

**Rebuttal Letter for the manuscript “Microbiota shaping: the effects of probiotics, prebiotics and fecal microbiota transplants on cognitive functions. A systematic review.” of Baldi S et al.**

**REVIEWER 1**

**Q/S 1:** Minor comments, The differential effects caused by the different gut microbiota intervention methods needs to be compared strictly in RESULTS.

The details of the mechanism in these reports need more in-depth analysis and summary.

**Q/S 1 Reply:** *We thank the reviewer for the careful analysis of our paper and the right suggestion. In agreement with his observation, we have discussed the requested aspects (please see lines 273-275, 322-324, 390-400)*

**Q/S 2:** The uncertainties and risks associated with microbiota intervention, especially FMT, need to be analysed and discussed.

**Q/S 2 Reply:** *In agreement with the suggestion of reviewer, we added and discussed this important aspect in the discussion section (please see lines 437-461)*

**REVIEWER 2**

**Q/S 1:** Without decreasing the importance of this work, to the eyes of this reviewer, the work lacks interesting information about the use of nutritional interventions used similarly to treat deficiencies in the cognitive functions. There are some suggestions to improve the work, made directly to the reviewed text (attached: ca857959-9f4c-4ea4-a2f0-c597d4071f70\20210312\_64869-Manuscript File-reviewed.pdf) which are highlighted in magenta color.

**Q/S 1 Reply:** *We thank the reviewer for the careful and focused analysis of our manuscript. We agree with the right suggestions and we add the requested information (please see lines 107-111).*

**REVIEWER 3**

**Q/S 1:** Authors must clarify if the review refers to cognitive disorders (in general) or specifically about dementia.

**Q/S 1:** *We thank the reviewer for the suggestion and so the opportunity to clarify this point. Although dementia is the most common and studied cognitive disorder, as reported by the used search string (please see lines 136-138) our systematic review refers to the effects of probiotics, prebiotics and FMT on different neurological situations, including memory impairments, cognitive disorders and dementia.*

**Q/S 2:** In introduction, authors stated that “...the administration in animal models of an adequate posology of multistrain probiotics reduced both Firmicutes/Bacteroidetes ratio and the intestinal permeability...”, however, there are some clinical trials addressing the role of such approach in gut microbiota modulation.

**Q/S 2 Reply:** *We thank the reviewer for the appropriate observation, we have re-evaluated the literature and found only a RCT conducted on obese adolescents and we add the reference (please see the reference 18).*

**Q/S 3:** In page 11, please clarify FMT studies T?

**Q/S 3 Reply:** *Sorry, the T is a mistake and we have removed it.*

**Q/S 4:** As *Lactococcus* spp may also be used as probiotics in different contexts, the species of microorganisms used in the review must be written with their full names by the first time they are cited in the text

**Q/S 4 Reply:** *As rightly suggested by the reviewer, we provided the full name of microorganism by the first time that we cited it in the text.*

**Q/S 5:** Authors must describe the putative mechanisms used by probiotics to modulate the activity of central nervous system

**Q/S 5 Reply:** *We thank the reviewer for the right suggestion and in agreement, we discussed this interesting aspect (please see lines 390-400)*

**Q/S 6:** In its current form the manuscript is merely descriptive. The text lacks a more in-depth discussion concerning pros and cons of using microbial modulation to treat or constrain the development of cognitive disorders. Authors must describe the limitations of each approach highlighting the concerns regarding the use of live microorganisms (probiotics and FMT) in targeted populations, including immunosuppressed and the risk of FMT in the transmission of pathogenic multi-resistant bacteria

**Q/S 6 Reply:** *In agreement with the precious suggestion of reviewer, we have discussed the limitations of each GM modulation approach highlighting the concerns regarding the use of live microorganisms probiotics and FMT) in targeted populations (such as immunocompromised people) and the FMT risk of in the transmission of pathogenic multi-resistant bacteria (please see the discussion section, in detail the lines 437-461).*

**Q/S 7:** There are several typos throughout the text. E.g. “synbiotics” ; “week” – page 11

**Q/S 7 Reply:** *Sorry for these various typos, we checked all the manuscript text, correcting the different them*

**Q/S 8:** Please, replace the word “flora” by “microbiota”

**Q/S 8 Reply:** *As rightly suggested by the reviewer, we have changed flora with microbiota.*

**Q/S 9:** “mL” rather than “ml”

**Q/S 9 Reply:** *Thank you, we correct the mistakes.*