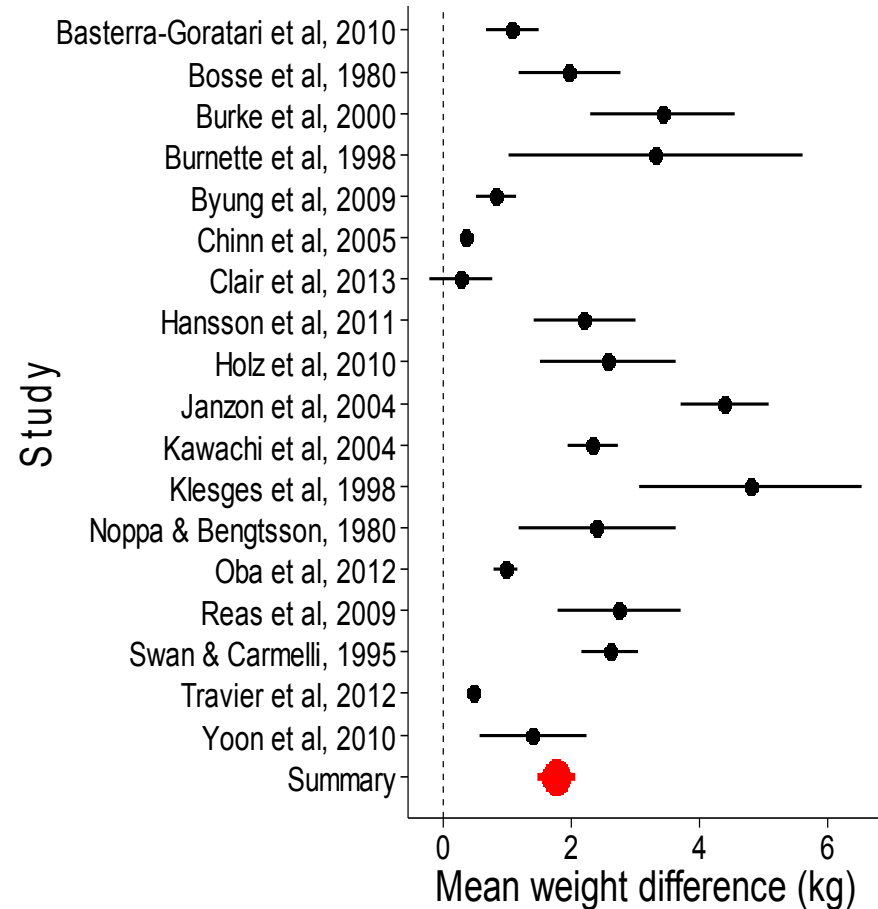


Systematic review and meta-analysis

Heterogeneity and meta-regression
Petr Otahal, Statistical Officer

- Variation between study effect-sizes.
- Caused by methodological, clinical differences between studies/trials.
- Quantified with I^2 : the ratio of between study variance to total variance.



Meta-regression – an exploration of heterogeneity

- A regression model to relate *summary* study covariates to effect-size estimates. (Not covariates on individuals)
- May explain *some* of the heterogeneity between studies. Not reasonable to assume all can be explained.
- Should be used for exploration of heterogeneity in clinical trials and observational studies.

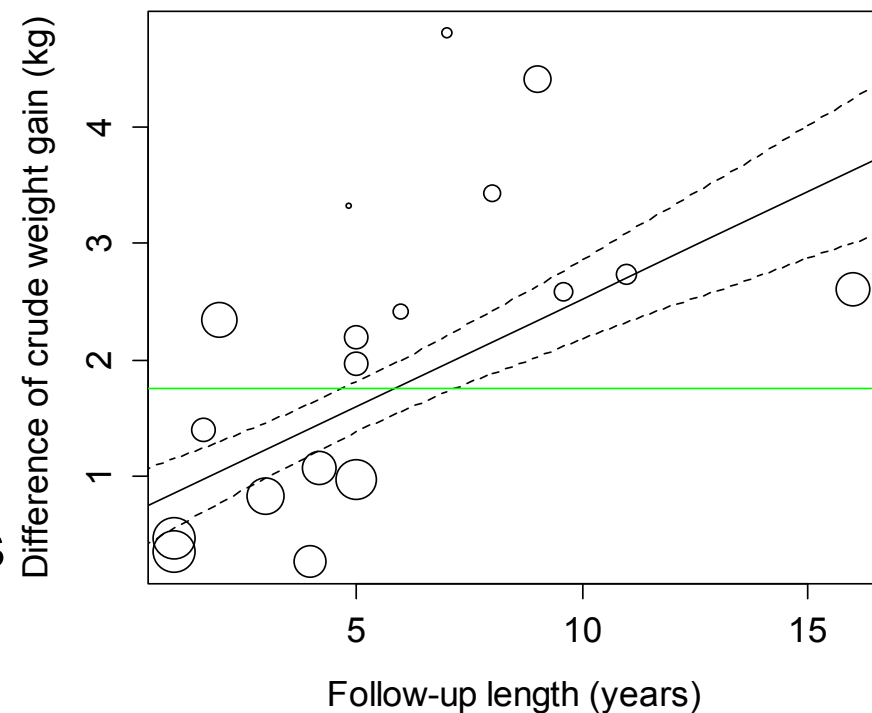
- Always appropriate to conduct meta-regression even if tests of heterogeneity fail to be significant.
 - Test of heterogeneity is under-powered.
 - Test is for overall variation and doesn't examine relationship with study-level covariates

- The relationship between a study covariate and the summary effect size is **observational**, even when studies are randomised controlled trials.
- Can be viewed as a study of the epidemiology of trials.

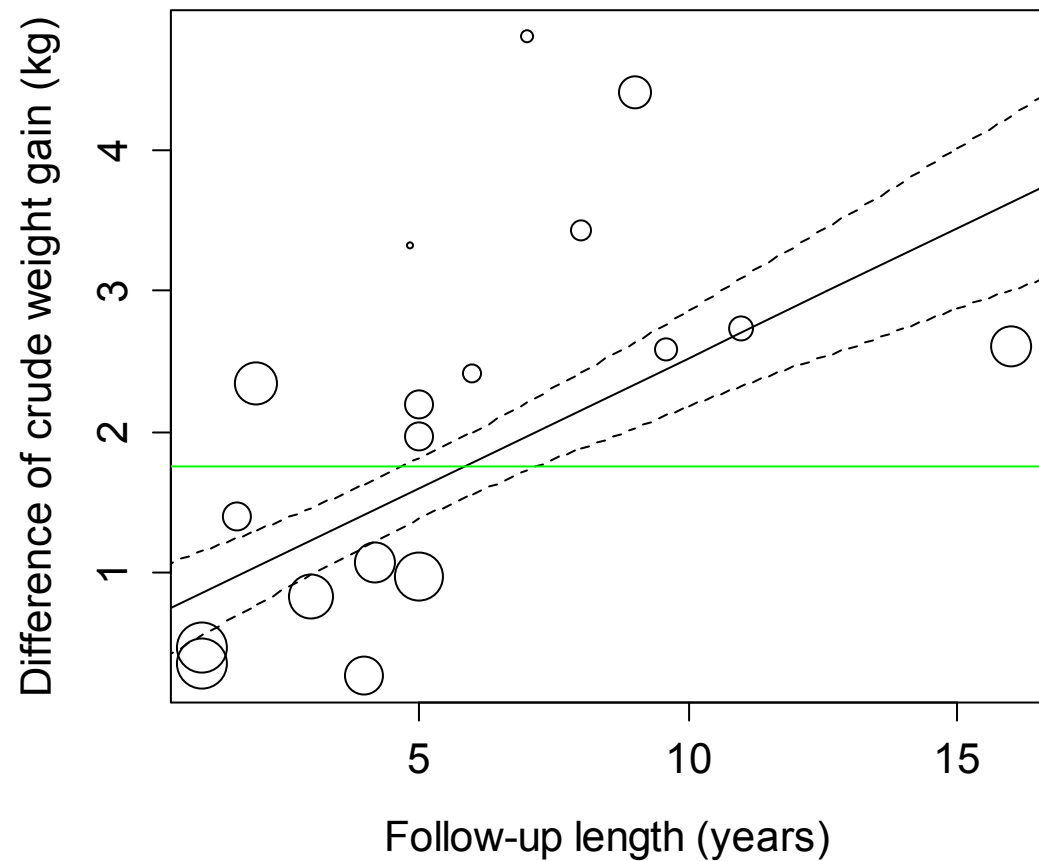
- Meta-regression should be weighted just as meta-analysis – more precise studies should be given greater weight.
- Weighting should be “random effects” – since it is not safe to assume that all heterogeneity can be explained.

- Meta-regression with few studies is unlikely to be useful, suffers from poor estimation (minimum 10).
- Confounding adjustment is at trial level and may not reflect the same confounding at individual level.

- Coefficient is interpreted in the usual manner; for the meta-regression shown is 0.18 [0.13-0.24].
- When using patient averages from within studies (e.g. average age), the relationship observed between studies may be entirely different to that observed within studies.



- Plot markers sized according to meta-analytic weight.
- Identify studies that drive associations



- Ideally covariates for investigation of heterogeneity should be pre-specified to avoid bias or data-dredging (false-positive conclusions)
- Often hard to achieve because of non-uniformity in reporting, and knowledge of investigators.

Subgroup analysis \equiv meta-regression

- Meta-regression with categorical covariates is equivalent to sub-group analysis.
- Moreover it is superior since (through random effects) it allows for residual heterogeneity not explained by subgrouping, and focusses the analysis on group differences, rather than generating pooled effect-sizes for the subgroups.

- Useful tool for examining heterogeneity inherent in meta-analysis, for both categorical or continuous covariates.
- A visual representation is important.
- Observational, discovered associations are not causal.
- Prone to data-dredging unless covariates are pre-specified.