0.0638	0.59	0.61	0.97
FINRISK97	1150	56	0.0731 (-0.0628, 0.2090)	0.0693	0.64	0.52	0.83
EAS	741	60	-0.0339 (-0.1505, 0.0826)	0.0595	0.68	0.70	1.11
BRUN	817	66	0.0610 (-0.0387, 0.1607)	0.0509	0.75	0.96	1.47
MOGERAUG2	1265	74	0.0620 (-0.0571, 0.1811)	0.0607	0.84	0.67	1.06
HISAYAMA	2577	77	0.0258 (-0.0885, 0.1402)	0.0583	0.87	0.73	1.15
MOGERAUG1	873	79	0.0336 (-0.0462, 0.1134)	0.0407	0.90	1.50	2.16
BWHHS	2652	81	0.0558 (-0.0601, 0.1716)	0.0591	0.92	0.71	1.12
MESA	6722	83	-0.0164 (-0.0894, 0.0566)	0.0372	0.94	1.79	2.51
QUEBEC	1219	95	0.0231 (-0.0822, 0.1284)	0.0537	1.08	0.86	1.33
FINRISK92	891	104	0.0311 (-0.0883, 0.1505)	0.0609	1.18	0.67	1.06
AFTCAPS	5613	106	0.0187 (-0.0799, 0.1173)	0.0503	1.20	0.98	1.50
PREVEND	5819	115	0.0066 (-0.0472, 0.0603)	0.0274	1.31	3.31	4.00
NHANESIII	2359	127	-0.0037 (-0.0749, 0.0676)	0.0363	1.44	1.89	2.61
ULSAM	926	146	0.1003 (-0.0025, 0.2030)	0.0524	1.66	0.91	1.39
WHITEII	7326	158	0.1047 (0.0215, 0.1880)	0.0425	1.79	1.38	2.01
RANCHO	1381	161	0.0528 (-0.0216, 0.1271)	0.0379	1.83	1.73	2.43
WHITEI	3808	202	0.1362 (0.0550, 0.2174)	0.0414	2.29	1.45	2.10
ROTT	4437	229	0.0282 (-0.0268, 0.0832)	0.0280	2.60	3.16	3.87
WHS	23287	238	-0.0212 (-0.0668, 0.0245)	0.0233	2.70	4.59	4.97
PROSPER	3180	262	0.0612 (-0.0039, 0.1263)	0.0332	2.98	2.25	3.01
SHS	3112	281	0.0425 (-0.0023, 0.0873)	0.0228	3.19	4.77	5.10
USPHS2	10715	311	-0.0084 (-0.0629, 0.0461)	0.0278	3.53	3.22	3.92
WOSCOPS	5452	336	0.0310 (-0.0177, 0.0798)	0.0249	3.82	4.02	4.57
EPICNOR	15902	368	0.0420 (0.0038, 0.0803)	0.0195	4.18	6.54	6.13
ARIC	9326	387	-0.0072 (-0.0513, 0.0370)	0.0225	4.39	4.92	5.19
KIHD	2020	395	0.0458 (-0.0094, 0.1011)	0.0282	4.49	3.13	3.84
COPEN	7772	458	0.0583 (0.0287, 0.0879)	0.0151	5.20	10.93	7.86
CHS	4211	614	0.0113 (-0.0303, 0.0528)	0.0212	6.97	5.54	5.58
REYK	14927	2876	0.0547 (0.0340, 0.0754)	0.0106	32.66	22.33	10.01
Overall (I-squared = 25.6%, p = 0.081)							
Overall # events WT			0.0414 (0.0309, 0.0520)	0.0414	100		
Overall IV fixed effect WT			0.0369 (0.0271, 0.0467)	0.0369		100	
Overall IV random effect WT			0.0342 (0.0214, 0.0470)	0.0342			100
Random effect 95% prediction interval			(-0.0042, 0.0725)				

D change with addition of log CRP

Meta-analysis of D change

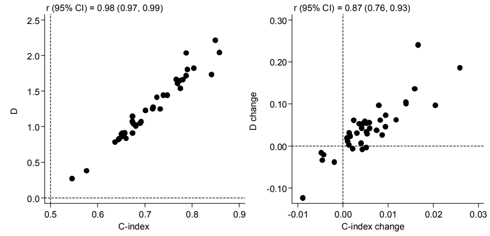
Comparison of study weights



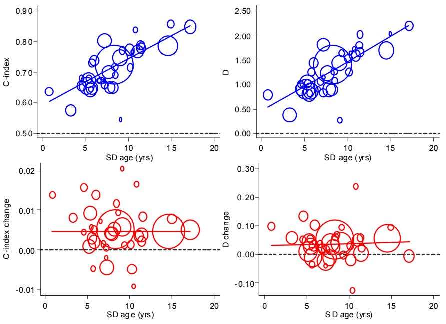
The pooled estimates for the 4 weighting methods respectively are:
0.0414 (p = 0.000), 0.0331 (p = 0.000), 0.0369 (p = 0.000), and 0.0342 (p = 0.000)

D change with addition of log CRP

Good study-level correlation between absolute values of C-index and D, as well as between changes.



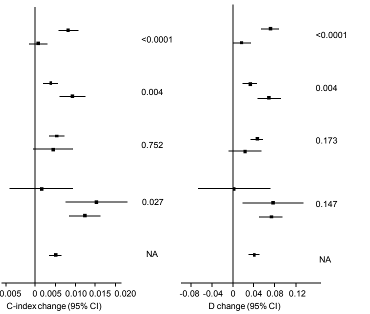
The large between-study heterogeneity in absolute values of C-index or D is explained by age distribution.



Size of circle is proportional to 1/variance of estimate

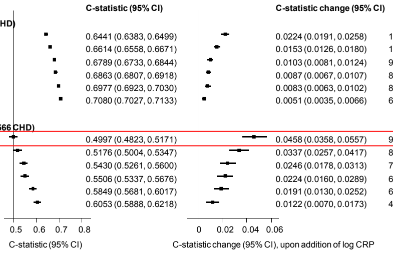
Examination of subgroup effects need necessarily restrict inferences to studies with all levels observed.

Variable\ Subgroup	No. of studies	No. of participants	CHD cases	P-value for heterogeneity	P-value for heterogeneity
Sex					
Male	24	53037	4189	<0.0001	<0.0001
Female	24	58199	2515		
Smoking status					
Other	36	128676	5403	0.004	0.004
Current	36	35507	3380		
History of diabetes					
No	36	144353	7491	0.752	0.173
Yes	36	10788	1004		
Framingham 2008 10-yr CVD risk					
0%-<10%	30	62715	932	0.027	0.147
10%-<20%	30	47161	2527		
>=20%	30	47069	4808		
Overall	37	165856	8806	NA	NA



Case-control studies are particularly problematic because of matching on predictive covariates.

Study design \ Base model variables	C-statistic (95% CI)	C-statistic change (95% CI)	Z	P-value
Cohort (37 studies, 8806 CHD)				
Age	0.6441 (0.6383, 0.6499)	0.0224 (0.0191, 0.0258)	13.2	<0.0001
Above + smoking status	0.6614 (0.6558, 0.6671)	0.0153 (0.0126, 0.0180)	11.1	<0.0001
Above + systolic BP	0.6789 (0.6733, 0.6844)	0.0103 (0.0081, 0.0124)	9.2	<0.0001
Above + history of diabetes	0.6863 (0.6807, 0.6918)	0.0087 (0.0067, 0.0107)	8.5	<0.0001
Above + total cholesterol	0.6977 (0.6923, 0.7030)	0.0083 (0.0063, 0.0102)	8.4	<0.0001
Above + HDL cholesterol	0.7080 (0.7027, 0.7133)	0.0051 (0.0035, 0.0066)	6.3	<0.0001
Case-control (8 studies, 1566 CHD)				
Age	0.4997 (0.4823, 0.5171)	0.0458 (0.0358, 0.0557)	9.0	<0.0001
Above + smoking status	0.5176 (0.5004, 0.5347)	0.0337 (0.0257, 0.0417)	8.2	<0.0001
Above + systolic BP	0.5430 (0.5261, 0.5600)	0.0246 (0.0178, 0.0313)	7.1	<0.0001
Above + history of diabetes	0.5506 (0.5337, 0.5676)	0.0224 (0.0160, 0.0289)	6.8	<0.0001
Above + total cholesterol	0.5849 (0.5681, 0.6017)	0.0191 (0.0130, 0.0252)	6.1	<0.0001
Above + HDL cholesterol	0.6053 (0.5888, 0.6218)	0.0122 (0.0070, 0.0173)	4.6	<0.0001



Reclassification

- Methods proposed to give a more clinically relevant assessment of the improvement in risk prediction given by a new marker.
- Examine the net movement of participants between clinically relevant groups of predicted risk (e.g. 10-year CVD risk groups of 0-10%, 10-20%, and ≥20%).
- The Net Reclassification Improvement (NRI)
  - Retrospective NRI (Pencina et al 2008)
  - Prospective NRI } Pencina et al 2010
  - Continuous NRI } Pencina et al 2010

‘Retrospective’ NRI (Pencina et al 2008)

- Measure of appropriate reclassification (ie: events move up and non-events move down the risk categories)

$$\text{NRI} = \underbrace{P(\text{up}|\text{event}) - P(\text{down}|\text{event})}_{\text{Net proportion of events appropriately reclassified}} + \underbrace{P(\text{down}|\text{non-event}) - P(\text{up}|\text{non-event})}_{\text{Net proportion of non-events appropriately reclassified}}$$

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Reclassification table

Reclassification table for addition of CRP to conventional CVD risk factors (22 studies, 72574 participants):

Model without CRP	Model with CRP: 10 yr CVD risk (%)		
10-yr CVD risk	0 to <10%	10% to <20%	≥20%
Observed to have a CVD event within 10 years (n=6848)			
0 to <10%	2424	🟩 162	🟩 0
10% to <20%	🟥 131	1684	🟩 213
≥20%	🟥 0	🟥 144	2088
Observed to be event free at 10 years (n=65728)			
0 to <10%	53102	🟥 922	🟥 0
10% to <20%	🟩 993	6959	🟥 432
≥20%	🟩 0	🟩 403	2917

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Summary measures of reclassification

Addition of CRP to CVD risk factors (22 studies, 72574 participants)	**N (%) or Statistic**	**P-value**
Participants who developed CVD within 10 years	6846	
Appropriately reclassified	375 (5.48%)	
Inappropriately reclassified	275 (4.02%)	
No change	6196 (90.51%)	
NRI (95% CI),	1.46% (0.73%, 2.19%)	<0.0001
Participants event free at 10 years	65728	
Appropriately reclassified	1396 (2.12%)	
Inappropriately reclassified	1354 (2.06%)	
No change	62978 (95.82%)	
NRI (95% CI),	0.06% (-0.09%, 0.22%)	0.423
Overall		
NRI (95% CI)	1.52% (0.78%, 2.27%)	<0.0001
IDI (95% CI)	0.0036 (0.0028, 0.0043)	<0.0001

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Issue with the ‘Retrospective’ NRI

- Probabilities estimates are regarding the likelihood of moving up or down through risk categories among events and non-events:

NRI = P(up|event) - P(down|event) + P(down|non-event) - P(up|non-event)

- Need to know whether each participant has or has not had an event by 10 years.
- Cannot include participants whose records are censored before 10 years.

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Prospective NRI (Pencina et al 2010)

- Pencina et al rearranged the ‘retrospective’ equation, borrowing from Bayes theorem to give:

$$\text{NRI} = \frac{P(events\,|\,up)\times n_U - P(event\,|\,down)\times n_D}{n\times P(event)} + \frac{(1-P(events\,|\,down)\times n_D - (1-P(event\,|\,up))\times n_U}{n\times(1-P(event))}$$

- Now we only need to know whether a person moves up or down a risk category (this is defined for all participants).

- The quantities P(event | up) and P(event | down) are easily estimated using Kaplan-Meier methods, and hence all censored observations can be included.

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ERFC methods: Reclassification

- Reclassification: NRI(0.10, 0.20), NRI(>0), IDI.
  - 10-year risk calculated from stratified Cox model.
  - Category NRI(0.10, 0.20) calculated based on reclassification tables collapsed across studies by observed event status at 10-years (i.e. 1-stage). IDI also calculated by 1-stage method.
  - Sensitivity analysis using 2-stage method (i.e. pooling study-specific NRI(0.10, 0.20) and IDI by meta-analysis).
  - Continuous NRI(>0) calculated within studies based on K-M estimates of 10-year risk among those reclassified up vs. down and then pooled across studies by meta-analysis (i.e. 2-stage).
  - Appropriate weighting of the study-specific NRI’s remains to be determined.

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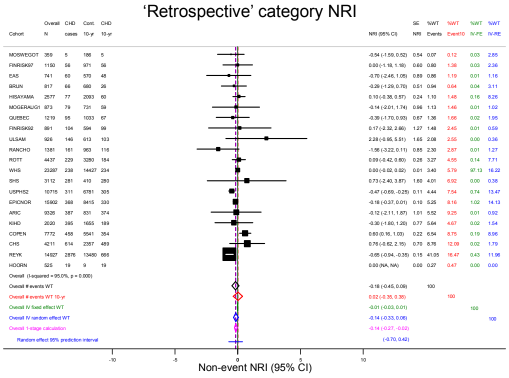
Meta-analysis of Non-event NRI(0.10, 0.20)

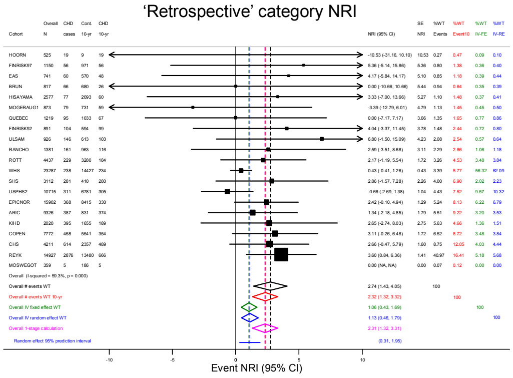
'Retrospective' category NRI



NRI with addition of log CRP

Meta-analysis of Event NRI(0.10, 0.20)

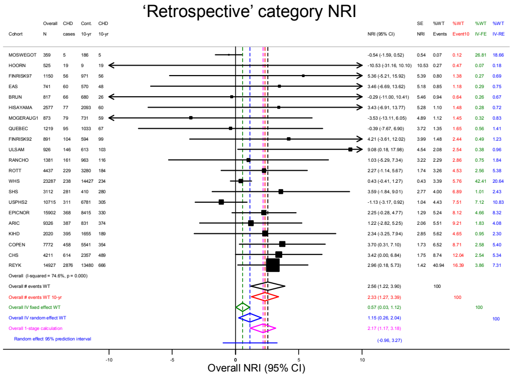
'Retrospective' category NRI



NRI with addition of log CRP

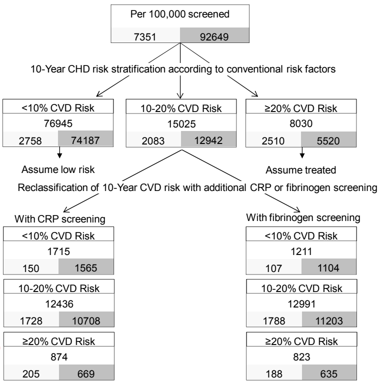
Meta-analysis of Overall NRI(0.10, 0.20)

'Retrospective' category NRI



NRI with addition of log CRP

Potential public health impact of (sequential) screening



Per 100,000 screened

7351 | 92649

10-Year CHD risk stratification according to conventional risk factors

<10% CVD Risk: 76945 (2758 | 74187)

10-20% CVD Risk: 15025 (2083 | 12942)

≥20% CVD Risk: 8030 (2510 | 5520)

Assume low risk

Assume treated

Reclassification of 10-Year CVD risk with additional CRP or fibrinogen screening

With CRP screening			With fibrinogen screening		
<10% CVD Risk	1715	150 / 1565	<10% CVD Risk	1211	107 / 1104
10-20% CVD Risk	12436	1728 / 10708	10-20% CVD Risk	12991	1788 / 11203
≥20% CVD Risk	874	205 / 669	≥20% CVD Risk	823	188 / 635

Assume:
Treated if risk > 20%
RR reduction = 20% (statins)

Number needed to screen (NNS) per event avoided: 366 400

Remarks

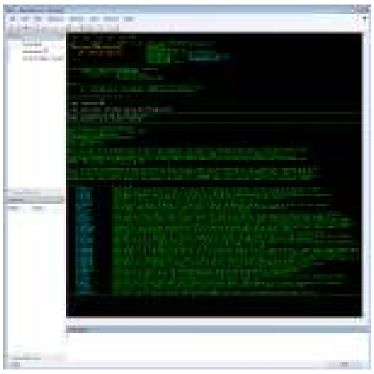
- IPD meta-analysis provides a powerful means for quantifying improvements in risk prediction, but comes with challenges in choice of weighting across studies.
- In particular, uncertainties remain in 2-stage methods for meta-analysis of NRI/IDI because of the separate calculations in Events and Non-Events.
  - What weight is most appropriate for the meta-analysis of the Event and Non-Event NRI's (possibly N and Events)?
  - How should the overall NRI be calculated? Pool the study-specific overall NRI's? or calculate from pooled Event and Non-Event NRI's (possibly the former, but what weights?).
  - To what extent should we be concerned of sparse data in small studies?

Stata software for IPD meta-analysis

http://www.phpc.cam.ac.uk/ceu/research/erfc/stata/

Installable from within Stata

. net from http://www.phpc.cam.ac.uk/ceu/research/erfc/stata/



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Remarks

- Large-scale IPD meta-analysis is helping to powerfully unravel finer details of exposure-disease associations and assessment of improvement in risk prediction than possible in individual studies.

- Methods and software developed in ERFC have been made publicly available.
  - Methods paper: Int J Epidemiol 2010(39)1345-59.
  - Stata software website: http://www.phpc.cam.ac.uk/ceu/research/erfc/stata/

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- ERFC collaborators
  - http://www.phpc.cam.ac.uk/ceu/research/erfc/studies/

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