**General meta-analysis (before removing the papers)**

strong effect

The Q statistic (96.53) with a p-value < 0.0001 strongly indicates significant heterogeneity among the studies, justifying the use of a random effects model over a common effect model. The wide confidence intervals in some individual studies (e.g., "Keshavarz4\_tissue") indicate considerable uncertainty in those effect estimates, highlighting the need for cautious interpretation of these results.

Average effect

A **Q value** of 87.21 with 22 degrees of freedom (d.f.) and a **p-value** less than 0.0001 strongly indicate significant heterogeneity across studies, reinforcing the variability observed in the study-specific results and the heterogeneity measures. The significant heterogeneity and the wide range of effect sizes observed in individual studies underline the importance of interpreting the overall results cautiously. It also suggests that future research might explore the reasons behind this variability, potentially leading to more tailored and effective interventions or recommendations.

**General meta-analysis (after removing the papers)**

**Stored in the *results* Excel document, *meta\_analysis* sheet, and the forest plot *forestplot\_strongeffect.pdf* and *forestplot\_average.pdf***

**strong effect**

* Studies like **Zhang14** show a strong negative association (OR = 0.38), suggesting a decreased odds of the outcome with exposure.
* In contrast, studies like **Zhou17** (OR = 3.57) indicate a strong positive association, suggesting increased odds of the outcome with exposure.
* The wide CIs in some studies (e.g., **Morgan20\_ovarian**: [0.2984; 6.6632]) reflect substantial uncertainty in those effect estimates.

**Random Effects Model**: Provides a slightly higher OR of 1.3312, taking into account the variability among study outcomes. The broader CI ([1.0776; 1.6446]) reflects the increased uncertainty due to heterogeneity.

**Heterogeneity Measures**

* **Tau^2 (τ^2)** and **Tau** quantify the variance among true effect sizes across studies. A τ^2 of 0.1473 and τ of 0.3838 suggest significant variability.
* **I^2** of 77.8% indicates that a large portion of the variation across studies is due to heterogeneity rather than chance.
* **H** statistic of 2.12 supports the presence of significant heterogeneity among study outcomes.

**Test of Heterogeneity**

* A **Q value** of 81.08 with 18 degrees of freedom and a **p-value** less than 0.0001 strongly suggests significant heterogeneity, reinforcing the variability observed in the study-specific results and heterogeneity measures.

**Interpretation**

The meta-analysis indicates a moderate positive association across the included studies. However, the significant heterogeneity (I^2 = 77.8%) and the test of heterogeneity highlight that the study results are not entirely consistent with one another. This inconsistency may stem from differences in study designs, populations, interventions, or outcomes measured across the included studies.

The random effects model is more appropriate here as it accounts for the observed heterogeneity, providing an estimate that more accurately reflects the variability across studies. It suggests that, on average, there is a positive association, but the strength of this association varies significantly across different settings or populations.

The considerable heterogeneity and the range of effect sizes observed among the individual studies underscore the need for cautious interpretation of the overall results. Additionally, it points to the importance of exploring the reasons behind this variability in future research, potentially leading to more nuanced and effective interventions or recommendations.

**Average effect**

**Study-Specific Results**

* Each study's **OR** and **95%-CI** quantify the strength and direction of the association under investigation and the uncertainty of these estimates, respectively.
* **Weights (%W)** under both common and random effects models signify the relative importance or contribution of each study to the overall meta-analysis outcome. Studies with larger sample sizes or more precise estimates (narrower CIs) tend to have higher weights.

**Meta-Analysis Summary Results**

* **Common Effect Model**: An OR of 1.2547 suggests a moderate positive association across the studies, with a narrow CI ([1.1882; 1.3250]), indicating high precision of this pooled estimate.
* **Random Effects Model**: Provides a slightly lower OR of 1.2328, reflecting a moderate positive association but with a broader CI ([1.0255; 1.4822]). This model accounts for variability among study outcomes and suggests greater uncertainty in the overall effect estimate compared to the common effect model.

**Heterogeneity Measures**

* **Tau^2 (τ^2)** and **Tau** estimate the variance among true effect sizes across studies. A τ^2 of 0.1007 and τ of 0.3173 indicate noticeable variability.
* **I^2** of 74.8% shows a considerable proportion of the total variation across studies is due to heterogeneity rather than chance.
* **H** statistic of 1.99 further supports the presence of significant heterogeneity among the study outcomes.

**Test of Heterogeneity**

* The **Q statistic** of 71.29 with 18 degrees of freedom (d.f.) and a **p-value** less than 0.0001 strongly indicates significant heterogeneity across studies, justifying the use of a random effects model over a common effect model.

**Interpretation**

The meta-analysis indicates a moderate positive association across the included studies, as seen in both the common and random effects models. However, the substantial heterogeneity highlighted by the I^2 statistic and confirmed by the Q test suggests that the study outcomes are not entirely consistent with each other. This inconsistency might stem from differences in study designs, populations, interventions, or outcomes measured across the included studies.

Given the significant heterogeneity, the random effects model is more appropriate as it incorporates the variability among study outcomes, providing a more conservative estimate of the overall effect. This model indicates that, while there is a positive association on average, the strength and direction of this association vary significantly across different settings or populations.

The considerable heterogeneity and the range of effect sizes and confidence intervals among the individual studies underscore the need for cautious interpretation of the overall results. It also points to the importance of exploring the reasons behind this variability in future research, potentially leading to more targeted and effective interventions or recommendations.

**Assess the publication bias**

**– stored in the *results* Excel document, *publication\_bias* sheet**

**These two funnel plot, *funnelplot\_strongeffect.pdf* and *funnelplot\_average.pdf***

**Strong effect**

**Egger’s test**

* Coefficients: The intercept (Xintrcpt) has an estimate of 0.23185 with a standard error of 0.09063, resulting in a t-value of 2.558 and a p-value of 0.0204. The significance of the intercept (p < 0.05) suggests evidence of publication bias, as it indicates that the effect sizes are correlated with the precision of the studies, with smaller studies possibly showing larger effect sizes.
* The coefficient for Xsei (representing the effect of standard error on the effect size) has an estimate of 0.25441 with a large standard error (0.74939), leading to a t-value of 0.339 and a non-significant p-value (0.7384). This suggests that the slope of the regression line (which would indicate a trend in effect sizes with respect to the standard errors of studies) is not significantly different from zero.

The significant intercept in Egger's regression test suggests the presence of publication bias in the meta-analysis dataset. This indicates that smaller or less precise studies may be more likely to report larger effect sizes, possibly due to a tendency for such studies to be published only if they have significant or dramatic results. The findings from this test highlight the need for caution when interpreting the meta-analysis results, considering the potential influence of publication bias.

**Begg’s test**

* **Kendall's tau**: A measure of rank correlation, with your result being 0.0409. Kendall's tau values range from -1 to 1, where 0 indicates no correlation, 1 indicates perfect agreement, and -1 indicates perfect disagreement. A value of 0.0409 suggests a very weak positive correlation between the effect sizes and the precision of the studies included in your meta-analysis.
* **p-value**: The p-value associated with Kendall's tau is 0.8360. In hypothesis testing, a common threshold for significance is a p-value less than 0.05. A p-value of 0.8360 is much higher than this threshold, indicating that the observed correlation (or lack thereof) could very likely be due to chance.

The results from the Begg's test (Kendall's tau = 0.0409, p = 0.8360) suggest that there is no statistically significant evidence of publication bias within the dataset of the meta-analysis. The funnel plot, based on these results, is likely to be symmetric, indicating that the effect sizes are not dependent on the precision of the studies. It's important to remember that the absence of statistical evidence for publication bias does not definitively prove its absence, but rather that the test did not detect it in this instance. Furthermore, Begg's test can have limited power to detect bias, especially in meta-analyses with a small number of studies. Thus, these results should be interpreted as part of a broader assessment of publication bias and the quality of the meta-analysis.

**Trim and Fill test**

Missing Studies Estimation

* **Estimated number of missing studies on the left side**: 0, with a Standard Error (SE) of 1.4142. This result suggests that, according to the Trim and Fill method, there are no missing studies on the left side of the funnel plot that would indicate publication bias.
* **Test of H0 (no missing studies on the left side)**: The p-value is 0.5000, indicating no statistical evidence to reject the hypothesis of no missing studies on the left side. This suggests a lack of evidence for publication bias in the meta-analysis.

The Trim and Fill test results indicate no evidence of publication bias in this meta-analysis, as suggested by the estimated number of missing studies and the p-value of the test for missing studies. However, there is significant heterogeneity among the studies, as indicated by the high I^2 value and the significant Q test for heterogeneity. Despite this heterogeneity, the adjusted effect size remains statistically significant, suggesting a real effect size that is robust to the potential impact of publication bias. The high level of heterogeneity and the statistical significance of the adjusted effect size highlight the importance of understanding the sources of variability among the studies and interpreting the overall effect size with caution.

**Average Effect**

**Egger’s test**

Coefficients:

* **Xintrcpt (Intercept)**: The estimate of the intercept is 0.23617 with a standard error of 0.08501, leading to a t-value of 2.778 and a p-value of 0.0129. The significance of the intercept (*p* < 0.05) provides evidence of publication bias, suggesting that the effect sizes reported by the studies are, to some extent, correlated with their precision. This could mean that smaller or less precise studies are more likely to report larger effect sizes, potentially due to selective publication practices.
* **Xsei (Slope)**: The coefficient for the slope is -0.10277 with a large standard error of 0.70154, resulting in a t-value of -0.146 and a non-significant p-value of 0.8853. This indicates that there is no significant trend of effect sizes increasing or decreasing with the precision of the studies, as the slope of the line relating effect size to standard error is not significantly different from zero.

The significant intercept from Egger's test suggests the presence of publication bias within the meta-analysis data set. This finding indicates that smaller, less precise studies might be disproportionately influencing the overall effect size estimate due to a tendency towards publishing studies with significant or more dramatic results. However, the lack of a significant slope suggests that this bias does not systematically increase or decrease with the precision of the studies. The evidence of publication bias underscores the importance of interpreting the meta-analysis results with caution, acknowledging that the reported effect sizes might be overestimations of the true effects.

**Begg’s test**

* **Kendall's tau**: A measure of rank correlation, here reported as 0.0760. Kendall's tau ranges between -1 and 1, where 0 suggests no correlation, 1 indicates perfect positive correlation, and -1 indicates perfect negative correlation. A tau of 0.0760 indicates a very weak positive correlation between the effect sizes and the precision of the studies in your meta-analysis.
* **p-value**: The p-value for Kendall's tau is 0.6787. This is a measure of the statistical significance of the observed correlation. A common threshold for declaring statistical significance is a p-value less than 0.05. Therefore, a p-value of 0.6787 is much higher than this threshold, suggesting that the observed weak positive correlation is likely due to chance.

The results from this Begg's test (Kendall's tau = 0.0760, p = 0.6787) indicate no statistically significant evidence of publication bias in the dataset of the meta-analysis. The likely symmetric appearance of the funnel plot suggests that the precision of the studies does not systematically influence the reported effect sizes. However, it's crucial to remember that the lack of statistical evidence for publication bias does not conclusively prove its absence. Begg's test, particularly in meta-analyses with fewer studies, may not always have sufficient power to detect bias. Thus, these results should be considered as part of a comprehensive evaluation of potential publication bias and the overall quality and reliability of the meta-analysis findings.

**Trim and Fill test**

Missing Studies Estimation

* **Estimated number of missing studies on the left side**: 0, with a standard error (SE) of 1.4142. This outcome suggests that, according to the Trim and Fill method, no studies are estimated to be missing due to publication bias on the left side of the funnel plot.
* **Test of H0 (no missing studies on the left side)**: The p-value of 0.5000 indicates no statistical evidence to suggest the presence of missing studies due to publication bias. This high p-value supports the null hypothesis that there is no asymmetry in the funnel plot attributable to unpublished studies.

The Trim and Fill test results suggest no evidence of publication bias in this meta-analysis, as indicated by an estimated zero missing studies and a non-significant test for missing studies. However, significant heterogeneity among the included studies is a critical consideration when interpreting the results. Despite this heterogeneity, the adjusted overall effect size remains statistically significant, indicating a real association in the meta-analyzed data after accounting for potential biases and heterogeneity. The findings should be interpreted cautiously due to the heterogeneity observed.