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Dealing with Heterogeneity in Network Meta-analysis

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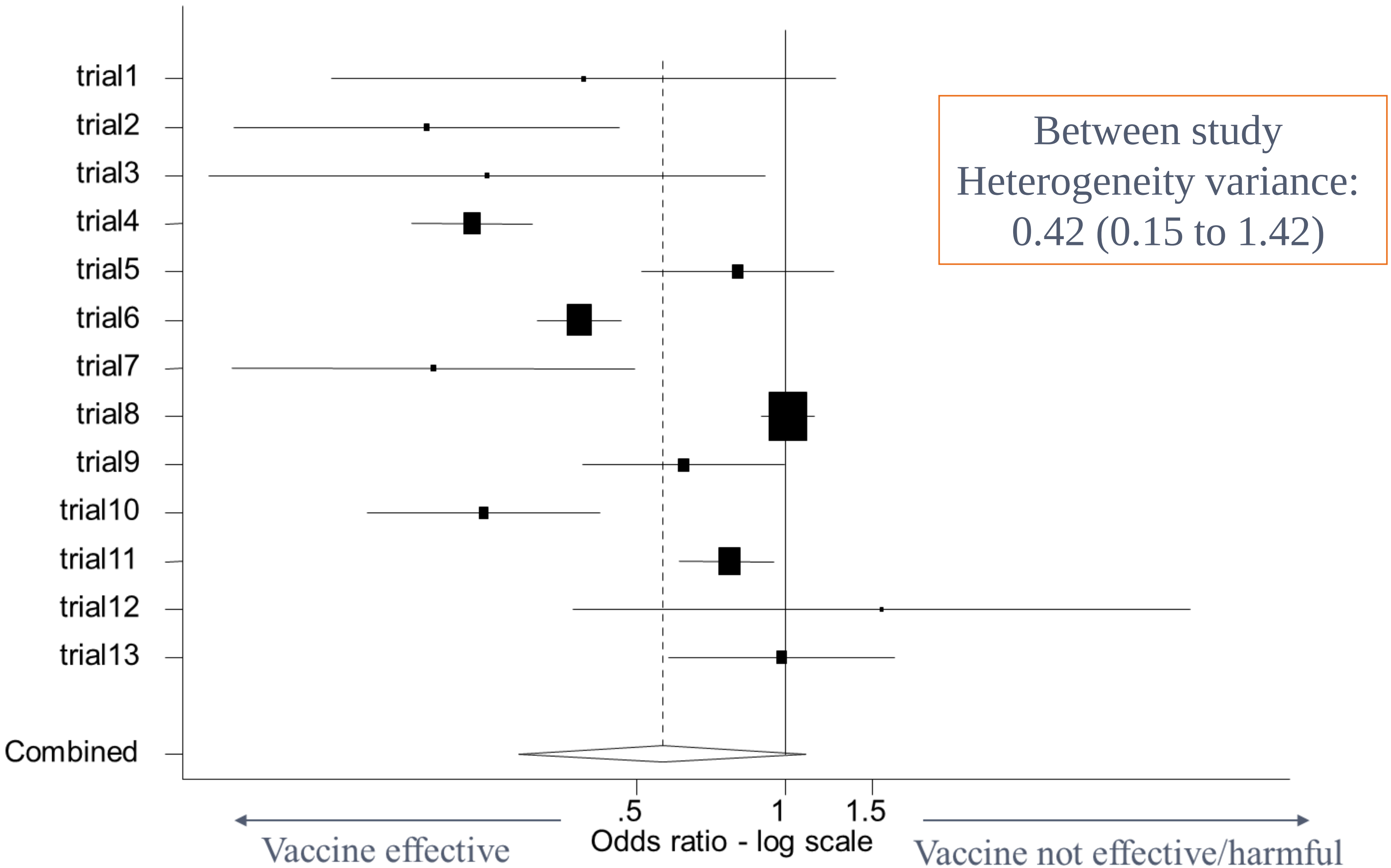
Heterogeneity

- What causes **between study heterogeneity**?
  - Differences in patients
  - Differences in study design/conduct
  - Chance
- Can fit **Random Effects** models but these **only account** for the heterogeneity – they do not **explain** it!

Example: Vaccine for the prevention of TB



Exploring Heterogeneity

- **Subgroup analyses** or **Meta-regression** methods can help to explain heterogeneity by examining associations between study characteristics and treatment effects
  - **Subgroup analysis**
    - Fits separate analyses to each subgroup; therefore, estimating the between-study heterogeneity (τ^2) separately for each subgroup
  - **Meta-regression**
    - Fits covariates within the meta-analysis framework; therefore assuming between-study heterogeneity (τ^2) to be the same for all subgroups
    - Estimates the difference in intervention effect between subgroups

SUBGROUP ANALYSIS
Pairwise and Network Meta-analysis

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Subgroup analyses

Two types of subgroup analyses are possible:

- i) Stratification by **study characteristics**
  - Subsets of "whole" studies defined by study *(e.g. length of follow-up)* or patient characteristics *(e.g. trial eligibility criteria)* can be combined separately
- ii) Stratification by **patient characteristics**
  - "Split" data from individual studies in an attempt to identify effect modifiers *(e.g. young/old, etc)*
  - Has more power than such analyses of individual trial which may be under-powered
  - Data may not be available in trial reports to do this

Example: Cholesterol data

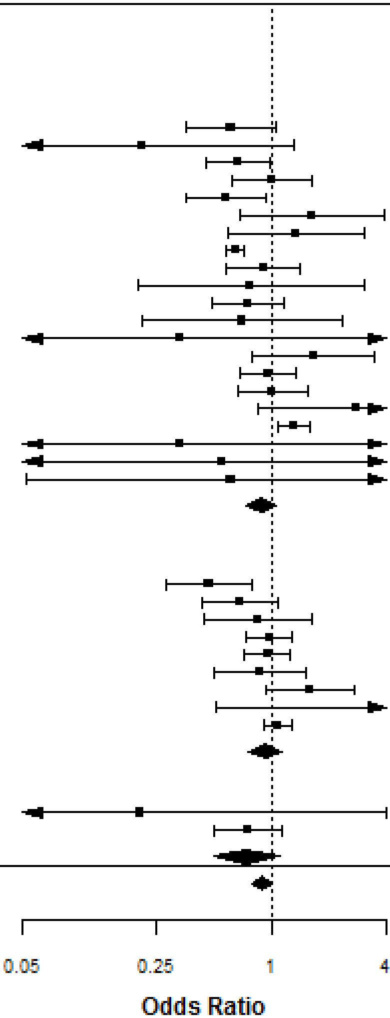
- Meta-analysis of 34 RCTs to assess the effect of cholesterol lowering interventions on overall mortality

1 = drug,
2 = diet,
3 = surgery

id	pub	nt	nc	rt	rc	chol_red	treat	fup
1	1992	204	202	28	51	7	2	2
3	1963	156	119	37	40	3	1	5
4	1981	88	30	2	3	8	1	1
6	1988	279	276	61	82	13	1	5
7	1970	206	206	41	55	14	2	5
8	1965	123	129	20	24	7	2	3
9	1989	1018	1015	111	113	4	2	2
10	1968	427	143	81	27	6	1	3
…								
…								
…								
30	1991	6582	1663	33	3	24	1	1
31	1978	5331	5296	236	181	9	1	5
32	1990	48	49	0	1	25	1	2
33	1990	94	52	1	0	25	1	3
34	1973	23	29	1	2	10	1	1

Cholesterol data: Subgroup analysis stratified by treatment type (32 RCTs)

ID and Year	Experimental Events	Experimental Total	Control Events	Control Total	Odds Ratio [95% CI]
Drug					
3, 1963	37	156	40	119	0.61 [0.36, 1.04]
4, 1981	2	88	3	30	0.21 [0.03, 1.32]
6, 1988	61	279	82	276	0.66 [0.45, 0.97]
10, 1968	81	427	27	143	1.01 [0.62, 1.63]
11, 1971	31	244	51	253	0.58 [0.35, 0.94]
12, 1961	17	50	12	50	1.63 [0.68, 3.91]
13, 1972	23	47	20	48	1.34 [0.60, 3.02]
15, 1975	1025	5552	723	2789	0.65 [0.58, 0.72]
18, 1971	42	350	48	367	0.91 [0.58, 1.41]
19, 1991	4	79	5	78	0.78 [0.20, 3.01]
20, 1978	37	1149	48	1129	0.75 [0.48, 1.16]
23, 1984	5	71	7	72	0.70 [0.21, 2.33]
26, 1987	0.5	95	1.5	95	0.33 [0.01, 8.20]
27, 1993	19	311	12	317	1.65 [0.79, 3.47]
28, 1984	68	1906	71	1900	0.95 [0.68, 1.34]
29, 1987	44	2051	43	2030	1.01 [0.66, 1.55]
30, 1991	33	6582	3	1663	2.79 [0.85, 9.10]
31, 1978	236	5331	181	5296	1.31 [1.07, 1.59]
32, 1990	0.5	49	1.5	50	0.33 [0.01, 8.39]
33, 1990	0.5	95	0.5	53	0.56 [0.01, 28.41]
34, 1973	1	23	2	29	0.61 [0.05, 7.22]
RE Model for Subgroup	τ = 0.24 (0.09 to 0.50)				0.88 [0.74, 1.06]
Diet					
1, 1992	28	204	51	202	0.47 [0.28, 0.78]
7, 1970	41	206	55	206	0.68 [0.43, 1.08]
8, 1965	20	123	24	129	0.85 [0.44, 1.63]
9, 1989	111	1018	113	1015	0.98 [0.74, 1.29]
16, 1969	174	424	178	422	0.95 [0.73, 1.25]
17, 1968	28	199	31	194	0.86 [0.49, 1.50]
21, 1978	39	221	28	237	1.60 [0.95, 2.70]
22, 1965	8	54	1	26	4.35 [0.51, 36.77]
24, 1989	269	4541	248	4516	1.08 [0.91, 1.29]
RE Model for Subgroup	τ = 0.21 (0.00 to 0.91)				0.93 [0.76, 1.13]
Surgery					
14, 1992	0.5	31	4.5	61	0.21 [0.01, 3.95]
25, 1990	49	421	62	417	0.75 [0.50, 1.13]
RE Model for Subgroup	τ = 0.00 (0.00 to >10)				0.74 [0.49, 1.10]
RE Model for All Studies					0.89 [0.78, 1.01]



*2 studies excluded due to missing covariate data

META-REGRESSION
Pairwise and Network Meta-analysis

Meta-regression

- Continuous or categorical study level covariates can be included in Pairwise and Network Meta-analysis models to explore/adjust for systematic differences between studies
  - e.g. average age, % of patients female
- In Network Meta-analysis incorporation of study-level covariates can reduce both **heterogeneity** and **inconsistency** by allowing systematic variability between-trials to be explained.

i) **Heterogeneity** - *variation in treatment effects between trials within pairwise contrasts*, and

ii) **Inconsistency** - *variation in treatment effects between pairwise contrasts*

Example: BCG vaccine for the prevention of TB

Trial	Latitude (degrees from the equator)	Vaccinated		Not vaccinated	
		Disease	No Disease	Disease	No Disease
1	44	4	119	11	128
2	55	6	300	29	274
3	42	3	228	11	209
4	52	62	13,536	248	12,619
5	13	33	5,036	47	5,761
6	44	180	1,361	372	1,079
7	19	8	2,537	10	619
8	13	505	87,886	499	87,892
9	-27	29	7,470	45	7,232
10	42	17	1,699	65	1,600
11	18	186	50,448	141	27,197
12	33	5	2,493	3	2,338
13	33	27	16,886	29	17,825

- It is suspected that the *absolute* distance from the equator affects the efficacy of the vaccine (*Berkey 1995*)

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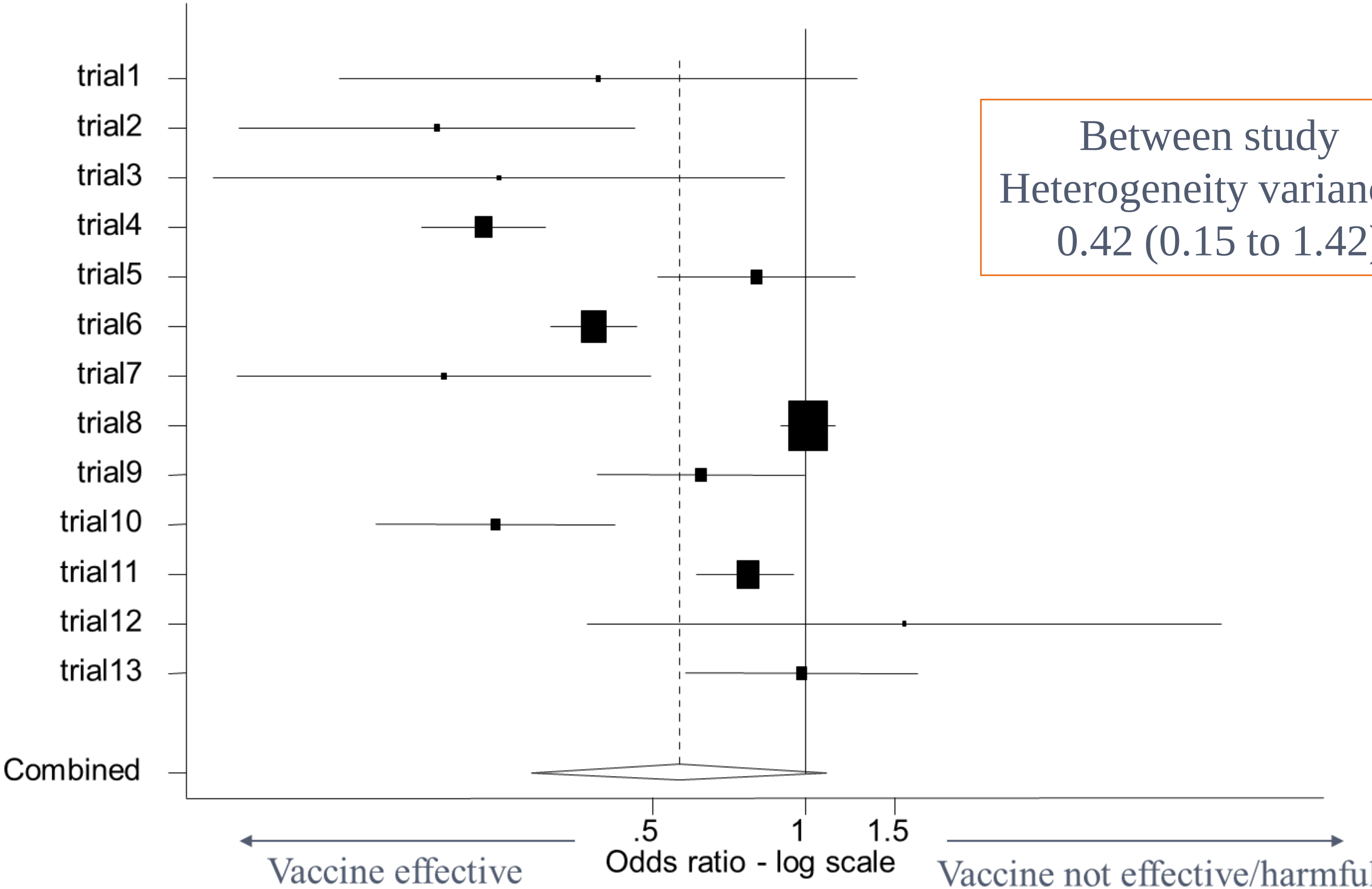
Pairwise Meta-analysis: Vaccine for the prevention of TB



Between study Heterogeneity variance: 0.42 (0.15 to 1.42)

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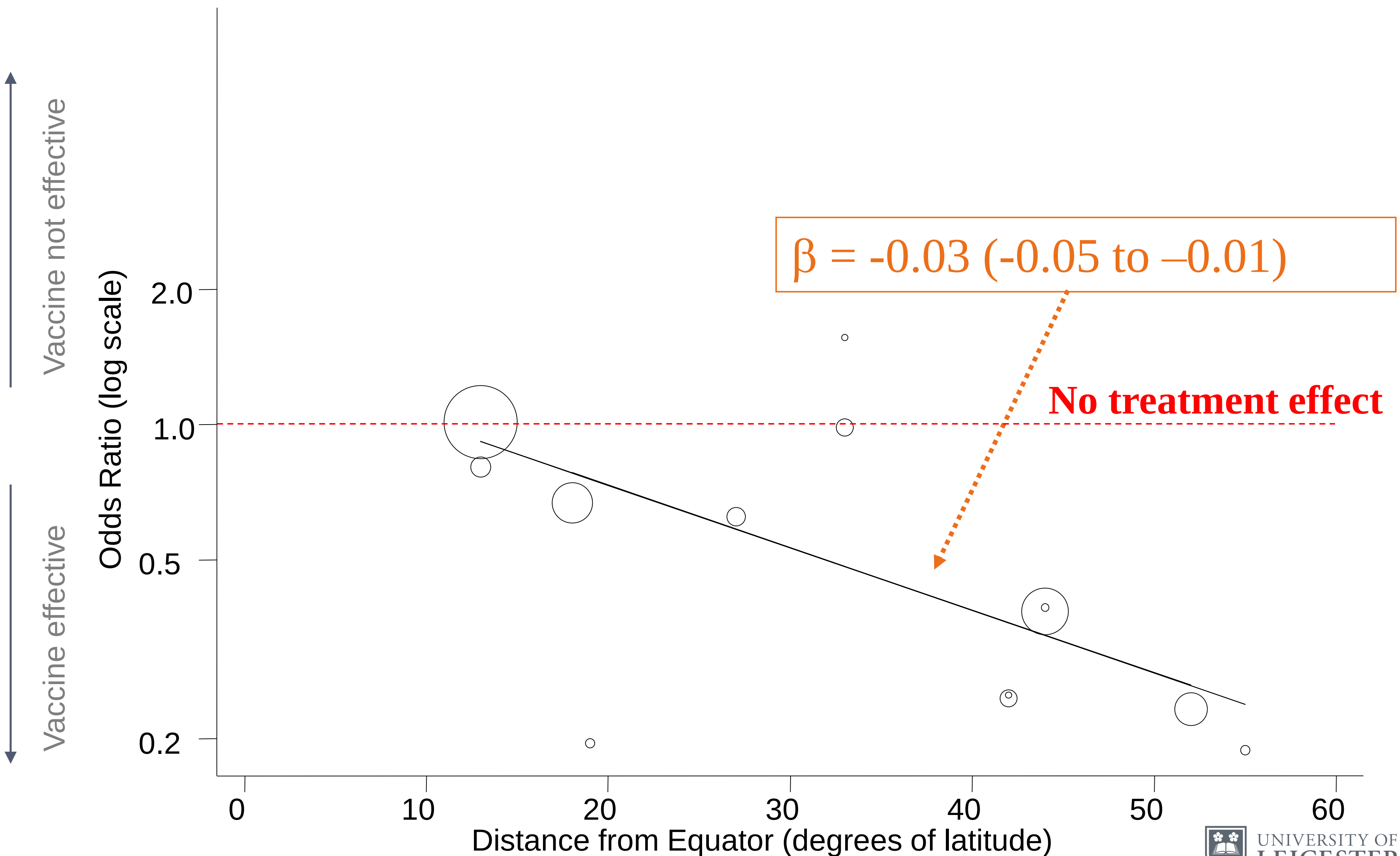
Meta-regression Results



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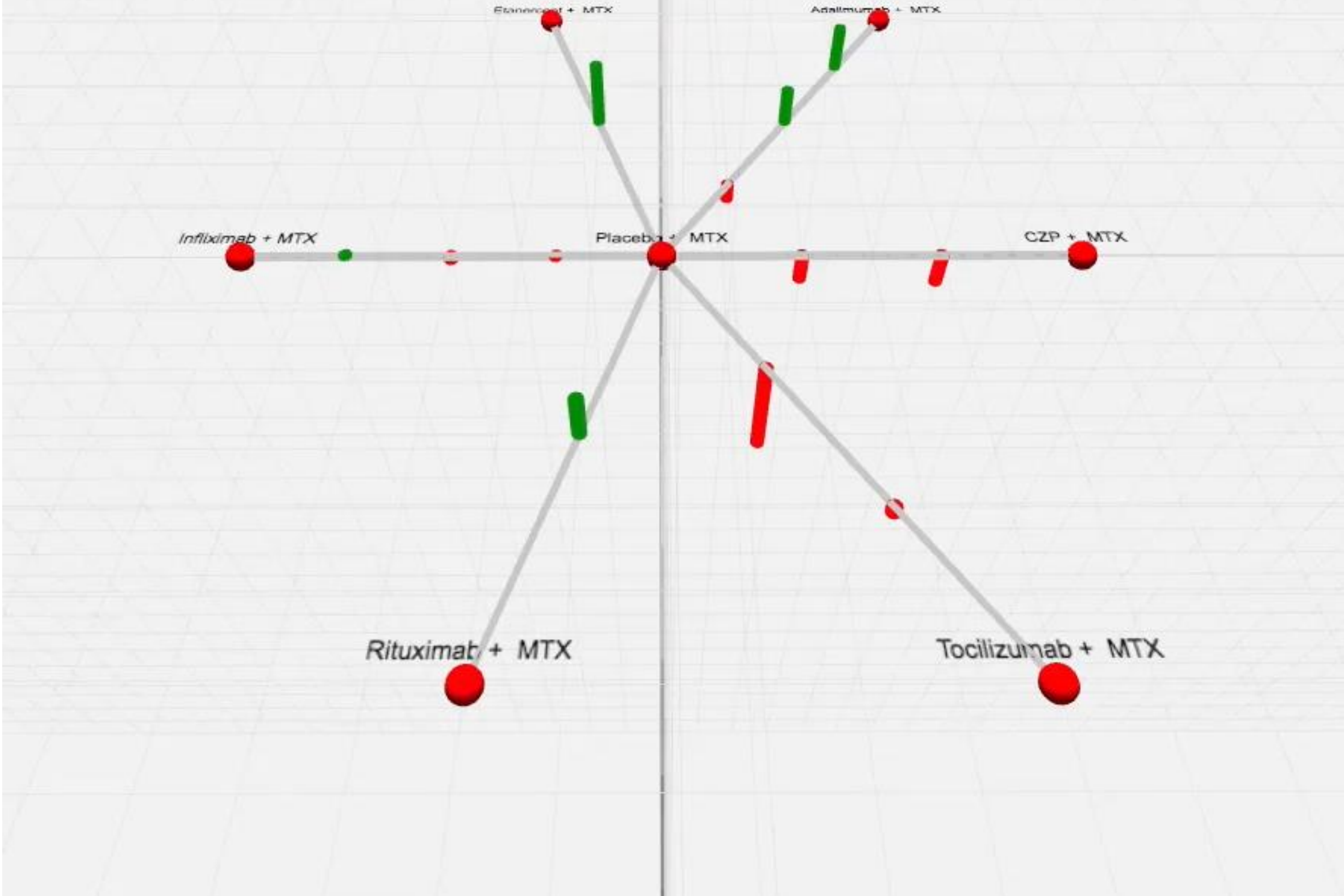
Meta-regression – Network Meta-analysis

- In Network Meta-analysis, a study-level covariate cab be seen as a variable that interacts with the intervention, but these interactions may differ for each intervention.

VISUALISING COVARIATES IN NETWORK META-ANALAYSIS: Duration of disease centred around mean



Batson et al 2017.

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Meta-regression – Network Meta-analysis

- In Network Meta-analysis, a study-level covariate can be seen as a variable that interacts with the intervention, but these interactions may differ for each intervention.
- Large number of different models with different assumptions for the interactions in a multiple intervention framework.
- Three potential models (not an exhaustive list):
  - **Independent, intervention-specific** interactions
  - **Exchangeable, related**, **intervention-specific** interactions:
  - **Same** interaction effect for all interventions:

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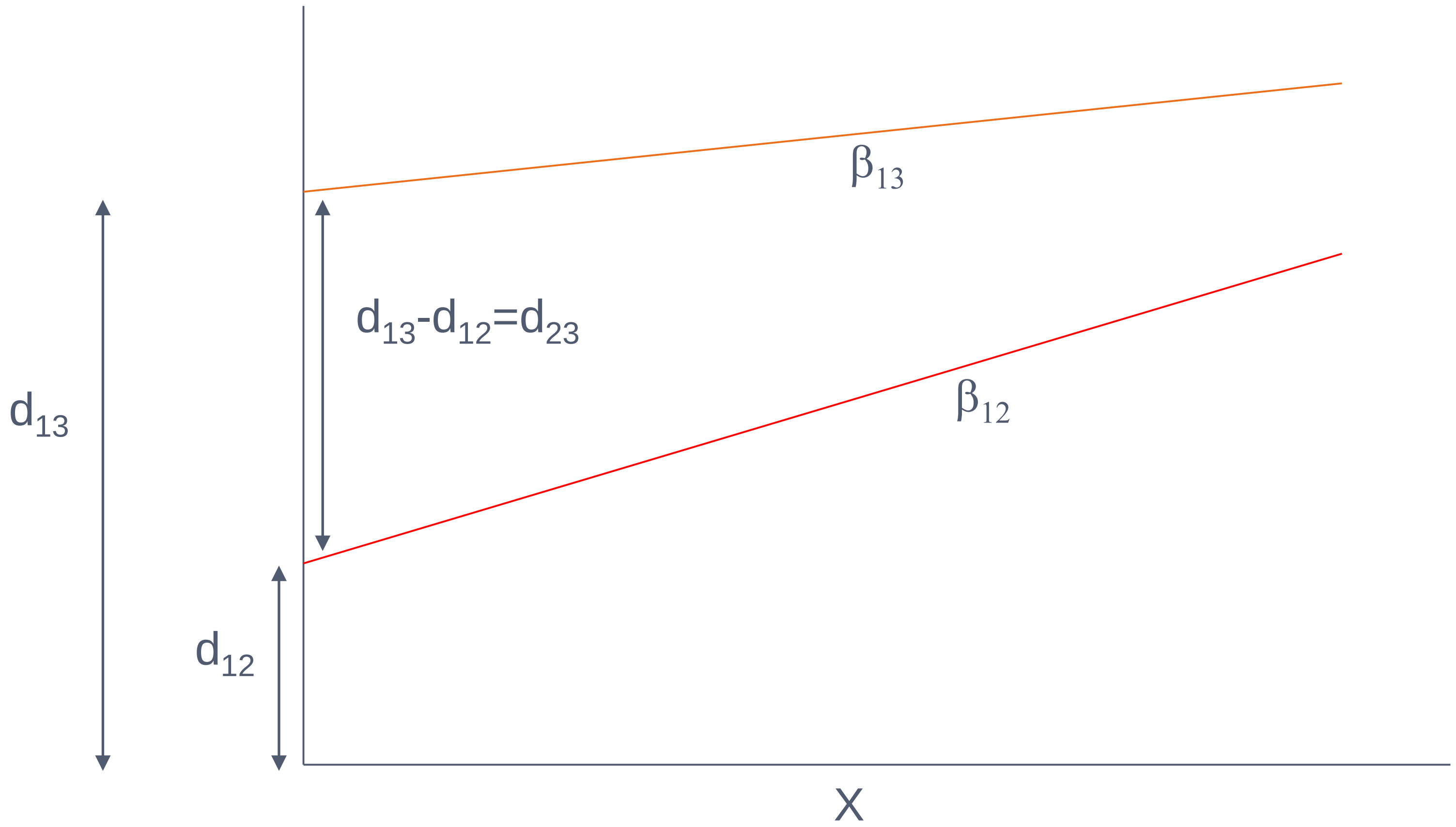
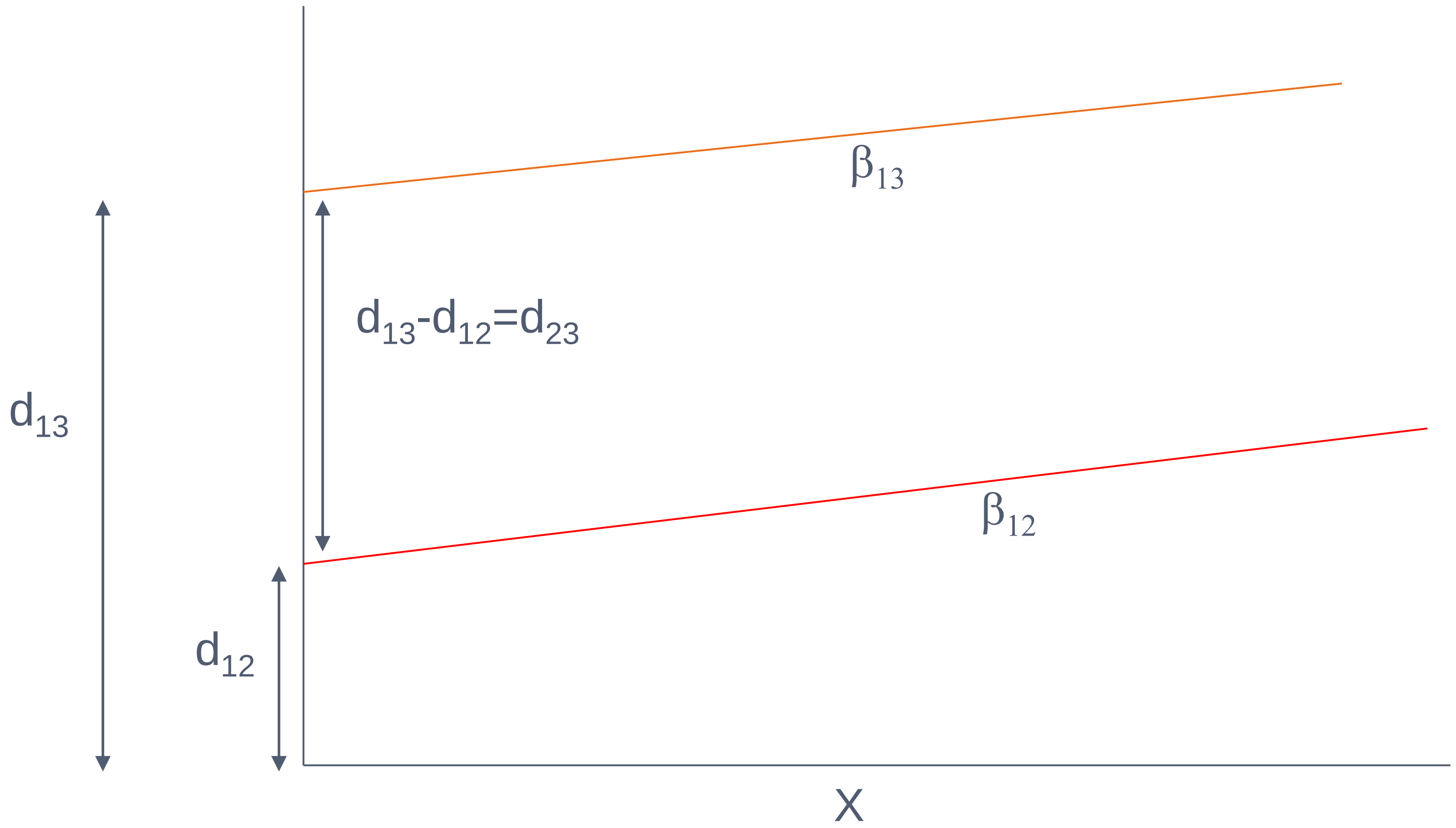
Independent, intervention specific interactions

- Independent 'beta' for each *intervention x covariate* interaction compared to intervention 1 (e.g. placebo)



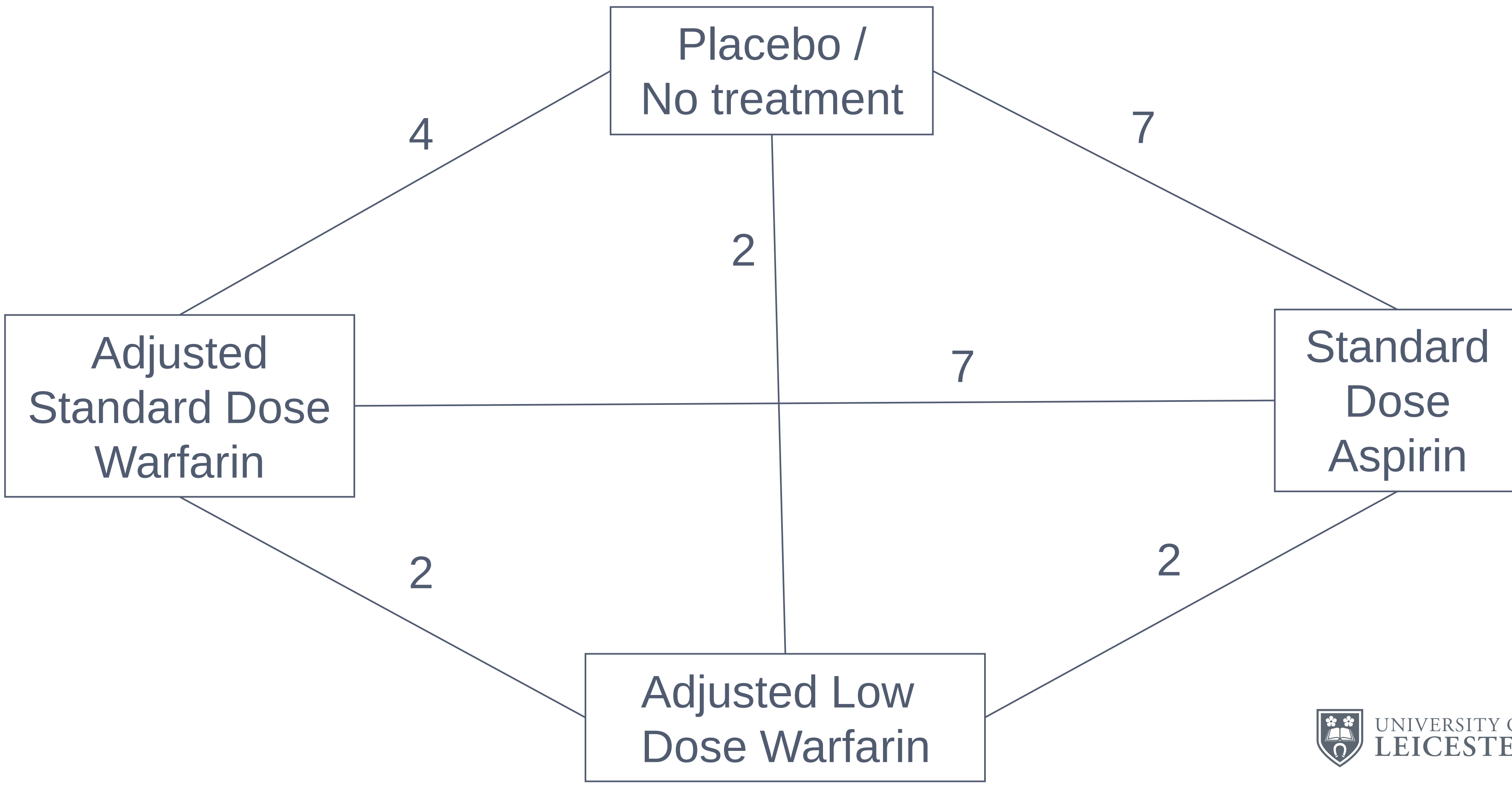
Same interaction effect for all interventions

- Common ‘beta’ for each *intervention x covariate* interaction compared to intervention 1 (e.g. placebo)

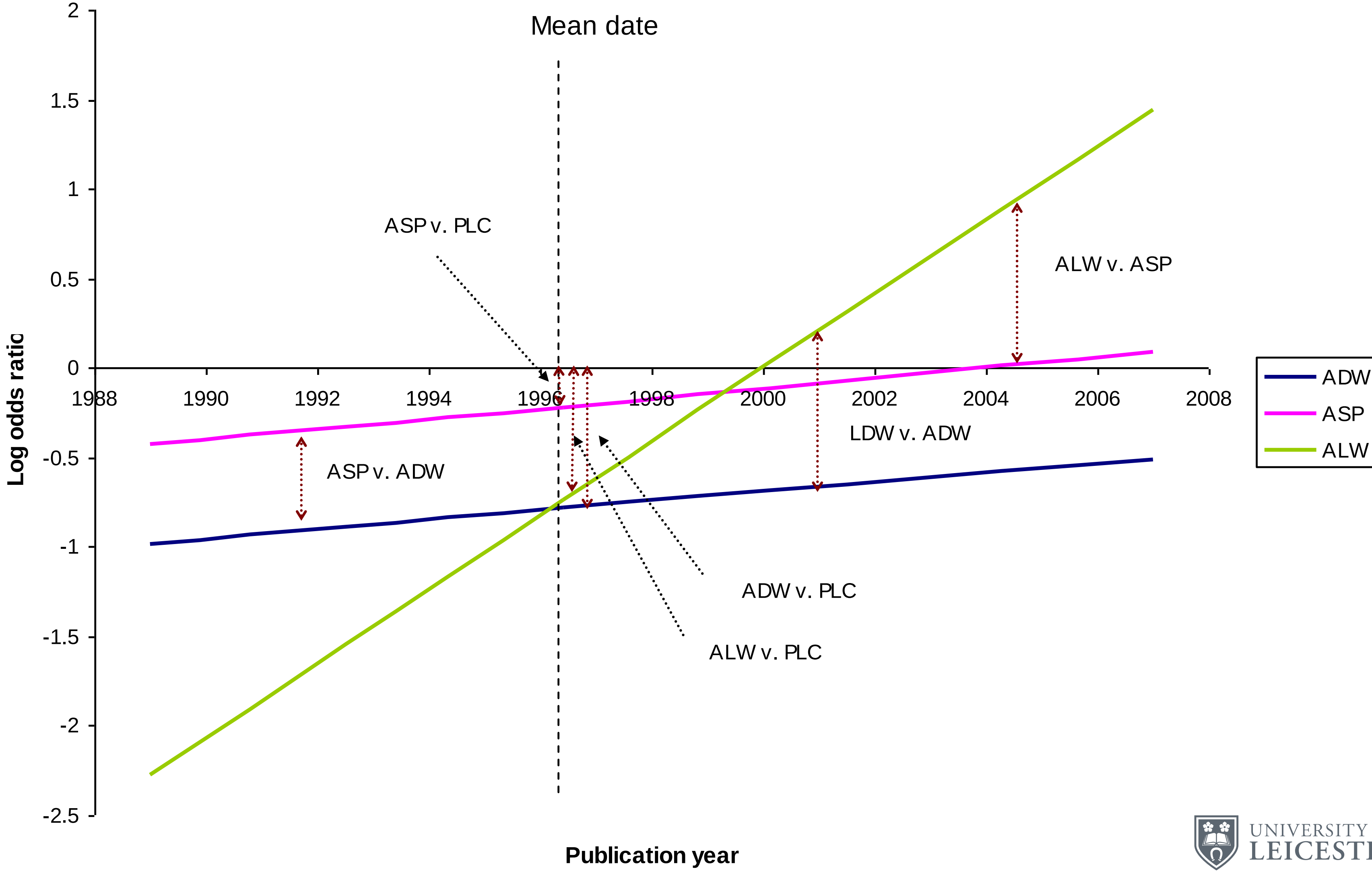


Example: Treatments to prevent stroke in non-rheumatic atrial fibrillation patients

Does date of publication *(proxy for factors relating to change in clinical practice over time)* affect treatment effects?



Example: Independent ‘beta’ for each *treatment x covariate* interaction compared to placebo



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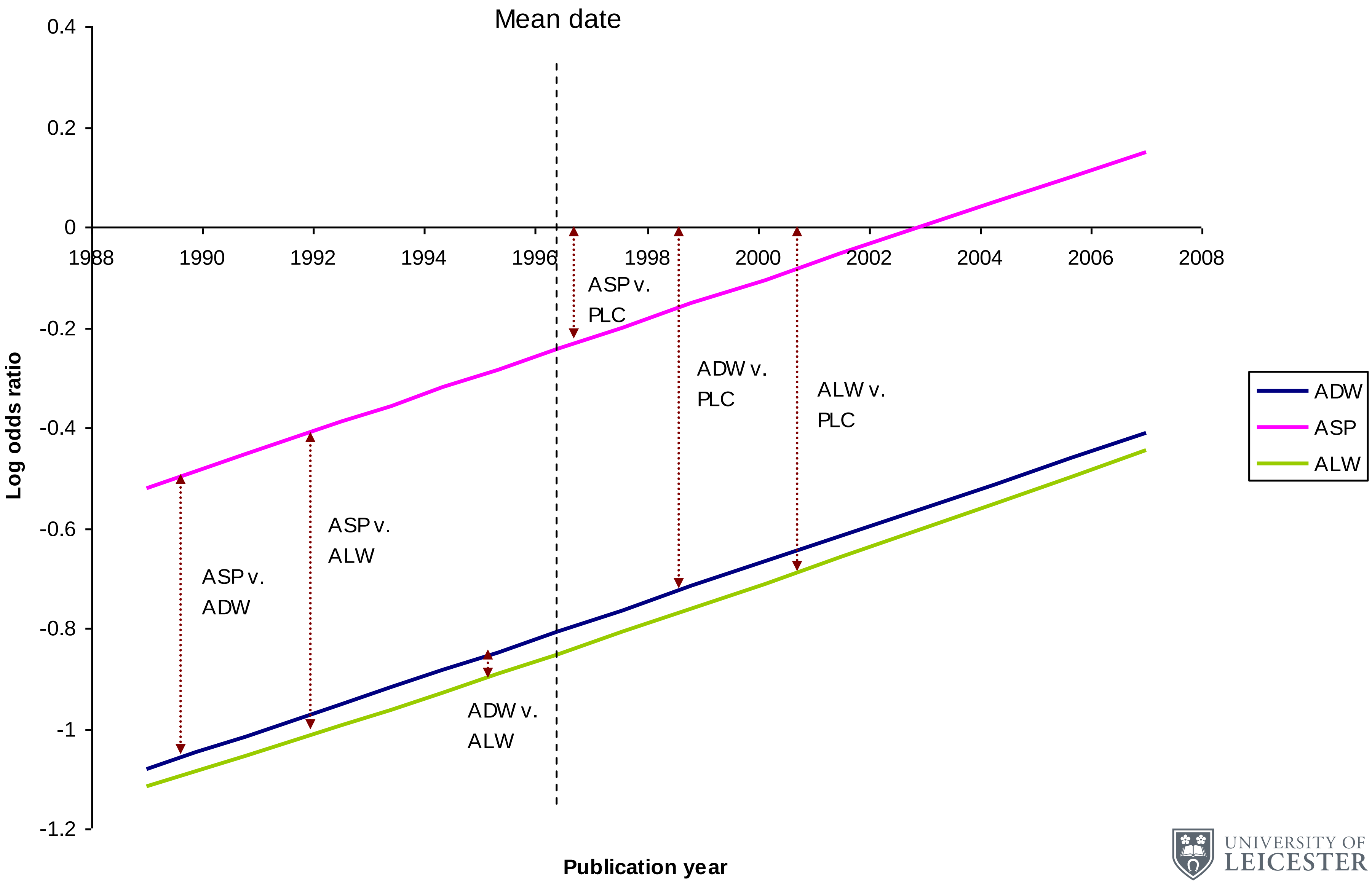
Example: Common 'beta' for *treatment x covariate* interactions compared to placebo



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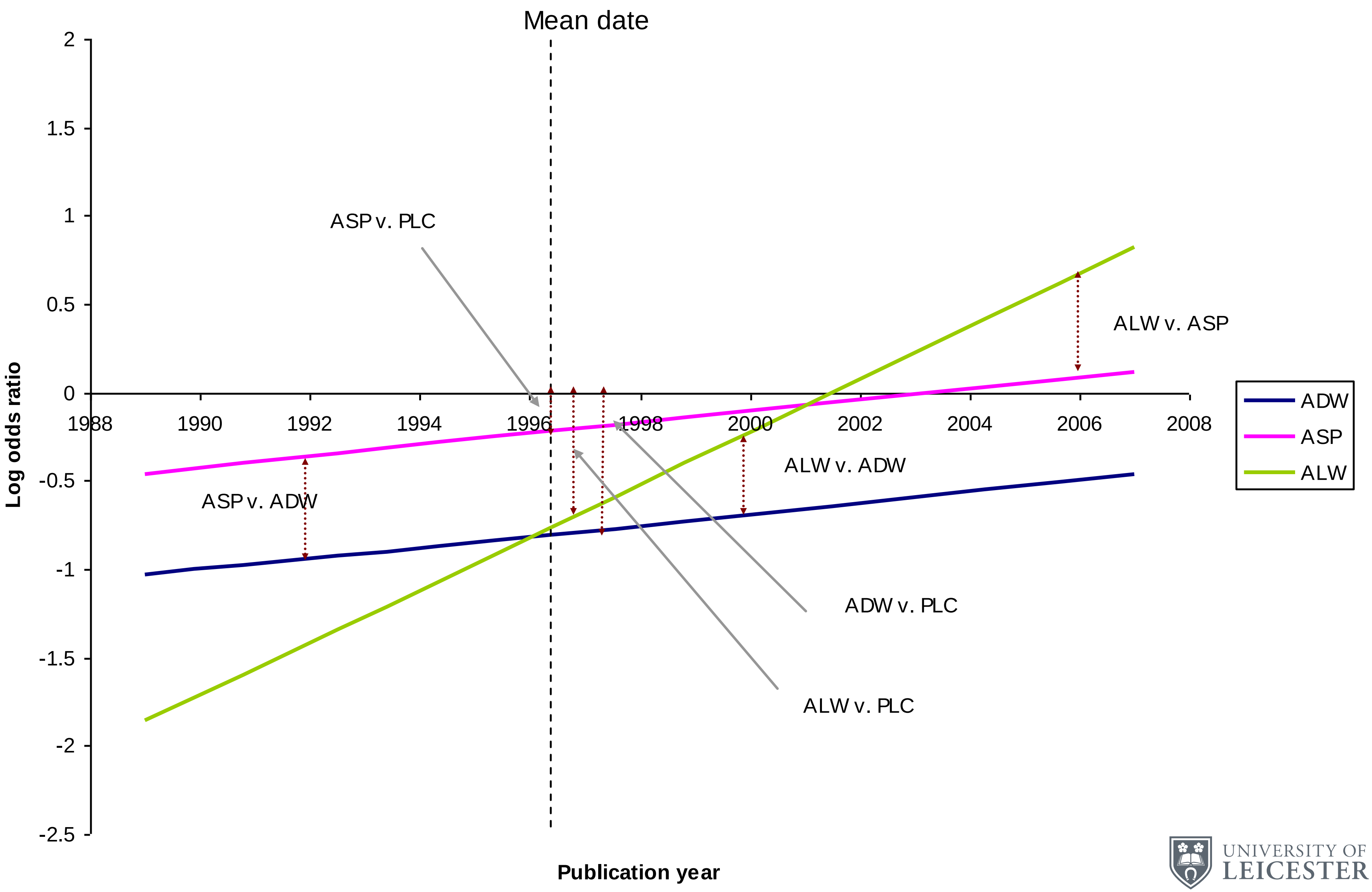
Example: Exchangeable ‘betas’ for *treatment x covariate* interactions compared to placebo



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Adjusting for Baseline Risk

- Special kind of covariate, **Baseline risk** is often defined as a proxy for underlying patient-level covariates thought to modify the intervention effect, but which cannot be accounted for directly in the model (i.e. unmeasured or unknown – e.g. medical history, co-morbidities, etc.).
  - That is, reflects the risk of an event for a patient under the reference intervention
- Need to take into account the correlation between the intervention effect and baseline risk.
  - Methods for including baseline risk as a covariate have been extended to Network Meta-analysis (*Dias et al. 2011, Achana et al. 2013*)

Summary

- Focused on using **Meta-regression with aggregate data**; however, often too few studies resulting in insufficient data to detect *intervention x covariate* interactions (Lambert et al., 2002)
- If **Individual Patient Data** (IPD) available, alternative strategy to relate intervention effect to individual patient characteristics to investigate heterogeneity
  - More powerful than average effect vs. average covariate value meta-regression
  - Few examples of IPD meta-regression with network meta-analysis (Veroniki et al. 2016)
- Other analyses
  - **Component network meta-analysis** for complex interventions (Welton et al. 2009, Freeman et al. 2018)
  - **Multiple outcomes** (Riley et al. 2017)

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