**Assess the publication bias – urine**

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

**These four funnel plots, *funnelplot\_strongeffect\_ur.pdf, funnelplot\_strongeffect\_ot.pdf,* and *funnelplot\_average\_ur.pdf, funnelplot\_average\_ot.pdf***

**Strong effect**

**Egger’s test**

**Coefficients**:

Xintrcpt (Intercept): The estimated intercept is 0.25686 with a standard error of 0.09948, resulting in a t-value of 2.582. The p-value associated with this t-test is 0.0217, indicating that the intercept is statistically significant at the conventional alpha level of 0.05. This suggests evidence of asymmetry in the funnel plot, which can be indicative of publication bias. In this context, the significant intercept may imply that smaller studies (or studies with less precision) are more likely to report larger effect sizes.

Xsei (Slope): The estimated slope is -0.15264 with a standard error of 0.88524, resulting in a t-value of -0.172. The p-value for the slope is 0.8656, indicating that there is no significant relationship between the study effect sizes and their precision. This part of the model assesses whether larger studies show systematically different effect sizes compared to smaller ones, beyond what is suggested by the intercept. The non-significant slope suggests that, aside from the potential bias indicated by the intercept, there's no clear trend of effect sizes increasing or decreasing with study precision.

The result of Egger's test, with a significant intercept at p=0.0217, suggests evidence of publication bias in the meta-analysis. This indicates that smaller or less precise studies may be reporting larger effect sizes, a common concern in publication bias where such studies are more likely to be published if they show significant or larger effects. Despite this, the model’s explanatory power and its overall significance suggest careful consideration of potential biases when interpreting the meta-analysis results. It's important for researchers to explore further the context of the included studies and consider additional methods to assess and adjust for publication bias.

**Begg’s test**

**Kendall's tau:** A measure of rank correlation, with the result being 0.0000. Kendall's tau ranges from -1 to 1, where 0 indicates no correlation, 1 indicates perfect positive correlation, and -1 indicates perfect negative correlation. A tau of 0.0000 suggests that there is no correlation between the effect sizes and their precision among the studies included in the meta-analysis. This means that the likelihood of a study being published does not appear to be related to its effect size or precision.

**p-value:** The p-value associated with Kendall's tau is 1.0000. This tests the null hypothesis, which in the case of Begg's test, is that there is no correlation between study effect sizes and their precision. A p-value of 1.0000 is highly unusual and indicates that the observed data perfectly match the null hypothesis of no correlation. In practical terms, this means there is no statistical evidence of publication bias in this meta-analysis according to Begg's test.

The result from Begg's test (Kendall's tau = 0.0000, p = 1.0000) suggests that there is no evidence of publication bias within the dataset of the meta-analysis based on the correlation between effect sizes and their precision. The test indicates a complete lack of association, suggesting that both smaller and larger studies have an equal likelihood of being published regardless of their outcomes or precision.

However, it's crucial to interpret these results with caution. The absence of statistically significant evidence for publication bias according to Begg's test does not definitively prove its absence. The test's sensitivity can be limited, especially with a small number of studies or when there is substantial heterogeneity among studies. Therefore, these results should be considered alongside other methods to assess publication bias and the overall quality and reliability of the meta-analysis findings. Additional analyses or qualitative considerations might provide more comprehensive insights into the presence of publication bias.

**Trim and Fill test**

Missing Studies Estimation

Estimated number of missing studies on the right side: 0, with a Standard Error (SE) of 1.4142. This suggests that, according to the Trim and Fill method, there are no missing studies due to publication bias on the right side of the funnel plot, which might indicate a tendency towards publishing studies with positive or significant results.

Test of H0 (no missing studies on the right side): The p-value of 0.5000 indicates there is no statistical evidence to reject the hypothesis of no missing studies. This suggests a lack of evidence for publication bias in this meta-analysis based on the Trim and Fill method.

The Trim and Fill test indicates no evidence of publication bias, as suggested by an estimated zero missing studies and a non-significant test for missing studies. Despite this, the observed substantial heterogeneity among the studies and the adjusted overall effect size nearing significance suggest a possible genuine association in the meta-analyzed data. However, given the high level of heterogeneity (I^2=90.96%), these results should be interpreted with caution. The significant variability among study results underscores the need for careful consideration of the individual study contexts when applying these findings. Further research incorporating more studies could help clarify the nature of the effect and its consistency across different populations and settings.

**Average effect**

**Egger’s test**

**Coefficients**:

Xintrcpt (Intercept): The estimate of the intercept is 0.26683 with a standard error of 0.09089, leading to a t-value of 2.936. The p-value associated with this t-test is 0.0109, indicating that the intercept is statistically significant at the conventional alpha level of 0.05. This significant intercept suggests evidence of asymmetry in the funnel plot, which may be indicative of publication bias. Specifically, it implies that smaller studies (or studies with less precision) are more likely to report larger effect sizes.

Xsei (Slope): The estimated slope is -0.59362 with a standard error of 0.80732, resulting in a t-value of -0.735. The p-value for the slope is 0.4743, indicating that there is no significant relationship between the study effect sizes and their precision. This suggests that, beyond the potential bias indicated by the intercept, there's no clear trend of effect sizes increasing or decreasing with study precision.

The result of Egger's test, with a significant intercept at p=0.0109, suggests evidence of publication bias in the meta-analysis. This indicates that smaller or less precise studies may be reporting larger effect sizes, a common phenomenon in publication bias where such studies are more likely to be published if they show significant or larger effects. The lack of a significant slope suggests that the magnitude of the effect sizes does not systematically increase or decrease with precision beyond the bias indicated by the intercept.

Given the significant intercept, researchers should be cautious when interpreting the results of the meta-analysis, considering the potential influence of publication bias. Further exploration of the context of the included studies and the use of additional methods to assess and adjust for publication bias might be warranted.

**Begg’s test**

**Kendall's tau:** A measure of rank correlation, with the result being 0.0000. Kendall's tau ranges from -1 to 1, where 0 indicates no correlation, 1 indicates perfect positive correlation, and -1 indicates perfect negative correlation. A tau of 0.0000 suggests that there is no correlation between the effect sizes and their precision among the studies included in the meta-analysis. This means that the likelihood of a study being published does not appear to be related to its effect size or precision.

**p-value:** The p-value associated with Kendall's tau is 1.0000. This tests the null hypothesis, which in the case of Begg's test, is that there is no correlation between study effect sizes and their precision. A p-value of 1.0000 is highly unusual and indicates that the observed data perfectly match the null hypothesis of no correlation. In practical terms, this means there is no statistical evidence of publication bias in this meta-analysis according to Begg's test.

The result from Begg's test (Kendall's tau = 0.0000, p = 1.0000) suggests that there is no evidence of publication bias within the dataset of the meta-analysis based on the correlation between effect sizes and their precision. The test indicates a complete lack of association, suggesting that both smaller and larger studies have an equal likelihood of being published regardless of their outcomes or precision.

However, it's crucial to interpret these results with caution. The absence of statistically significant evidence for publication bias according to Begg's test does not definitively prove its absence. The test's sensitivity can be limited, especially with a small number of studies or when there is substantial heterogeneity among studies. Therefore, these results should be considered alongside other methods to assess publication bias and the overall quality and reliability of the meta-analysis findings. Additional analyses or qualitative considerations might provide more comprehensive insights into the presence of publication bias.

**Trim and Fill test**

Missing Studies Estimation

Estimated number of missing studies on the right side: 0, with a Standard Error (SE) of 1.4142. This result indicates that, according to the Trim and Fill method, there are no missing studies due to publication bias on the right side of the funnel plot. The right side often represents studies with positive or more significant results.

Test of H0 (no missing studies on the right side): The p-value of 0.5000 suggests there is no statistical evidence to support the presence of missing studies due to publication bias, indicating a symmetric distribution of studies in the meta-analysis.

The Trim and Fill test indicates no evidence of publication bias in this meta-analysis, based on the estimated zero missing studies and the lack of statistical evidence to suggest the contrary. However, there is significant heterogeneity among the studies, which the random effects model attempts to account for. Despite the adjustment, the overall effect size remains non-significant, but it is essential to note the high level of heterogeneity (I^2 = 85.84%) among the included studies. This substantial variability underscores the need for cautious interpretation of the meta-analysis results and suggests that further research, possibly incorporating more studies or exploring sources of heterogeneity, could provide more definitive insights.

**Assess the publication bias – other (0, 2, and 3)**

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

**These four funnel plots, *funnelplot\_strongeffect\_ur.pdf, funnelplot\_strongeffect\_ot.pdf,* and *funnelplot\_average\_ur.pdf, funnelplot\_average\_ot.pdf***

**Strong effect**

**Egger’s test**

**Coefficients**:

Xintrcpt (Intercept): The estimated intercept is 0.41922 with a standard error of 0.05332, leading to a t-value of 7.862. The p-value associated with this is 0.0805, which is marginally above the conventional threshold of 0.05 for statistical significance. The intercept in Egger's test assesses the presence of small-study effects, which can indicate publication bias. Here, the result suggests a possible small-study effect, although not statistically significant by conventional standards.

Xsei (Slope): The slope's estimate is 0.96183 with a standard error of 0.17374, resulting in a t-value of 5.536. The p-value for the slope is 0.1138, indicating that the relationship between effect sizes and their precision is not statistically significant. The slope examines whether larger studies (with smaller standard errors, hence higher precision) tend to report systematically different effect sizes compared to smaller ones.

The Egger's test results hint at a possible small-study effect, which could indicate publication bias, though the p-values for both the intercept and the slope do not reach conventional levels of statistical significance. Given the extremely limited number of studies (only three), the robustness of these findings is questionable. The high R-squared values and the significant overall model might be misleading due to overfitting in such a small dataset.

The interpretation of Egger's test in this context should be approached with caution. The potential indication of publication bias or small-study effects necessitates further investigation, ideally with a larger set of studies to provide more reliable statistical analysis. In meta-analyses with very few studies, results from statistical tests like Egger's test should be considered tentative and exploratory rather than definitive.

**Begg’s test**

**Kendall's tau:** This is a measure of correlation between the effect sizes of the studies and their variances or standard errors. A tau value of 1.0000 indicates a perfect positive correlation, suggesting that as the variance or standard error decreases (implying larger or more precise studies), the effect size increases, or vice versa. In the context of funnel plot asymmetry, this could suggest a systematic relationship between study size and reported effect sizes.

**p-value:** The p-value associated with Kendall's tau is 0.3333. This tests the null hypothesis, which in the case of Begg's test, is that there's no correlation between study effect sizes and their precision. A common threshold for rejecting the null hypothesis and indicating significant results is a p-value less than 0.05. Since your p-value is much higher (0.3333), it indicates that the observed correlation (even though it's perfectly positive) is not statistically significant.

Despite the perfect positive correlation indicated by Kendall's tau, the p-value of 0.3333 suggests that there is no statistically significant evidence of publication bias according to Begg's test. This outcome means that the rank correlation observed does not significantly differ from what might be expected by chance alone.

However, it's important to note a couple of points:

A Kendall's tau of 1.0000 in this context might seem unusual, especially with a non-significant p-value. It could potentially be due to a very small number of studies included in the meta-analysis, where pairwise comparisons lead to a perfect correlation by chance.

The lack of statistical significance in detecting publication bias does not necessarily mean its absence; it indicates that the test did not find strong enough evidence to conclude its presence. Additional methods and considerations should be employed to comprehensively assess publication bias in 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 indicates that the Trim and Fill method did not identify any missing studies due to publication bias on the left side of the funnel plot, which typically represents smaller or less significant studies that are unpublished or harder to find.

**Test of H0 (no missing studies on the left side):** The p-value of 0.5000 suggests there's no statistical evidence to reject the hypothesis of no missing studies. This indicates a lack of evidence for publication bias in this meta-analysis based on the Trim and Fill method.

The Trim and Fill test indicates no evidence of publication bias in this small meta-analysis (k=3), with no missing studies estimated. Despite the small number of studies, the significant overall effect size suggests a positive association or effect. However, the results should be interpreted with caution due to the very small number of studies involved, which limits the robustness and generalizability of the findings. Further research incorporating more studies could provide a more comprehensive understanding of the effect size and its consistency across different populations and settings.

**Average effect**

**Egger’s test**

**Coefficients**:

Xintrcpt (Intercept): The estimate of 0.32079 with a standard error of 0.01747 leads to a t-value of 18.36, and the p-value is 0.0346. This indicates the intercept is statistically significant, suggesting a potential asymmetry in the funnel plot, which can be indicative of publication bias. The significant intercept implies that smaller studies (or those with less precision) may systematically report larger effect sizes.

Xsei (Slope): The slope's estimate of 1.16279 with a standard error of 0.05691 results in a t-value of 20.43, and the p-value is 0.0311. This indicates a significant relationship between the effect sizes and their precision, suggesting that larger studies (with smaller standard errors, hence higher precision) do not necessarily show systematically different effect sizes compared to smaller ones, beyond the potential bias indicated by the intercept.

The results suggest evidence of publication bias in the meta-analysis, as indicated by the significant intercept in Egger's test. The significant slope further implies a relationship between study effect sizes and their precision. However, given the extremely limited number of studies, the robustness and reliability of these findings are questionable. High R-squared values and significant overall model might misleadingly suggest a good fit due to the potential overfitting in such a small sample size.

It's crucial to approach the interpretation of Egger's test results with caution in this context. The potential indication of publication bias or small-study effects necessitates further investigation, ideally with more studies, to provide a more stable and reliable statistical analysis. In scenarios with very few studies, the outcomes from statistical tests like Egger's test should be considered exploratory rather than definitive, and the possibility of overfitting or exaggerated statistical significance due to the small sample size cannot be overlooked.

**Begg’s test**

**Kendall's tau:** This is a measure of correlation between the effect sizes of the studies and their variances or standard errors. A tau value of 1.0000 indicates a perfect positive correlation, suggesting that as the variance or standard error decreases (implying larger or more precise studies), the effect size increases, or vice versa. In the context of funnel plot asymmetry, this could suggest a systematic relationship between study size and reported effect sizes.

**p-value:** The p-value associated with Kendall's tau is 0.3333. This tests the null hypothesis, which in the case of Begg's test, is that there's no correlation between study effect sizes and their precision. A common threshold for rejecting the null hypothesis and indicating significant results is a p-value less than 0.05. Since your p-value is much higher (0.3333), it indicates that the observed correlation (even though it's perfectly positive) is not statistically significant.

Despite the perfect positive correlation indicated by Kendall's tau, the p-value of 0.3333 suggests that there is no statistically significant evidence of publication bias according to Begg's test. This outcome means that the rank correlation observed does not significantly differ from what might be expected by chance alone.

However, it's important to note a couple of points:

A Kendall's tau of 1.0000 in this context might seem unusual, especially with a non-significant p-value. It could potentially be due to a very small number of studies included in the meta-analysis, where pairwise comparisons lead to a perfect correlation by chance.

The lack of statistical significance in detecting publication bias does not necessarily mean its absence; it indicates that the test did not find strong enough evidence to conclude its presence. Additional methods and considerations should be employed to comprehensively assess publication bias in the meta-analysis.

**Trim and Fill test**

Missing Studies Estimation

Estimated number of missing studies on the left side: 1, with a Standard Error (SE) of 2.0000. This result indicates that the Trim and Fill method identified one potentially missing study due to publication bias on the left side of the funnel plot, typically representing smaller or less significant studies that might not have been published or are harder to find.

Test of H0 (no missing studies on the left side): The p-value of 0.2500 suggests that there is not enough statistical evidence to conclusively reject the null hypothesis of no missing studies. While one missing study was estimated, the evidence for asymmetry (and by extension, publication bias) is not strong enough to be deemed statistically significant at conventional alpha levels (e.g., 0.05).

The Trim and Fill test suggests a possible presence of publication bias with one estimated missing study on the left side of the funnel plot, although the test of this hypothesis does not reach statistical significance. Despite the potential for publication bias, the overall effect size remains statistically significant, suggesting a positive association or effect in the meta-analysis. However, given the very small number of studies involved (k=4) and the identified potential for publication bias, the results should be interpreted with caution. Further research incorporating more studies could provide a more comprehensive and robust understanding of the effect size and its consistency across different populations and settings.