**Exercises - Day 2 - Workshop on Dose-Response Meta-Analysis**

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**Group 2: Continuous outcome**

**Intended Learning Outcomes:**

* Estimate and interpret meta-analysis of non-linear dose-response
* Use a quadratic function and restricted cubic spline function
* Conduct statistical inference (test, confidence) about the non-linear dose-response
* Compute and interpret common measures for quantifying statistical heterogeneity
* Conduct subgroup analyses and apply meta-regression models

Let’s consider 12 clinical trials investigating the association between Omega-3 Index and a cognitive score. Age is not considered an important confounding factor as it is believed to be unrealted with Omega-3 Index.

**Part I: Non-linear dose-response meta-analysis based on aggregated data**

1. **Quadratic function.** In a dose-response model, use a quadratic function to model the effect of Omega-3 Index on the mean outcome.
2. Based on the estimated meta-analytical model, is there any strong indication against a simpler linear trend? What is the result of the test for the overall effect of the dose on the mean difference?
3. Independenlty of the test result, visualize the estimated dose-response function (mean difference) with a 95% confidence interval using 7 units as referent.
4. **Restricted cubic spline function.** In a common-effect dose-response model, use restricted cubic splines with 3 knots at fixed percentiles (10th, 50th, 90th) of the overall distribution of Omega-3 Index to model the effect of Omega-3 Index on the mean outcome.
5. Based on the estimated meta-analytical model, is there any strong indication against a simpler linear trend? What is the result of the test for the overall effect of the dose on the mean difference?
6. Independenlty of the test result, visualize the estimated dose-response function (Mean Difference) with a 95% confidence interval using 7 units as referent.

**Part II: Quantify the statistical heterogeneity and its impact.**

1. Compute and interpret common measures of heterogeneity, such as the Q statistic and Q test, estimate of between-study heterogeneity, and I2, for the meta-analysis of linear trend.
2. Present graphically the observed heterogeneity in linear trend and its implication in terms of mean predicted linear trend, as well as predicted linear trend for a new study.
3. Repeat Questions 1-2 for meta-analysis of non-linear dose-response. Contrast the findings.
4. Consider the study-level covariate *z*. Is there any differential dose-response curve depending on the level of *z*? Perform a subgroup or meta-regression analysis, and present the predicted mean curves conditional on the levels of *z*.