**Supplementary file 2.1. Publication bias assessment using funnel plots of main outcomes using random effect models.**

**Supplementary Figure 2.1.a. Pro- and synbiotics effects on serum/plasma lipopolysaccharide (LPS).**

Egger's test for small-study effects:

Regress standard normal deviate of intervention

effect estimate against its standard error

Number of studies = 28 Root MSE = 3.773

------------------------------------------------------------------------------

Std\_Eff | Coefficient Std. err. t P>|t| [95% conf. interval]

-------------+----------------------------------------------------------------

slope | 2.187547 .8841234 2.47 0.020 .3702056 4.004889

bias | -8.295863 2.957561 -2.80 0.009 -14.37522 -2.216511

------------------------------------------------------------------------------

Test of H0: no small-study effects P = 0.009

****

Iteration Number of studies = 28

Model: Random-effects observed = 28

Method: REML imputed = 0

Pooling Model: Random-effects Method: REML

---------------------------------------------------------------

Studies | Effect size [95% conf. interval]

---------------------+-----------------------------------------

Observed | -0.559 -1.159 0.040

Observed + Imputed | -0.559 -1.159 0.040

---------------------------------------------------------------

****

**Supplementary Figure 2.1.b. Pro- and synbiotics effects on serum/plasma zonulin**

Egger's test for small-study effects:

Regress standard normal deviate of intervention

effect estimate against its standard error

.

Number of studies = 15 Root MSE = 1.999

------------------------------------------------------------------------------

Std\_Eff | Coefficient Std. err. t P>|t| [95% conf. interval]

-------------+----------------------------------------------------------------

slope | -1.070039 .5499668 -1.95 0.074 -2.25817 .1180922

bias | 1.858209 1.88675 0.98 0.343 -2.217867 5.934285

------------------------------------------------------------------------------

Test of H0: no small-study effects P = 0.343



**Supplementary Figure 2.1.c. Pro- and synbiotics effects on fecal calprotectin**

Funnel

Number of studies = 10 Root MSE = 3.452

------------------------------------------------------------------------------

Std\_Eff | Coefficient Std. err. t P>|t| [95% conf. interval]

-------------+----------------------------------------------------------------

slope | .6909156 .7000501 0.99 0.353 -.9234029 2.305234

bias | -3.080328 2.792966 -1.10 0.302 -9.520919 3.360262

------------------------------------------------------------------------------

Test of H0: no small-study effects P = 0.302



**Supplementary file 2.2. Influence/Sensitivity analyses results.**

**Supplementary figure 2.2.a. A leave-one-out sensitivity analysis of the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide (LPS).**

------------------------------------------------------------------------------

Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

1 | -.54292631 -1.0312183 -.05463436

2 | -.52180791 -1.0071666 -.03644914

3 | -.54554087 -1.046809 -.04427277

4 | -.55612135 -1.047425 -.06481768

5 | -.61738563 -1.0883726 -.14639868

6 | -.56372935 -1.0587821 -.06867664

7 | -.64045089 -1.0623114 -.21859035

8 | -.48203868 -.95607406 -.00800329

9 | -.51289409 -.99835449 -.02743372

10 | -.58379102 -1.0732696 -.09431243

11 | -.5689882 -1.0579309 -.08004556

12 | -.57521355 -1.0613428 -.08908425

13 | -.58340347 -1.0698558 -.0969511

14 | -.56839687 -1.0704722 -.06632146

15 | -.34670994 -.77959192 .08617205

16 | -.50669789 -.98876435 -.02463142

17 | -.5555104 -1.0452185 -.06580241

18 | -.52427578 -1.0102597 -.0382918

19 | -.52603954 -1.0172777 -.03480131

20 | -.55263311 -1.043681 -.06158511

21 | -.57625657 -1.065104 -.08740909

22 | -.5779022 -1.0674983 -.0883061

23 | -.55129743 -1.0373571 -.06523769

24 | -.55968428 -1.0520694 -.06729918

25 | -.57703775 -1.0647134 -.08936214

26 | -.50997406 -.99391621 -.02603194

27 | -.40437457 -.84818363 .0394345

28 | -.51008689 -.99345744 -.02671633

-------------------+----------------------------------------------------------

Combined | -.54055145 -1.0140037 -.06709918

------------------------------------------------------------------------------

****

**Supplementary file 2.2. Influence/Sensitivity analyses results.**

**Supplementary figure 2.2.b. A leave-one-out sensitivity analysis of the impact of pro- and synbiotics administration on serum/plasma zonulin.**

------------------------------------------------------------------------------

Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

1 | -.4682121 -.78759408 -.1488301

2 | -.42865601 -.736579 -.12073302

3 | -.3925302 -.63363171 -.15142873

4 | -.50459588 -.83643591 -.17275591

5 | -.48939148 -.82591814 -.15286483

6 | -.5017193 -.82902569 -.17441288

7 | -.4775067 -.81272668 -.14228673

8 | -.55812061 -.85466367 -.26157752

9 | -.4643988 -.78580314 -.14299449

10 | -.51253092 -.82693201 -.19812982

11 | -.52044499 -.83456337 -.20632654

12 | -.51866966 -.83666164 -.20067766

13 | -.52215827 -.84324419 -.20107228

14 | -.48600656 -.81432283 -.15769029

15 | -.47923276 -.80919886 -.14926666

-------------------+----------------------------------------------------------

Combined | -.48835989 -.79493043 -.18178935

------------------------------------------------------------------------------



**Supplementary file 2.2. Influence/Sensitivity analyses results.**

**Supplementary figure 2.2.c. A leave-one-out sensitivity analysis of the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide binding protein (LBP).**

------------------------------------------------------------------------------

Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

1 | .30866683 -.18307042 .80040401

2 | .15845095 -.09869841 .4156003

3 | .33130533 -.16311006 .82572073

4 | .37042817 -.07053386 .81139016

5 | .38976285 -.0836448 .8631705

6 | .36560476 -.05175059 .78296012

7 | .35779628 -.07224437 .78783697

8 | .22028394 -.19298594 .6335538

-------------------+----------------------------------------------------------

Combined | .30427142 -.09363347 .70217632

------------------------------------------------------------------------------



**Supplementary file 2.2. Influence/Sensitivity analyses results.**

**Supplementary figure 2.2.d. A leave-one-out sensitivity analysis of the impact of pro- and synbiotics administration on fecal calprotectin.**

------------------------------------------------------------------------------

Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

1 | -.30465099 -.8549422 .2456402

2 | .06270856 -.41572002 .5411371

3 | -.1483136 -.7995711 .50294387

4 | -.18447901 -.88166714 .51270908

5 | -.05518268 -.70739889 .5970335

6 | -.06951652 -.72154301 .58250993

7 | .09428772 -.46978995 .65836543

8 | -.1763885 -.8826347 .5298577

9 | -.16935804 -.83444804 .49573198

10 | -.18613362 -.819004 .44673678

-------------------+----------------------------------------------------------

Combined | -.10217521 -.69001811 .4856677

------------------------------------------------------------------------------



**Supplementary file 2.2. Influence/Sensitivity analyses results.**

**Supplementary figure 2.2.e. A leave-one-out sensitivity analysis of the impact of pro- and synbiotics administration on fecal zonulin.**

------------------------------------------------------------------------------

Study omitted | Estimate [95% Conf. Interval]

-------------------+----------------------------------------------------------

1 | .07159203 -.43650582 .57968986

2 | .08109583 -.38492221 .5471139

3 | -.10728747 -.65798509 .44341019

-------------------+----------------------------------------------------------

Combined | .02521814 -.38690239 .43733868



**Supplementary file 2.3. The evaluation of evidence certainty using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.**

| **Certainty assessment** | | | | | | **Certainty** |
| --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** |
| **Serum/ plasma Lipopolysaccharide** | | | | | | |
| 24 | Not serious a | Very Serious b | Not serious c | Serious d | Not serious e | Very low |
| **Serum/ plasma zonulin** | | | | | | |
| 13 | Not serious a | Not serious f | Not serious g | Not serious | Serious h | Moderate |
| **Fecal calprotectin** | | | | | | |
| 10 | Not serious a | Very Serious b | Not serious i | Serious d | Not serious | Very low |
| **Serum/ plasma lipopolysaccharide binding protein** | | | | | | |
| 8 | Not serious a | Not serious j | Not serious c | Serious d | Not serious k | Moderate |
| **Fecal zonulin** | | | | | | |
| 3 | Not serious a | Serious l | Serious m | Serious d | Not serious k | Very low |

a. Less than 50% of studies and participants were at high risk of bias, therefore it was not downgraded. Not downgraded

b. Downgraded two levels since the heterogeneity was more than 90% and the source of heterogeneity was not found.

c. Not downgraded as a major proportion of the participants suffered from a type of cardiometabolic risk factor, and the results were attributed to the population who are at risk of chronic disorders.

d. Downgraded one level, since 95% CIs of SMD included null effect.

e. Although publication bias was significant, in trim and fill analysis, no study was added and the SMD and 95% CIs were the same as original analysis

f. Although I2= 87%, not downgraded. Because, after excluding one study (Karim et al. 2022) I2 became 16.8%.

g. Not downgraded as most of the participants were unhealthy and the result was attributed to population that were mainly unhealthy.

h. Asymmetry was seen in funnel plot, and three studies were included trim and fill analysis

i. Not downgraded as most of the participants had GI disorders, and the results were attributed to the population with GI disorders

j. Although I2 was > 50%, we did not downgrade for inconsistency since in one subgroup conducted by type of intervention in the synbiotic subgroup [SMD=0.13 (95% CI: -0.21, 0.47), I2=0.0 %; n=4] heterogeneity was reduced. Not downgraded

k. Not downgraded as the number of studies was <10.

l. Downgraded one level as I2= 55.3%

m. Downgraded one level, because the participants in the tree studies included individuals with migraines, obesity, and endurance-trained men.

**Supplementary file 2.4. Subgroup analysis results.**

**Supplementary Figure 2.4.a. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide (LPS) levels according to health conditions of participant.**

****

**Supplementary Figure 2.4.b. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide (LPS) levels according to type of intervention.**

****

**Supplementary Figure 2.4.c. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide (LPS) levels according to follow up duration.**

****

**Supplementary Figure 2.4.d. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide (LPS) levels according to total dose of bacteria prescribed.**

****

**Supplementary Figure 2.4.e. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide (LPS) levels according to study quality assessment (Good/Fair or Poor).**

****

**Supplementary file 2.5. Meta-regression analysis.**

**Supplementary figure 2.5 (a, b). A random-effects meta-regression to investigate the relationship between potential moderators (a. age and b. body mass index (BMI)) and estimated net changes in serum/plasma lipopolysaccharide (LPS) following supplementation with pro- and synbiotics using unrestricted maximum likelihood method**

**a. Age**

****

**b. BMI**

****

**Supplementary Figure 2.6.a. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma zonulin levels according to health conditions of participants.**

****

**Supplementary Figure 2.6.b. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma zonulin levels according to type of intervention.**

****

**Supplementary Figure 2.6.c. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma zonulin levels according to follow up duration.**

****

**Supplementary Figure 2.6.d. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma zonulin levels according to total dose of bacteria prescribed.**

****

**Supplementary Figure 2.6.e. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma zonulin levels according to study quality.**

****

**Supplementary figure 2.7 (a, b). A random-effects meta-regression to investigate the relationship between potential moderators (a. age and b. body mass index (BMI)) and estimated net changes in serum/plasma serum/plasma zonulin following supplementation with pro- and synbiotics using unrestricted maximum likelihood method.**

1. **Age**



**b. BMI**

****

**Supplementary Figure 2.8.a. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide binding protein (LBP) levels according to health conditions of participants.**

****

**Supplementary Figure 2.8.b. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide binding protein (LBP) levels according to type of intervention.**

****

**Supplementary Figure 2.8.c. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide binding protein (LBP) levels according to total dose of bacteria prescribed.**

****

**Supplementary Figure 2.8.d. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on serum/plasma lipopolysaccharide binding protein (LBP) levels according to study quality (Good/Fair/Poor).**

****

**Supplementary figure 2.9 (a, b). A random-effects meta-regression to investigate the relationship between potential moderators (a. age and b. body mass index (BMI)) and estimated net changes in serum/plasma lipopolysaccharide binding protein (LBP) following supplementation with pro- and synbiotics using unrestricted maximum likelihood method.**

1. **Age**

****

**b. BMI**

****

**Supplementary Figure 2.10.a. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on fecal calprotectin levels according to health conditions of participants.**



**Supplementary Figure 2.10.b. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on fecal calprotectin levels according to total dose of bacteria prescribed.**



**Supplementary Figure 2.10.c. Forest plot depicting standardized mean differences (SMD) and the 95% confidence interval (CI) for the impact of pro- and synbiotics administration on fecal calprotectin levels according to study quality (Good/Fair/Poor).**



**Supplementary figure 2.11 (a). A random-effects meta-regression to investigate the relationship between potential moderators (a. age) and estimated net changes in fecal calprotectin following supplementation with pro- and synbiotics using unrestricted maximum likelihood method.**

**a. Age**

****

\*Not enough data was available for BMI.