



Effect of Probiotics on Mental Health and their Association with Serum Neurometabolites in Adults with Depression or Anxiety: A Systematic Review and Meta-Analysis.

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INTRODUCTION

- According to Centers for Disease Control and Prevention (CDC), the percentage of individuals with anxiety and depressive disorders in the United States rose from 36.4% to 41.5% between August 2020 and February 2021.¹
- Given increasing rates of mental illness, difficulty accessing mental health resources, and lack of healthcare providers nationally, there is an urgent need to find accessible treatments for mental illness.
- One promising potential target for managing mental illness is nutritional measures via the mind-gut axis.
- Studies have shown that our guts influence our mental health by modulating neuroactive chemicals like kynurenine and serotonin- neuroactive metabolites of the essential amino acid tryptophan.²⁻⁴
- Treatments that target our gut microbiota have emerged as a burgeoning field of research as a means to improve mental health.

Objective: To conduct a systematic-review and meta-analysis to assess the effectiveness of probiotic intake in altering the kynurenine-tryptophan ratio (K:T ratio), serum neurotransmitters, and mental health.

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METHODS AND MATERIALS

Databases: We searched five databases from inception to February 2022. Medline (via PubMed), SCOPUS, Cochrane Library (CENTRAL & CDSR), PsycINFO, and CINAHL. We utilized ClinicalTrials.gov to search for additional studies associated with the overlapping themes of metabolites and probiotics. Reference lists from selected articles were searched. There were no constraints on language or publication status.

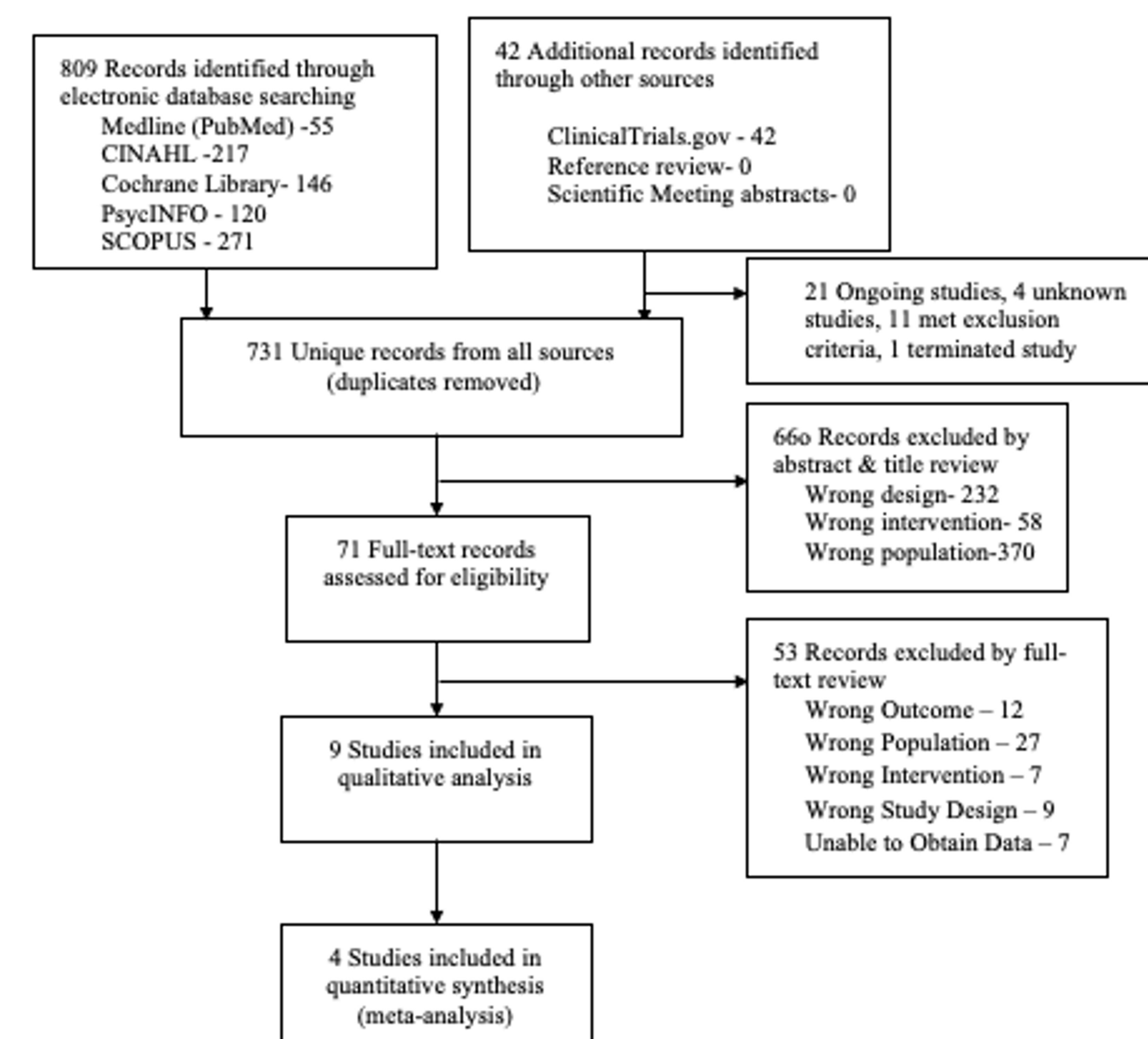
Eligibility Criteria: (1) Randomized controlled trials (RCTs) that studied adults with diagnosed depression or anxiety (2) Studies that utilized probiotics containing *Lactobacillus* or *Bifidobacterium* as the intervention (3) Studies that reported measures of neurometabolites (4) Studies that had at least 4 weeks of follow-up.

Primary Outcome: Change in depression and anxiety scores.

Secondary Outcomes: (1) Change in serum kynurenine levels (2) Change in serum tryptophan levels (3) Change in serum serotonin levels (4) Change in the K:T ratio.

Data Collection: Data from eligible studies were extracted and summarized separately by four non-expert reviewers, and all reviewers used the same standardized data collection form. If we were unable to obtain additional data from the authors, we used WebPlotDigitizer⁵ to extract data from the figures in those articles.

Figure 1. Study Selection Flow Diagram [with Cochrane Library on LEFT]



ANALYSIS

Changes in depression and anxiety scores, changes in kynurenine levels, and changes in tryptophan levels were reported as standard mean difference (SMD) and 95% confidence intervals (CI). The data for changes in serotonin levels and changes in the K:T ratio were summarized qualitatively using mean post-intervention levels and corresponding standard deviations (SD). A statistically significant reduction in serum serotonin levels and the ratio after probiotic use was used to determine if the intervention was favored. Random effects models were used in our analyses.

RESULTS

- We identified 809 studies from electronic databases and 42 additional records from ClinicalTrials.gov. Nine studies were included in the qualitative review and four studies were included in the meta-analysis (**Figure 1**).
- The overall effect estimate of the association between probiotic exposure and change in depression scores showed significant improvement in symptom reporting scores (standardized mean difference [SMD] = -0.49; I² = 0%; p = 0.002; 95% CI = -0.80 to -0.19) (**Figure 2**).
- The impact of probiotics in anxiety symptoms showed significant improvement in symptom reporting scores (SMD= -2.76; I² = 28%, p = 0.03, 95% CI = -5.27 to -0.25) (**Figure 3**).
- The effect of probiotics on kynurenine showed a significant reduction (SMD = -0.41; I² = 0%, p = 0.01, 95% CI = -0.72 to -0.10) (**Figure 4**), but the effect of probiotics showed no change in serum tryptophan levels (SMD = -0.19; I² = 74%, p = 0.54, 95% CI = -0.81 to 0.42) (**Figure 5**).
- Results for K:T ratio and changes in serum serotonin levels are forthcoming.

Figure 2: Association between probiotic use and Depression Scores

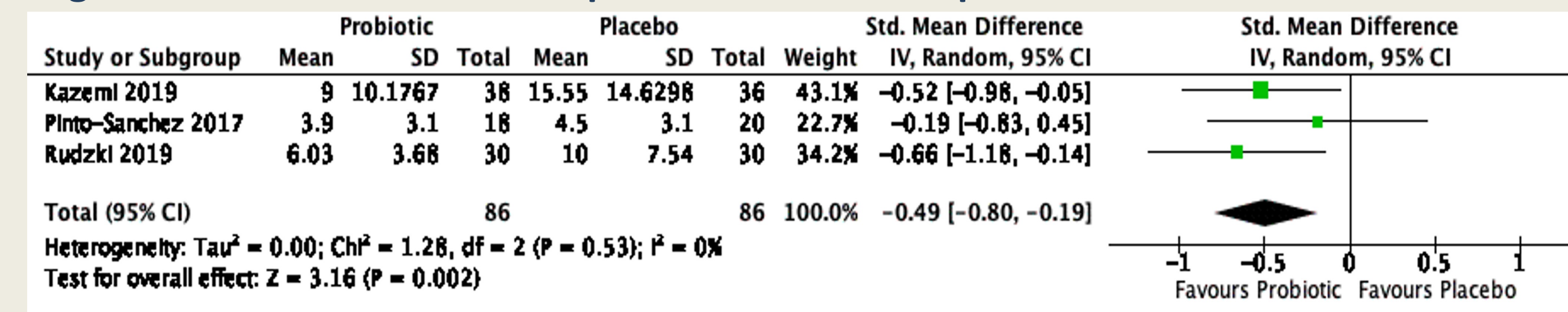


Figure 3: Association between probiotic use and Anxiety Scores

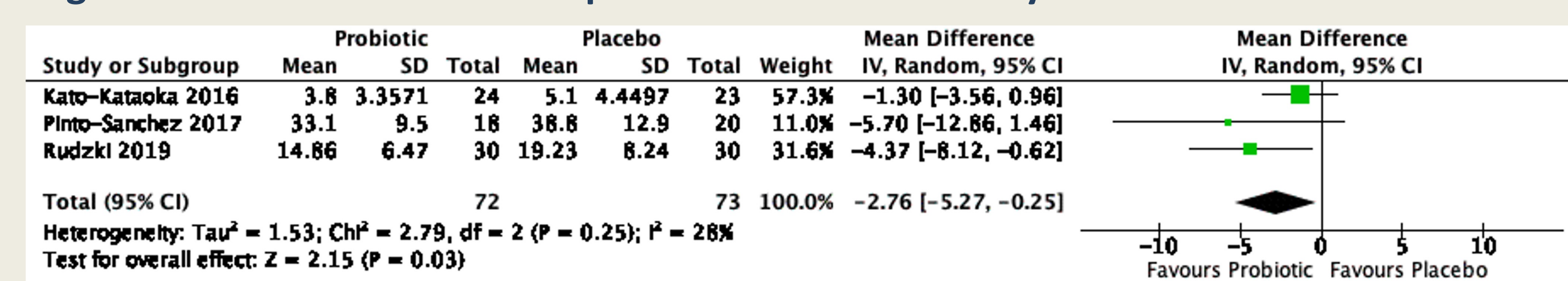


Figure 4: Association between probiotic use and Kynurenine Levels

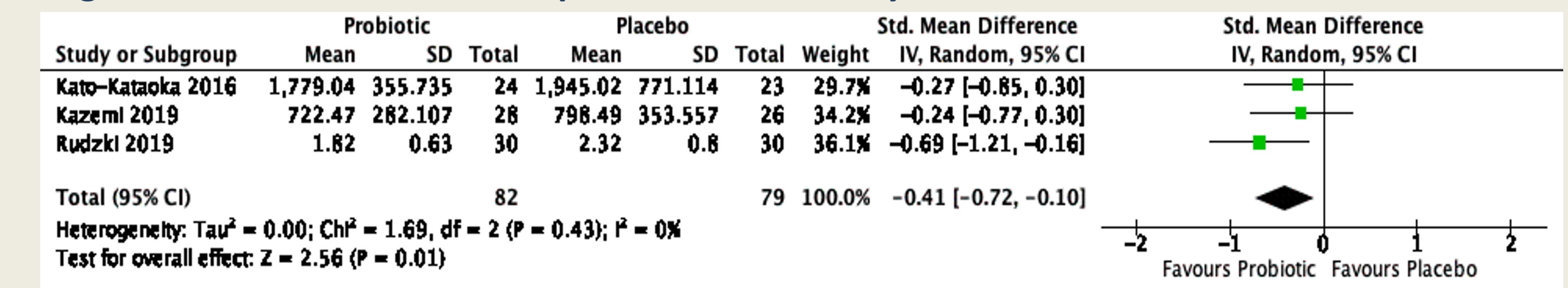
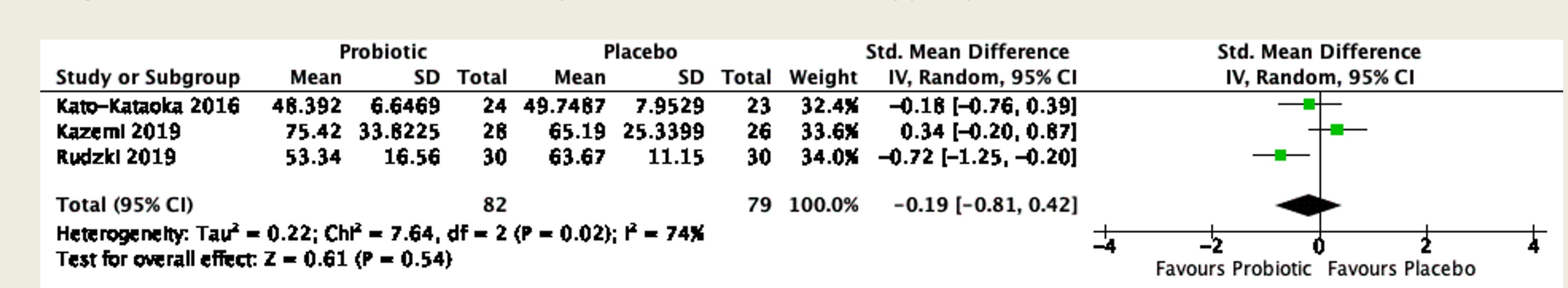


Figure 5: Association between probiotic use and Tryptophan Levels



DISCUSSION

This study is the first systematic review assessing the outcome of tryptophan derived serum neurometabolites (kynurenine, tryptophan, serotonin and the K:T ratio) over a minimum of 4 weeks and investigating their association with the improvement of mental health symptoms. Our results agree with the conclusions from previous reviews highlighting the potential role of probiotics in reducing the symptoms of depression. Another systematic review discusses that probiotics can modulate kynurenine pathway metabolism, but this study included healthy individuals, as opposed to individuals with mental health disorders.⁶ There is a need for further evidence with larger samples and more rigorous studies to determine whether probiotics can significantly reduce the overall risk of depression and anxiety via the tryptophan kynurenine pathway.

CONCLUSIONS

- Probiotics significantly improved depression and anxiety symptoms and reduced kynurenine levels in adults.
- However, there was no significant change in serum tryptophan levels.
- More research is needed to assess the impact of probiotic intake on gut metabolism of neurometabolites.
- This systematic review has important implications for further elucidating the relationship between the gut metabolism and mental health.

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