

## INTRODUCTION

- Gut microbiota influences brain function through immune modulation, neurotransmitter production, and direct effects on the HPA axis<sup>1</sup>
- Probiotics are explored for their potential benefits in conditions such as depression, anxiety, PCOS, autism, cognitive impairment, obesity, and stress<sup>2-4</sup>
- They may affect levels of bioactive substances, including hormones and inflammatory, immunological, and oxidative markers<sup>2</sup>

## OBJECTIVE

Assess the effect of probiotics on neuroendocrine biomarkers (cortisol, BDNF, DHEA, AA, ACTH, oxytocin, norepinephrine, and epinephrine)

## METHODOLOGY

- Protocol:** PROSPERO (CRD42024538539)
- Data Sources:** Searched seven databases from inception to March 18, 2024
- Inclusion Criteria:** Participants across all age groups; no specific medical condition order requirement; probiotics given as a standalone or as a part of a combination therapy; Placebo, routine care or any active comparator other than probiotics, randomized controlled trials
- Pooled estimate:** Standardized mean difference (SMD) with 95% confidence interval (CI) for each biomarker
- Random-effects model, heterogeneity assessed with I<sup>2</sup> and 95% prediction interval
- Subgroup analyses** - population (diseased or healthy), treatment duration ( $\leq 6$  or  $> 6$  weeks), number of strain ( $\leq 1$  or  $> 1$ ), presence or absence of concomitant medications, and region
- Sensitivity analysis** - leave-one-out meta-analysis, and outlier detection.
- Publication bias** detected using contour-enhanced funnel plots and Egger's regression ( $p < 0.1$ )
- Analyses performed in R software (v4.3.0)
- Quality assessment using Cochrane Risk of Bias 2.0 tool
- Certainty of evidence assessed with GRADE methodology

## RESULTS

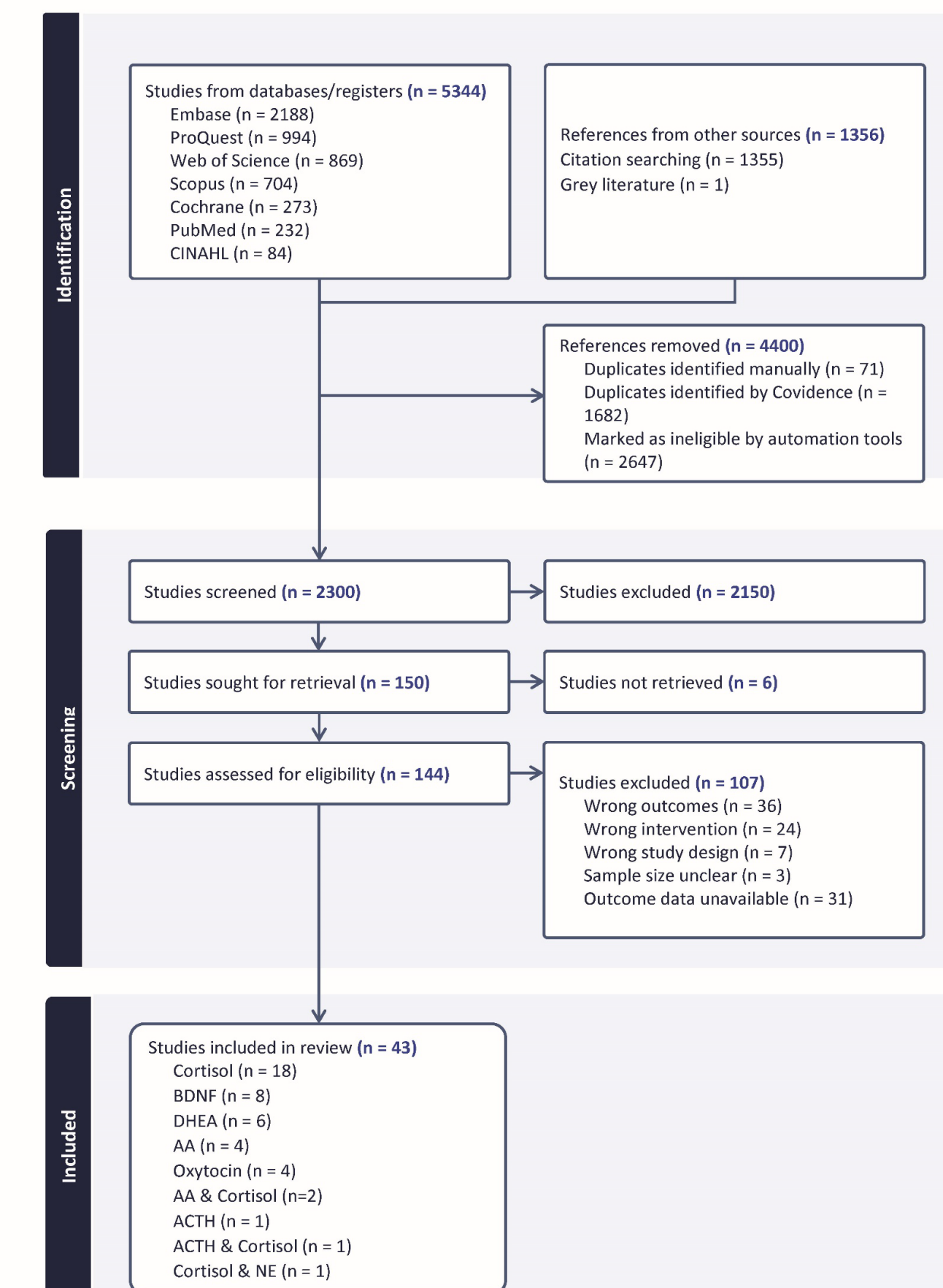


Figure 1. PRISMA Flow Chart

Outcome	Assessed with	All studies included			After sensitivity analysis*			Certainty of evidence
		No. of studies	No. of patients	Pooled effect	No. of studies	No. of patients	Pooled effect	
Cortisol	Salivary/ Urinary/ Blood	22	836	-0.63 (-1.37, 0.12) [95.2% -4.18, 2.93]	19	660	-0.06 (-0.22, 0.11) [38.8% -0.66, 0.55]	⊕⊕⊕⊕ High
BDNF	Blood	8	192	-0.23 (-1.01, 0.56) [87% -2.54, 2.09]	7	164	0.14 (-0.8, 0.36) [0% -0.15, 0.43]	⊕⊕⊕⊕ High
DHEA	Blood	6	240	0.02 (-0.38, 0.41) [42% -0.83, 0.87]	5	220	0.12 (-0.1, 0.35) [0% -0.22, 0.46]	⊕⊕⊕⊕ High
AA	Blood	6	239	-0.25 (-0.57, 0.07) [46% -0.89, 0.39]	5	169	-0.15 (-0.42, 0.13) [0% -0.50, 0.19]	⊕⊕⊕⊕ High
ACTH	Blood	2	174	2.23 [-25.06, 29.51] [99% NA, NA]	-	-	-	⊕⊕⊕⊕ Very Low
Oxytocin	Blood	2	61	0.84 [-4.37, 6.05] [78% NA, NA]	-	-	-	⊕⊕⊕⊕ Very Low

CI: confidence interval; SMD: standardised mean difference; PI: prediction interval; I<sup>2</sup>: heterogeneity; \*No. of studies included after outlier detection and influence analysis.

Table 1. Summary of analysis for all the biomarkers

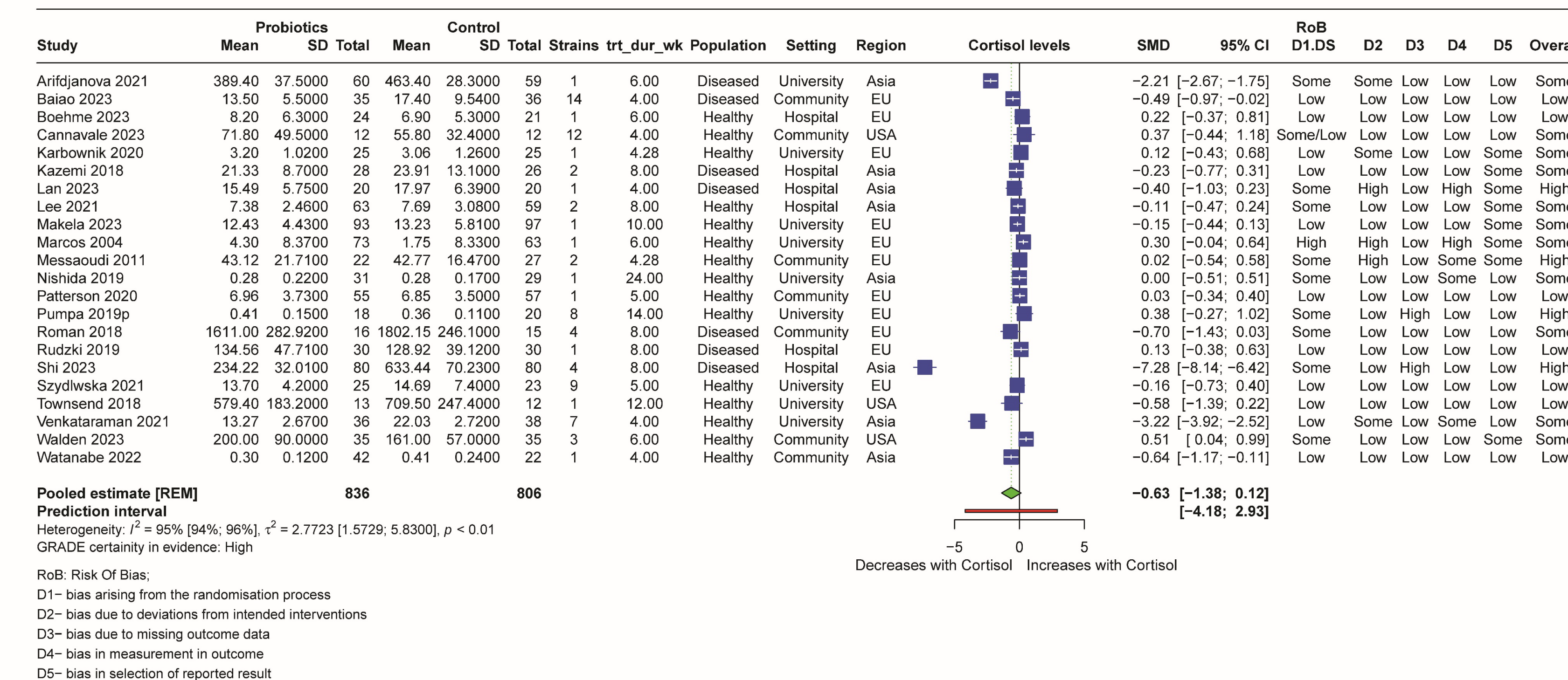


Figure 2. Forest Plot - Cortisol

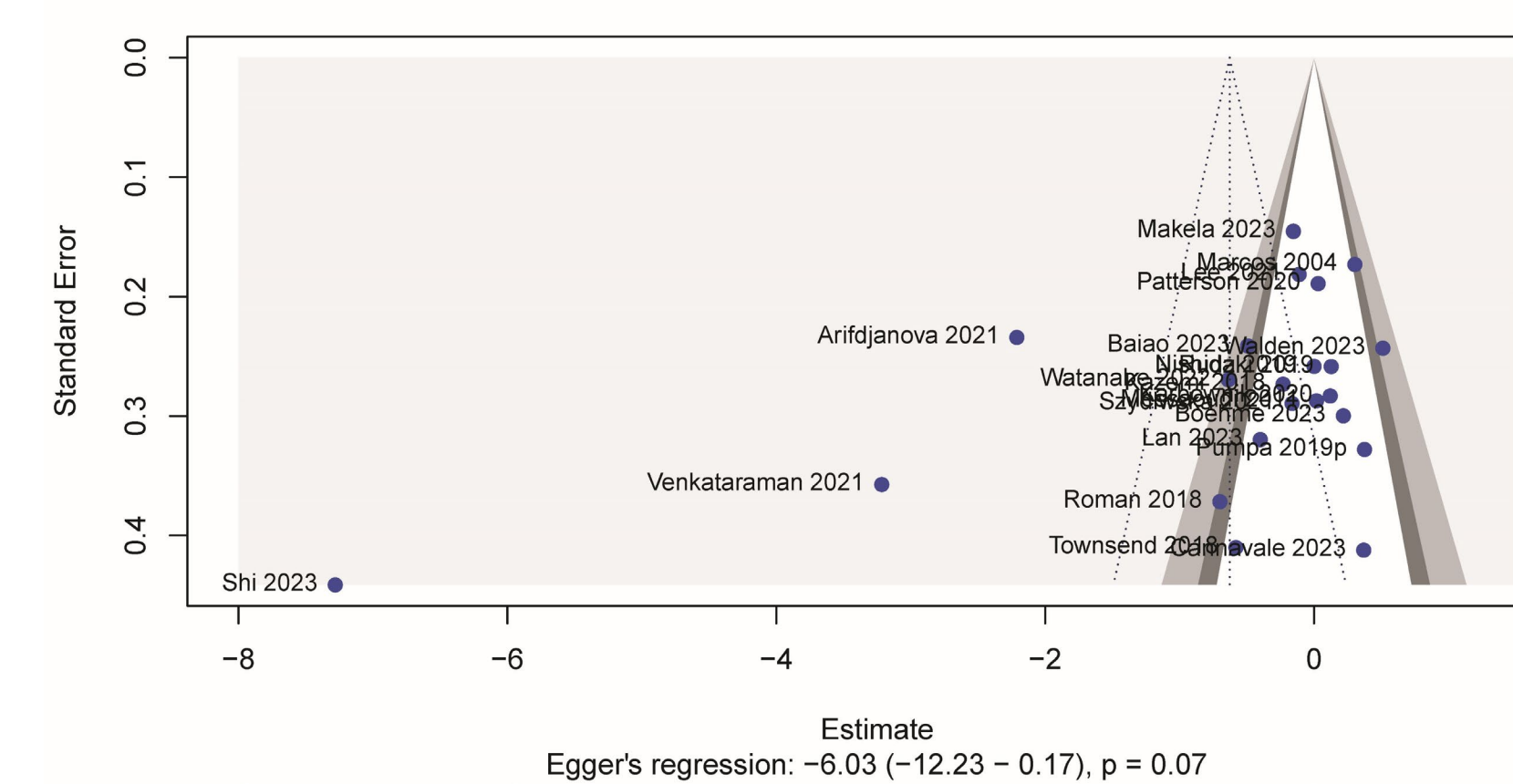


Figure 3. Funnel Plot - Cortisol

- Screening through 6700 records yielded 43 RCTs, including 3220 participants (Figure 1).
- Probiotics did not cause significant alterations in biomarker levels when all studies were analysed collectively for each outcome measure, but high heterogeneity rendered the evidence inconclusive (Table 1, Figure 2, 3).
- On subgroup analyses, heterogeneity remained very high in each subgroup for every outcome.
- Following sensitivity analyses, a considerable reduction in heterogeneity and narrowing of CI was observed, resulting in the inclusion of 19 studies for cortisol, 7 for BDNF, and 5 each for DHEA and AA in the final analysis (Table 1).
- Probiotics did not alter any biomarker levels significantly.
- The certainty of the evidence was high for cortisol, BDNF, and DHEA, AA, and very low for oxytocin and ACTH in this analysis.

## DISCUSSION & CONCLUSION

- Probiotics do not significantly alter neuroendocrine biomarker levels
- High heterogeneity indicated wide differences among the studies included, subgroups specified a priori failed to address heterogeneity in our analysis, indicating additional unmeasured factors involvement.
- Our results agreed to the previous findings, except for BDNF where a few subgroups showed increase levels<sup>2-5</sup>
- Evidence remains inconclusive for oxytocin and ACTH due to limited data availability

## IMPACT OF RESEARCH

- Challenges previous findings on probiotics modulating cortisol, BDNF, DHEA, and AA levels in various diseases
- Need for more targeted studies to identify specific conditions or subpopulations where probiotics may have beneficial effects
- Potential to guide future clinical recommendations for probiotic use

## REFERENCES

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