VRIJE UNIVERSITEIT BRUSSEL

Thesis submitted for the purpose of obtaining
of the degree of Master of Science in Clinical Psychology, profile Biological Psychology

MASTER'S THESIS: THE EFFECT OF PREBIOTICS AND PROBIOTICS ON HUMAN MEMORY

A systematic review and meta-analysis of randomized controlled trials

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2020-2021

Promoter: Prof. Dr. Natacha Deroost
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Titel van de Masterproef: The effect of prebiotics and probiotics on human memory. A systematic review and meta-analysis of randomized controlled trials

Promotor: Prof. Dr. Natacha Deroost

Samenvatting: (300 woorden)

We live in a microbial world. More and more research is establishing the link between the brain-gut axis, the microbiome and the brain. Research into interventions to influence the microbiome result from this. Both animal and human research shows positive and negative effects of pre- and probiotics on memory but a general conclusion about the effectiveness on humans is lacking. The databases PubMed, PsychInfo, and Web of Science were systematically searched for randomized controlled trials (RCTs) investigating the effect of pre- and probiotics until April 13, 2021. Standard mean difference (SMD) was used as a measure to verify effects. Moderator analyses were performed to determine possible influencing factors. Twelve studies were ultimately included in the systematic review. Two studies found a significant effect on long-term memory (LTM) in favor of probiotics. The same result was found on short-term memory (STM). One study found a significant effect of prebiotics on LTM and STM. Nine studies with were included in the meta-analysis. Both the meta-analysis and the moderator analyses found no significant effect on human memory in favor of probiotics. Due to limited data, publication bias could not be examined. A meta-analysis of prebiotics could not be performed due to incomplete data. This study could not establish a significant effect in favor or against prebiotics and probiotics on human memory. More qualitative experimental research is needed before a reliable statement can be made about the effectiveness.

Keywords: Prebiotics – Probiotics – Memory – Microbiome - Systematic review – Meta-analysis

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Opgesteld te Lille op 23/05/21

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Introduction

Few people dwell on the fact that we live in a microbial world, although no less than trillions of microorganisms live in and on our bodies (McFall-Ngal et al. 2013, Theis et al., 2016). The majority of these organisms are found in the intestines, where they form the gut microbiome. Scientific research on the impact and manipulation of this ecosystem on human health has increased significantly in recent years. Within neuroscience research, some researchers even speak of a paradigm shift (Mayer et al., 2014), which evidently also has an impact on psychological functions (Allen et al., 2017). This includes research on the effect of functional foods on the gut and on memory. Animal studies already show positive effects of pre- and probiotics (Oliveros et al., 2016; Savignac et al., 2015; Vázquez et al., 2015). Research in humans has also been taking place in recent years, unfortunately without clear conclusions regarding the effect of these agents on memory (Sarkar et al., 2018). This master's thesis will compile the conducted research through a systematic review. On the other hand, the effects of pre- and probiotics on human memory will be examined through a meta-analysis.

Memory

Human memory is a very important functional domain. It covers several processes including processing, storing and retrieving information (Lambrecht & Hermans, 2012). Thanks to memory, humans are able to use language, maintain relationships and develop an identity (Eysenck, 2012). Our society relies on a well-functioning memory. Consequently, many elderly people have fears of memory problems. As many as 56% of healthy elderly people living at home experience subjective memory complaints (Reid & Maclullich, 2006). Social phobias in the elderly often have their origin in fear of becoming forgetful (Vink et al., 2017). The importance of memory is additionally evidenced by the frequent problems that occur in numerous neurological and psychiatric disorders (Meeter & Hendriks, 2018; Pittenger, 2013).

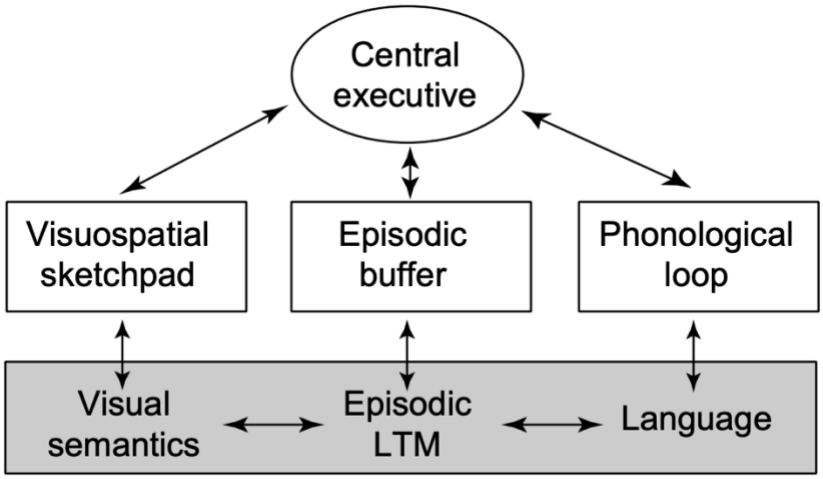
Short-term memory

Short-term memory (STM) is the "ability to keep small amounts of information available for a short period of time" (Camina & Güell, 2017, p.4). STM is also called working memory and refers to "the brain systems that provide temporary storage and manipulation of information needed for complex tasks" (Baddeley, 1992). Working memory is subdivided (see Figure 1) in the central

executive, the episodic buffer, the phonological loop, and the visuospatial sketchpad (Baddeley & Hitch, 1974; Baddeley, 2000). The central executive controls attention (Grigorenko et al., 2012), while the phonological loop and visuospatial sketchpad constitute respectively the verbal STM and visuospatial STM (Camina & Güell, 2017). The episodic buffer forms a temporary repository where different sources of information are integrated. This information is integrated in space and possibly in time. Information retrieved from the episodic LTM is first temporarily stored in the episodic buffer (Baddeley, 2000). Although subject to debate, it is believed that the central executive locates in the frontal cortex (Duncan & Owen, 2000; Shallice, 2002). In contrast, the visuospatial sketchpad is located in the parietal cortex on the one hand, on the other hand it includes a number of areas in the right hemisphere (Camina & Güell, 2017). The phonological buffer can be localized in the left hemisphere, specifically in Brodmann areas 40 and 44 (Baddeley, 2000). There can be no specific brain regions associated to the episodic buffer (Potter, 1999).

Figure 1.

The working memory model



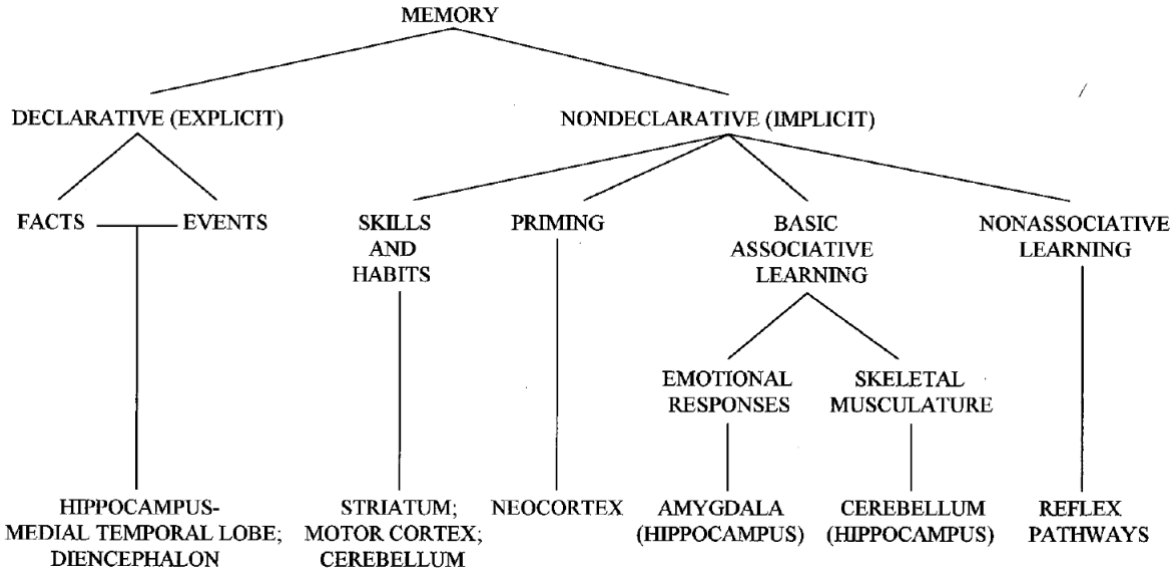
Note. From *The Episodic Buffer: A New Component of Working Memory?* by Baddeley, 2000, *Trends in cognitive sciences, 4*, p. 421. Copyright 2000 by Elsevier Science Ltd

Long-term memory

Long-term memory (LTM) consists of an infinite amount of information that can be retained for a long time. Some information can be remembered for life (Camina & Güell, 2017). Within the LTM, a distinction is made between declarative (or explicit) memory and nondeclarative (or implicit) memory (Squire, 2004). An overview with the components of the LTM and the structures involved can be consulted in Figure 2.

Figure 2.

A tentative taxonomy of the LTM and associated brain structures.



Note. From *Memory, hippocampus and brain systems* by R.F. Thompson & J.J. Kim, 1996, *Proceedings of the National Academy of Sciences of the United States of America, 93*, p. 13439. Copyright 1996 by The National Academy of Sciences of the USA

Declarative memory. The first component of LTM involves declarative (or explicit) memory. This memory includes the ability to consciously process information (Camina & Güell, 2017). It is divided into episodic memory and semantic memory (Squire, 2004). Episodic memory involves "the ability to learn, store and retrieve information about unique personal experiences that happen daily. These memories typically include information about the time and place of an event, as well as detailed information about the event" (Dickerson & Eichenbaum, 2010). There are a number of neuronal structures involved in declarative memory. The enthorinal cortex forms the link between the hippocampus and the neocortex so the structure likely provides the distribution of information. Next, the perirhinal cortex and parahippocampal cortex are involved in the visual recognition of objects and the processing of environmental information, respectively (Aguirre et al., 1996; Aguirre et al., 1998; Epstein & Kanwisher, 1998; Isha, et al., 1999). Finally, the hippocampus takes care of creating and retrieving memories (Craver, 2003). Semantic memory additionally refers to the knowledge of facts, ideas, meanings, and concepts that we build up throughout life (Mcrae & Jones, 2013). The neuronal structures involve the sensorimotor cortex (Vigliocco et al., 2009) and large parts of the inferior parietal and temporal cortex (Binder & Desai, 2011).

Nondeclarative memory. In addition to declarative memory, the LTM also consists of nondeclarative (or implicit) memory. This is subdivided into procedural memory, basic associative memory, non-associative memory and priming (Camina & Güell, 2017). Procedural memory is unconsciously evoked when performing motor, executive, or intellectual skills and habits (Camina & Güell, 2017). The repeated learning and recall of a complex skill calls upon several brain structures including the basal ganglia (Constantinidis & Procyck, 2004), het cerebellum (Kreitzer, 2009) and the limbic system (Camina & Güell, 2017). Priming refers to the phenomenon whereby exposure to a particular stimulus influences the subsequent response (Weingarten et al., 2016). The neocortex is involved in this process (Christian et al., 2014). Associative memory then refers to "the storage and retrieval of information by association with other information" (Camina & Güell, 2017, p.10). This memory is built up by both classical (Pavlov, 2010) as operant conditioning (Thorndike, 1932) and has neuronal correlates with the amygdala and cerebellum (Christian et al., 2014; Thompson & Kim, 1996). Finally, nonassociative memory refers to "newly learned behavior through repeated exposure to an isolated stimulus" (Camina & Güell, 2017, p.10). This behavior is divided into two processes: sensitization and habituation. The structures involved are the neuronal pathways involved in the occurrence of reflexes (Christian et al., 2014).

Prebiotics and probiotics

Much research is being done on ways to improve memory. One of the research areas focuses on the use of functional foods and, more specifically, pre- and probiotics (Hwang et al., 2019; Inoue et al., 2018; Kobayashi et al., 2019). Functional food can be defined as food with a beneficial effect on one or more bodily functions, physical or mental health, and/or the risk of disease. In addition, it must be part of a normal diet and it must be consumable through normal food. This means that no pills or capsules are used (Diplock, et al, 1999). Although there are various forms of functional foods, in recent years much attention has been paid to the specific use of pre- and probiotics.

Prebiotics

Prebiotics are "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one, or a limited number of bacteria in the colon that can improve the host health" (Gibson & Roberfroid, 1995, p. 1401). Prebiotics that are frequently used and internationally recognized include fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) (Belmonte et al., 2012; Floch et al., 2016). Prebiotics can be consumed through commercial

formulations as well as naturally. For example, FOS can be found in chicory, garlic, leeks, asparagus, onions, bananas and wholemeal bread (Campbell, et al., 1997). An important FOS involves inulin, which can be found in large concentrations in Jerusalem artichoke and yacon (Dimitriu, 2005). In addition, GOS occurs naturally in milk from mammals (Belorkar & Gupta, 2016). The components in prebiotics stimulate the activity and proliferation of *Bifidobacteria* (BD) and *Lactobacili* (LB), thus forming the food source for probiotics (Sarkar et al., 2016). However, they are no longer considered purely as stimulants for probiotics today (Gibson et al., 2017). In fact, they possess preventive properties against colon cancer (Moore et al., 2003), they can lower high cholesterol levels (Fernandez et al., 2003), they improve diarrhea (Drakoularakou et al., 2010) and they can be used as a calorie-free sweetener (Saminathan et al., 2011). Despite these findings, the strength of evidence to date is lower for prebiotics than for probiotics (Sanders et al., 2019). Although several possible models in favor of prebiotics have been explored, the mechanisms remain unclear (Markowiak & Śliżewska, 2017).

Probiotics

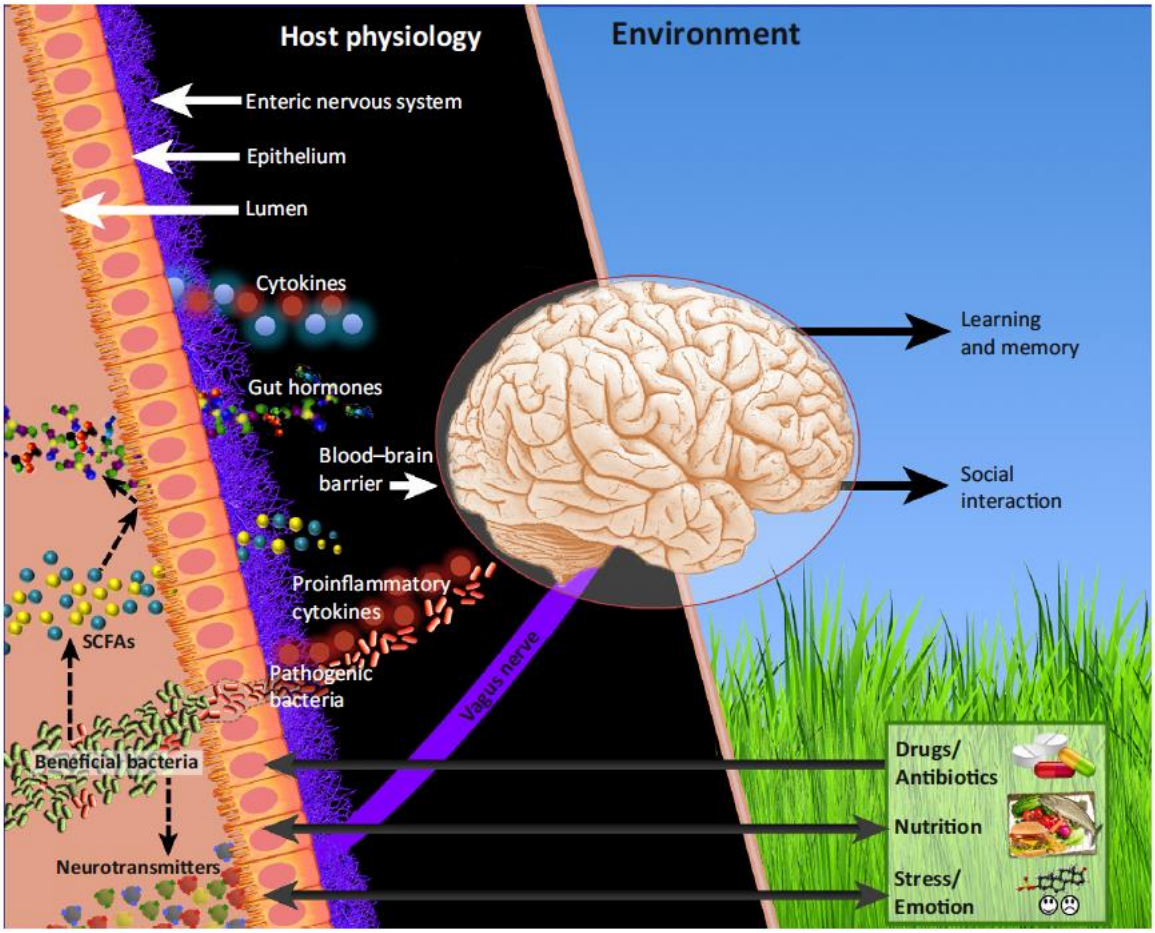
Probiotics are strands of live microorganisms that are largely of human origin and can contribute to a variety of health benefits through a given intake amount (Caselli et al., 2013; Senok et al., 2005). There are several criteria formulated regarding safety, functionality and technological usability according to which probiotics should comply (FAO, 2002; EFSA, 2005). Unlike prebiotics, probiotics involve living bacteria. It's often milk products containing large amounts of beneficial bacteria, including *Lactobacili* (LB) and *Bifidobecteria* (BD). The probiotics used primarily in commercial formulations involve the lactic acid bacteria *LB casei, reuteri, fermentum, plantarum, paracasei, salivarius* en *rhamnosus* on the one hand and *BD bifidum, infantis* and *longum* (Ahrne et al., 2011; Karczewski et al., 2010; McNaught et al., 2005) on the other. Probiotics have several health benefits, based on four basic mechanisms: antagonism through the production of antimicrobial substances (Vandenbergh, 1993), immunomodulation of the host (Isolauri et al., 2001), competition with pathogens for adhesion to the epithelium for nutrients (Guillot, 2003) and inhibition of bacterial toxin production (Brandao et al., 1998). Probiotics have been shown to provide clinically significant improvements in eczema (Niers et al., 2009), necrotizing enterocolitis (AlFaleh & Anabrees, 2014), acute diarrhea (Szajewska et al., 2019), moderate to severe chronic intestinal inflammation (Mardini & Grigorian, 2014), pouchitis (Sanders et al, 2013) and irritable bowel syndrome (Niv et al., 2005; Whorwell et al., 2006).

The gut microbiome, the brain-gut axis and the brain

The gut microbiome comprises the largest storehouse of microbes in the human body (Lin et al., 2018). The entirety of these microbes, which are considered an essential organ (O'Hara & Shanahan, 2006), form a vast and diverse ecological system. They cover 100 times (Hamady & Knight, 2009) to 150 times (Ursell et al., 2014) more genes than those contained in the human genome. The gut microbiome consists largely of thousands of species of bacteria (De Vos & De Vos, 2012; Lozupone et al., 2012), although archaea, fungi, protozoa and viruses are also present (Dinan, Stanton & Cryan, 2013). As illustrated in Figure 3, gut bacteria produce short-chain fatty acids (SCFA) through the fermentation of indigestible components, these can be supplied by prebiotics. SCFA's include propionate, butyrate and acetate. These fatty acids, in addition to having a direct impact on neural activity, also affect the production of gut hormones such as incretin and peptide tyrosine tyrosine (PYY) and the production of anti-inflammatory cytokines. Finally, the bacteria produce neurotransmitters in the form of metabolites (Sarkar et al., 2018). Figure 3 also shows the presence of pathogenic bacteria. They can generate pro-inflammatory cytokines through an opening in the intestinal wall, which in turn are related to depression. Medication, diet and stress all affect the intestinal wall, in the latter two the relationship is even bidirectional. The gut bacteria are connected to the brain through the brain-gut axis. This axis is a bidirectional communication network (Dinan & Cryan, 2016) consisting of the enteric nervous system, the gastrointestinal tract and the brain. The network contains immune, neural, endocrine and metabolic pathways (El Aidy, et al., 2015; Grenham et al., 2011; Mayer, 2014; Koh et al., 2016; Sommer & Bäckhed, 2016). Using synapses in the enteric nervous system, the vagus nerve (N.X) is the key element in the communication between the intestines, gut microbes and the brain (Dinan & Cryan, 2016; Sarkar et al., 2016).

Figure 3.

A model of the relationships between bacteria, brain and behavior



Note. From *The Microbiome in Psychology and Cognitive Neuroscience* by A. Sarkar, 2018, *Trends in Cognitive Sciences*, *22*, p. 619. Copyright 2018 by Elsevier Ltd.

The psychophysiological mechanism of pre- and probiotics on memory

Current research on pre- and probiotics frequently uses rodent models. The animals in these models are exposed to stress-inducing situations and, on the basis of behavioral diagnostics, statements are made about the animals' reactions (Sarkar et al., 2018). Study shows that prebiotics improve working memory and spatial learning in mice and rats (Oliveros et al., 2016; Vázquez et al., 2015). Probiotics also appear to have a positive effect on learning and memory in mice (Savignac et al., 2015). Germ-free animals however have been shown to have impaired STM (Gareau et al., 2011). One plasticity-related protein that has been consistently linked to cognitive improvements is brain-derived neurotrophic factor (BDNF), derived from the hippocampus (Heldt et al., 2007; Lu et al., 2008). The hippocampus has a crucial role in memory storage and information processing (Dinan

& Cryan, 2017). BDNF is transported neuronally through the vesicles in the axons and dendrites, in addition it is released by pre- and postsynaptic electrical stimuli. BDNF is commonly considered an essential mediator (Brigadski & Leßmann, 2014; Cunha et al., 2010) and instructor (Cunha et al., 2010) in synaptic plasticity and related processes. BDNF is the only neurotrophin that plays an important role in the formation of the LTM (Cunha et al., 2010). Research shows that the concentration of BDNF increases both when probiotics (Desbonnet et al., 2008) and prebiotics are administered (Burokas et al., 2017; Savignac et al., 2013; Vázquez et al., 2015; Williams et al., 2016), indicating that the bacterial strains in these studies could recover neuronal activation marked by BDNF expression in the CA1 region of the hippocampus (Gareau et al., 2011). However, it is noteworthy that improvements in memory are associated with a reduction in inflammation and biomarkers of stress (Allen, 2016; Dowlati et al., 2010; Wang et al., 2015). The question can thus be asked whether these improvements are directly due to pre- and probiotics, or whether these bacteria act as a mediator. Indeed, the hippocampus is highly sensitive to glucocorticoids (Lupien et al., 2009), suggesting that a general reduction in inflammation and glucocorticoids may be underlying rather than a singular neural process (Sarkar et al., 2018).

Positive effects on working memory and learning are also observed in humans (Allen et al., 2016; Chung et al., 2014), although negative effects are reported as well (Sarkar et al, 2018; Sarkar et al., 2016). Previous research in this context has already shown that an overexpression of BDNF can lead to a stimulation of inhibitory pathways, leading to negative effects on the learning processes (Cunha et al., 2010). However, to date there are no known clear guidelines regarding the use of appropriate amounts of pre- or probiotics in different target groups. As a result, unintentional overconsumption may occur with the previously reported effects on memory.

Research Question

Thus, despite the increased attention to the effect of pre- and probiotics on memory, there is still a great deal of uncertainty. Although systematic research has already been published on psychiatric disorders such as depression (Liu et al., 2019), schizophrenia (Ng et al., 2019) and anxiety (Liu et al., 2018), this is lacking on cognitive function domains.

This research focuses on memory. The main research question concerns, "What is the effect of pre- and probiotics on human memory?". It is hypothesized that both pre- and probiotics could lead to beneficial and adverse effects. Through a systematic review and meta-analysis, these effects are examined. In addition, a number of secondary research questions are posed, specifically:

- "Are there differences between individuals with and without a diagnosis on the ICD-10 (International Classification of Diseases - 10) or DSM-V (Diagnostic and Statistical Manual of Mental Disorders – 5)?" Hypothesis: Individuals with a diagnosis experience more positive effects.
- "Do persons over the age of 65 experience more effects than persons under the age of 18?" Hypothesis: Individuals over the age of 65 experience more positive effects than individuals under the age of 18.

Method

Search strategy and eligibility criteria

A systematic review was conducted using PubMed, PsycINFO, and Web of Science. These databases were last screened on 13/04/2021. In order to have relevant search results, the following search key was used on PubMed: (elderly OR adults OR children) AND (probiotics OR prebiotics OR functional food) AND (memory OR cognitive functioning OR cognition OR neuropsychological functioning). The same search key was used in PsycINFO. For Web of Science, the following combination was used: ((TS= elderly OR TS=adults OR TS=children) AND (TS=probiotics OR TS=prebiotics OR TS=functional food) AND (TS=memory OR TS=cognitive functioning OR TS=cognition OR TS=neuropsychological functioning)). The screening was limited to articles written in English and published in peer-reviewed journals. The literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009).

With respect to the included articles, the following inclusion criteria were used:

- The study is a randomized controlled trial (RCT) in which the participants are randomized among an intervention and control group
- It's a study conducted in human participants
- Pre- and/or probiotic compounds are internationally accepted (FAO, 2002; Floch et al., 2016 EFSA, 2005)
- Memory parameters are reported as a primary or secondary outcome measure
- Memory parameters are examined independently of other cognitive outcome measures
- Memory parameters are reported as mean scores at baseline and post-intervention

In addition, the following exclusion criteria were used:

- Research conducted on animals
- Study in which the consumed pre- and/or probiotics are examined by self-reporting
- Memory parameters are examined by self-reporting

Quality assessment

The quality of the included articles was examined using criteria established by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011). The following forms of bias were checked for each study: selection bias (participants are not randomized among the different interventions), allocation bias (randomization is not blinded), performance bias (the

condition is not offered blinded to the participants and researchers), detection bias (evaluators are not blinded), attrition bias (the presence of systematic errors or incomplete data) and reporting bias (research results are reported in a biased way). The results of the quality assessment were summarized in a risk of bias table, generated from Review Manager 5.3 (Revman 5.3) for Mac OS.

Data extraction

Data contributing to the effect of pre- and probiotics on memory were extracted from each study and tabulated. The Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) was used to compile the data. These data include demographic data of the participants (number, mean age, percentage female, sample type), variables related to the intervention (type of pre- and probiotics and length of treatment) and the outcome variables.

Statistical analysis

Statistical analysis was performed with Revman 5.3 for Mac OS. The primary outcome in this study is the standardized mean difference (SMD) using the Cohen's *d* (Field & Gillet, 2010). This measure of effect size is calculated using the changes between baseline and post-intervention between the probiotic groups and the placebo groups. To control for contributing factors, moderator analyses were conducted using Revman 5.3 as well. In this research, negative effect sizes indicate an effect on memory in favor of the treatment, on the other hand positive effect sizes represent an effect in favor of the placebo. Effect sizes can vary from small (0.20), medium (0.50) to large (0.80) (Field & Gillet, 2010). To check for heterogeneity across studies, the I^2-statistic was used. This measure of inconsistency examines whether the reported variation across studies is caused by heterogeneity rather than chance (Higgins et al., 2003). The researchers report an I^2 value of 25% as low heterogeneity. Moderate heterogeneity is considered from 50% and high heterogeneity from 75%. The I^2-statistic was accompanied by the Chi^2-statistic (or Q) for heterogeneity, which assesses the heterogeneity of effects sizes (Higgins & Green, 2011). No Duval & Tweedie's trim-and-fill analysis (Duval & Tweedle, 2000) was conducted to check for publication bias due to limited number of included studies. Using less than 10 studies leads to a power which is too low to differentiate coincidence from real asymmetry (Higgins & Green, 2011).

Results

Literature search, screening and basic information of included studies

The search through three databases (PubMed, PsychInfo and Web of Science) resulted in 1718 records. No additional records were identified through screening of relevant sources. After removing duplicates, 1354 publications remained. 1306 records were excluded after screening the title and abstract. Forty-eight studies were assessed for eligibility, of which 4 were excluded because the absence of a full text, 11 because there was no memory assessment included, 6 studies were no RCT's and in 9 studies did the implemented intervention not meet the criteria of pre- and probiotics. The remaining 12 studies (Chung et al., 2014; Hwang et al., 2019; Kim et al., 2021; Kobayashi et al., 2019; Lew et al., 2018; Ohsawa et al., 2018; Rudzki et al., 2019; Sanborn et al., 2020; Schmidt et al., 2015; Smith, 2005; Smith et al., 2015; Xiao et al., 2020) were included in qualitative synthesis, of which 3 (Schmidt et al., 2015; Smith, 2005; Smith et al., 2015) were excluded to conduct the quantitative synthesis through a meta-analysis. The process of the literature screening can be found in Figure 4.

Risk of bias assessment

Six (Chung et al., 2014; Ohsawa et al., 2018; Rudzki et al., 2019; Schmidt et al., 2015; Smith, 2005; Smith et al.2015) of the 12 included studies reported insufficient information regarding the method of random sequence generation. All studies except two (Hwang et al., 2019; Kim et al., 2021) reported insufficient information of allocation treatment. Concerning the blinding of participants and personnel provided five studies (Lew et al., 2018; Ohsawa et al., 2018; Schmidt et al., 2015; Smith, 2005; Smith et al., 2015) incomplete information. Five studies (Lew et al., 2018; Ohsawa et al., 2018; Schmidt et al., 2015; Smith, 2005; Smith et al., 2015) reported insufficient data regarding the blinding of outcome assessment. Three studies (Schmidt et al., 2015; Smith, 2005; Smith et al., 2015) had an unclear risk in attrition bias, whereas these same studies had a very high risk regarding a reporting bias due to incompletely reported primary outcomes and outcome data. Chung et al (2014) reported a high risk in this form of bias as well. Finally all studies reported some other form of bias, with one study (Chung et al., 2014) reporting a high risk due to sponsorship. An overview can be found in Table 1.

Figure 4

PRISMA flow chart of the literature search and abstraction process

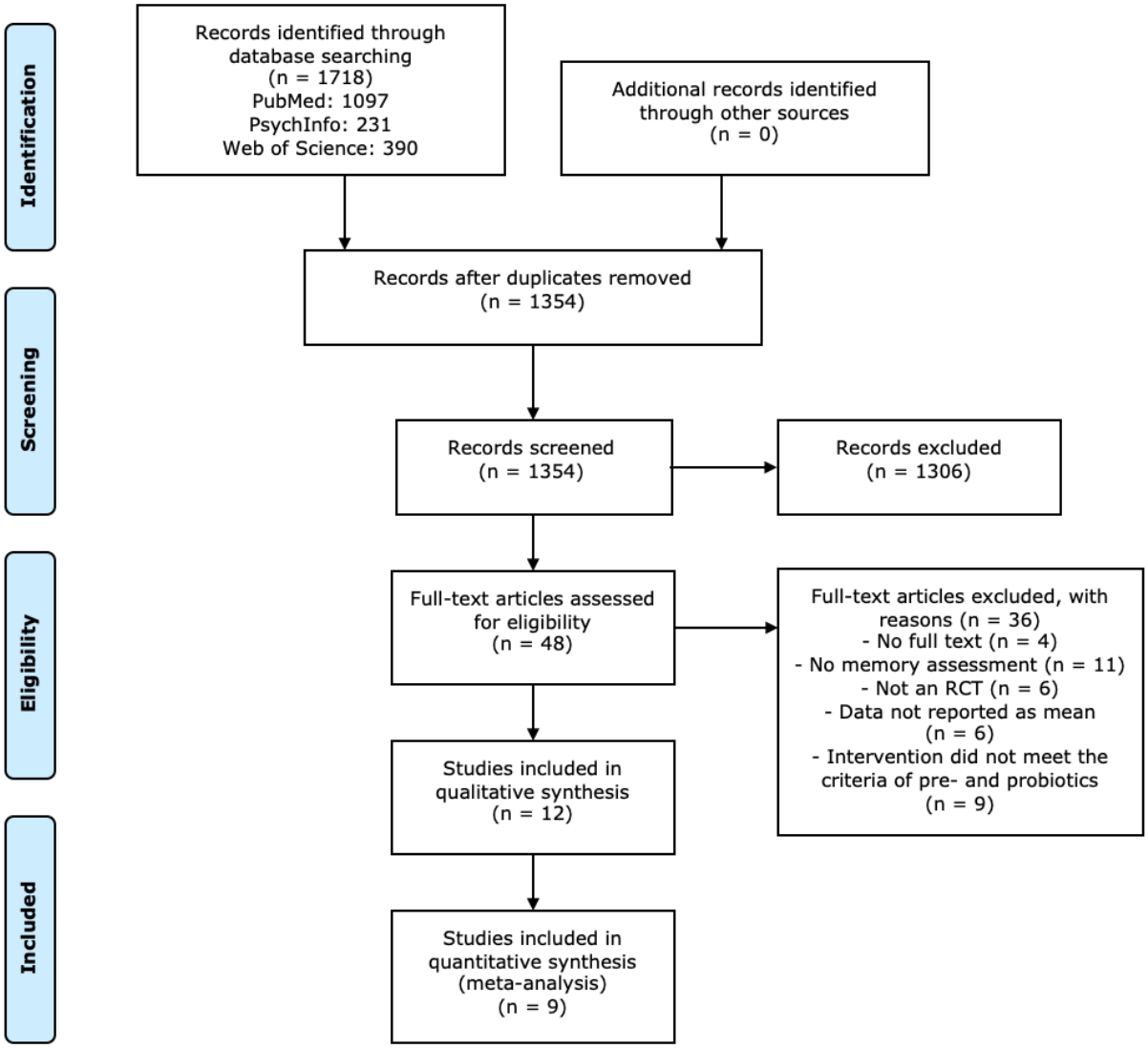
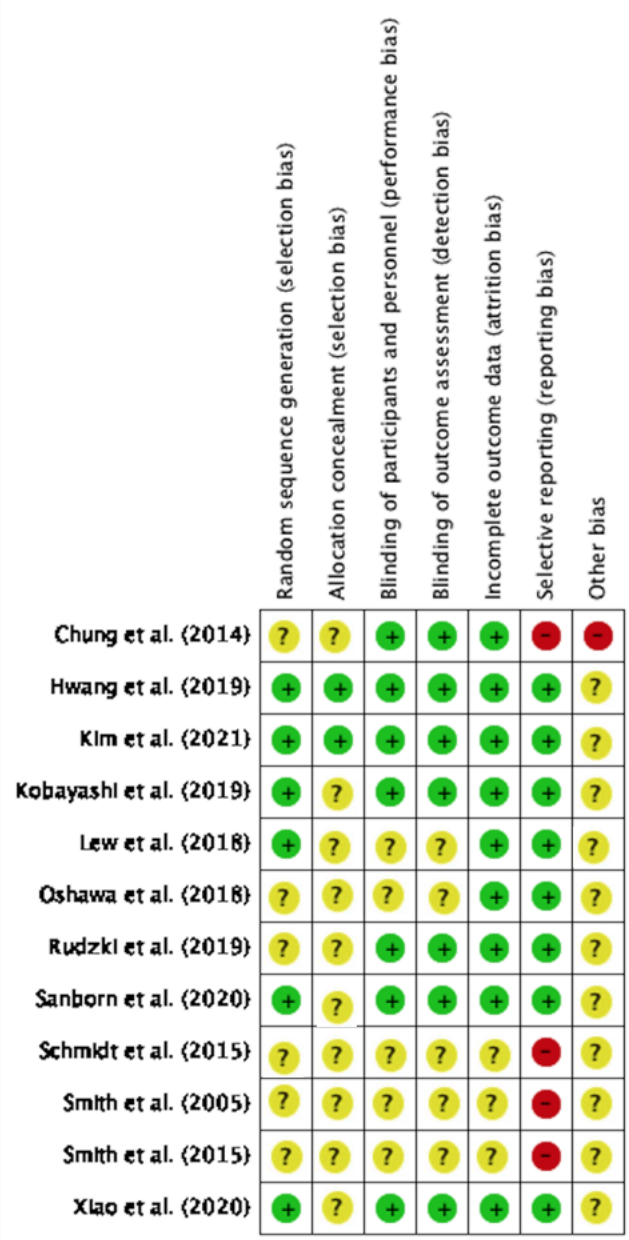


Table 1

Summary of risk of bias assessment: evaluation of the author on each risk of bias for the included studies.



Note. + = Low risk of bias; ? = Moderate risk of bias; - = High risk of bias

Systematic review: main results

All three studies (Schmidt et al., 2015; Smith, 2005; Smith et al., 2015) which included the usage of prebiotic compounds, were conducted with participants recruited in the community. All these studies reported a classical design of a randomized controlled trial, with only one (Schmidt et al., 2015) reporting a three-arm study. The length of treatment varied from 4 hours to 3 weeks.

Smith (2005) and Smith et al. (2015) documented no scale regarding the memory. All studies reported outcome measures regarding the STM. One study (Schmidt et al., 2015) reported no LTM-measure. Schmidt et al. (2015) determined no significant effect of both B-GOS and FOS interventions on STM and more specifically on working memory. No significant effect on LTM and STM was reported by Smith (2005). However Smith et al. (2015) determined, in comparison with the control group, an improvement on both LTM and STM after a 4-hour treatment.

Regarding studies investigating the effect of probiotics, three (Hwang et al., 2018; Rudzki et al., 2019; Xiao et al., 2020) of nine studies were conducted on clinical samples. Only one study (Rudzki et al., 2019) was completed on a sample group whose mean age was below 40 years. All studies reported probiotic microbes representing the two most recognized genera *Lactobacillus* (LB) and *Bifidobacterium* (B). Three studies (Hwang et al., 2019; Lew et al., 2018; Rudzki et al., 2019) applied *LB plantarum*, more specifically strains C29, P8 and 299v. Two studies reported *LB helveticus* (Chung et al., 2014; Ohsawa et al., 2018) and *B. Breve A1* (Kobayashi et al., 2019; Xiao et al., 2020). Only one study (Kim et al., 2021) reported the usage of a multiple strain consisting of *B. bifidum BGN4* and *B. longum BORI*. One study (Sanborn et al., 2020) applied *LB rhamnosus GG*. Length of treatment varied from 8 weeks to 16 weeks, with five studies (Chung et al., 2014; Hwang et al., 2019; Lew et al., 2018; Kim et al., 2021; Kobayashi et al., 2019) reporting a duration of 12 weeks. All studies investigated the effect of probiotics on LTM, only one study (Rudzki et al., 2019) did not include STM. Six (Chung et al., 2014; Hwang et al., 2019; Kobayashi et al., 2019; Ohsawa et al., 2018; Rudzki et al., 2019; Sanborn et al., 2020) out of nine studies determined no significant improvement on LTM and STM in the intervention group when compared to the control group. Lew et al. (2018) reported a significant improvement in LTM after 12 weeks of administration with *LB plantarum P8*. No improvement was detected on STM. However Kim et al. (2020) reported a significant improvement after 12 weeks of administration with *B. bifidum BGN4* and *B. longum BORI* on STM but not on LTM. Finally, Xiao et al. (2020) established a significant improvement after 16 weeks of administration with *B. breve A1* on LTM and STM in comparison with the control group. The latter used a clinical sample consisting of individuals with an MCI-diagnosis.

Table 2

Summary of the main characteristics of included trials

Study	N	% female	Mean age	Sample	Prebiotic compound(s)/ probiotic microbe(s)	Length of treatment	Outcome measure	Subscore used	LTM/ STM	Domain of memory	Principal results
Probiotics											
Chung et al. (2014)	36	44.4	65.0	Community	Sole, *LB helveticus IDCC3801* 500-1000-2000 mg/day (tablet)	12 weeks	VLT DST	A20 delayed recall Forward	LTM STM	Verbal memory Working memory	No significant difference
Hwang et al. (2019)	100	66	68.6	Clinical (MCI)	Sole, *LB plantarum C29* $1.25x10^{10}$ CFU/day (freeze-dried)	12 weeks	VLT DST	Delayed recall /	LTM STM	Verbal memory Working memory	No significant difference
Lew et al. (2018)	103	?	31.7	Community	Sole, *LB plantarum P8* $2x10^{10}$ CFU/day (sachet)	12 weeks	ISLT OCB	Total score Speed	LTM STM	Episodic memory Working memory	Intervention > placebo (LTM) No significant difference (STM)
Kim et al (2021)	63	?	71.55	Community	Multiple, *B. bifidum BGN4, B. longum BORI* $1x10^{9}$ CFU/day (capsule)	12 weeks	CERAD-K DST	Word list recall /	LTM STM	/ Working memory	No significant difference (LTM) Intervention > placebo (STM)
Kobayashi et al. (2019)	121	51	61.5	Community	Sole, *B. breve A1* $>1x10^{10}$ CFU/day (capsule)	12 weeks	RBANS	Delayed memory Immediate memory	LTM STM	/	No significant difference
Ohsawa et al. (2018)	60	56	58.2	Community	Sole, *LB helveticus* 190g/day (fermented milk)	8 weeks	RBANS	Delayed memory Immediate memory	LTM STM	/	No significant difference
Rudzki et al. (2019)	60	72	39	Clinical (MDD)	Sole, *LB plantarum 299v* $10x10^{9}$ CFU/day (capsule)	8 weeks	CVLT	Total recall	LTM	Episodic verbal memory	No significant difference
Sanborn et al. (2020)	103	59.3	64.4	Community	Sole, *LB rhamnosus GG* (capsule)	13 weeks	PSMT LSWMT		LTM STM	Episodic memory Working memory	No significant difference
Xiao et al. (2020)	80	51	61.1	Clinical (MCI)	Sole, *B. breve A1* $2x10^{9}$ CFU/day (capsule)	16 weeks	RBANS	Delayed memory Immediate memory	LTM STM	/	Intervention > placebo (LTM) Intervention > placebo (STM)
Prebiotics											
Schmidt et al (2015)	45	51.11	23.69	Community	B-GOS 5,5g/day (powder) FOS 5,5g/day (powder)	3 weeks	DST	/	STM	Working memory	No significant difference
Smith (2005)	142	51	32	Community	FOS-enriched inulin 10g/day (powder)	2 weeks	?	Delayed recall Immediate recall	LTM STM	Episodic memory Working memory	No significant difference
Smith et al. (2015)	47	60	23	Community	FOS-enriched inulin 5g (powder)	4 hours	?	Delayed recall Immediate recall (number correct)	LTM STM	Episodic memory Working memory	Intervention > placebo (LTM) Intervention > placebo (STM)

Note. B. = Bifidobacterium; B-GOS = Bimuno-galactooligosaccharide; CERAD-K = Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet – Korean; CVLT = California Verbal Learning Test; DST = Digital Span Test; FOS = fructooligosaccharide; ISLT = International Shopping List Test; LB = lactobacillus; LSWMT = List Sorting Working Memory Test; LTM = Long Term Memory; MCI = Mild Cognitive Impairment; MDD = Major Depressive Disorder; N = Number of participants; OCB = One Card Back; PSMT = Picture Sequence Memory Test; RAVLT = Rey Auditory Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SRT = Story Recall Test; STM = Short Term Memory; VLT = Verbal Learning Test; WMS = Wechsler Memory Scale

Meta-analysis: main results

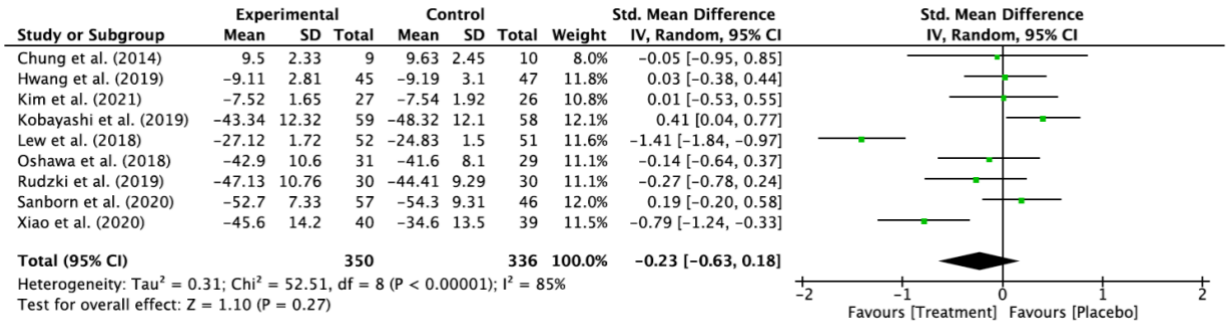
Due to limited data, no meta-analyses could be calculated regarding the effect of prebiotics on LTM and STM. No standard deviations were reported in Smith (2015) and Smith (2005).

With regarding to the effect of probiotics on LTM (see Figure 5), this study included 350 subjects in the experimental group and 336 subjects in the control group, retrieved from nine included studies (Chung et al., 2014; Hwang et al., 2019; Kim et al., 2021; Kobayashi et al., 2019; Lew et al., 2018; Ohsawa et al., 2018; Rudzki et al., 2018; Sanborn et al., 2020; Xiao et al., 2020). Due to high heterogeneity ($Q(8) = 52.51$, $p < 0.00001$) between the different studies, a random effect model was used for quantitative synthesis (Higgins et al., 2003). An overall Cohen's *d* of -0.23 ($Z = 1.10$, $p = 0.27$, 95% CI [-0.63; 0.18]) in favor of probiotics was calculated, representing a small but insignificant effect (Field & Gillet, 2010) of probiotics administration on LTM. Eight studies (Chung et al., 2014; Hwang et al., 2019; Kim et al., 2021; Kobayashi et al., 2019; Lew et al., 2018; Ohsawa et al., 2018; Sanborn et al., 2020; Xiao et al., 2020) were included examining the effect of probiotics on STM. In total 331 subjects were included in the experimental group and 303 in the control group (see Figure 6). With an overall Cohen's *d* of -0.17 ($Z = 1.38$, $p = 0.17$, 95% CI [-0.42; 0.07]), no effect (Field & Gillet, 2010) of probiotics on STM was established. A moderate heterogeneity ($Q(7) = 15.68$, $p = 0.03$) was observed, so a random effect model was used (Higgins et al., 2003). The forest plot of the meta-analyses is shown in figures 5 and 6.

Due to high ($Q(8) = 52.51$, $p < 0.00001$) and moderate ($Q(7) = 15.68$, $p = 0.03$) heterogeneity between the different studies regarding the effect of probiotics on LTM and STM, a moderator analysis was appropriate.

Figure 5

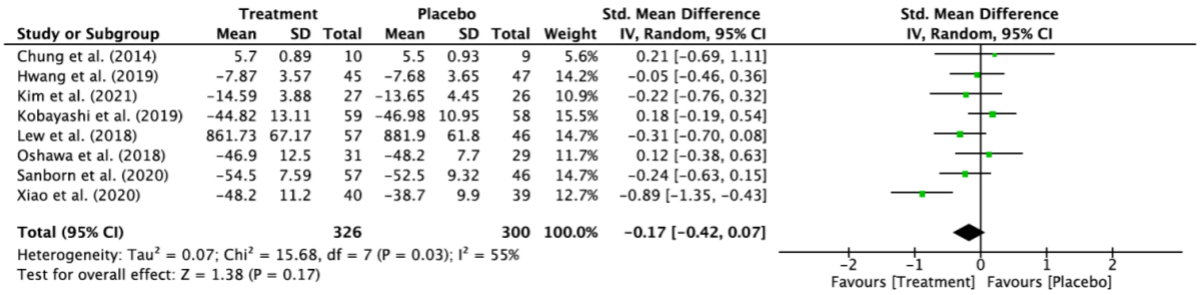
Forest plot of probiotics versus placebo in improving LTM



Note. Chi² = Chi-squared test for heterogeneity; df = Degrees of freedom; SD = Standard deviation; I^2 = I-squared test for heterogeneity; Tau² = Tau-squared test for heterogeneity

Figure 6

Forest plot of probiotics versus placebo in improving STM



Note. Chi² = Chi-squared test for heterogeneity; df = Degrees of freedom; SD = Standard deviation; I^2 = I-squared test for heterogeneity; Tau² = Tau-squared test for heterogeneity

Moderator analyses for LTM were conducted for type of sample, length of treatment, mean age and strains of flora (see Table 3). When stratified by type of sample, a larger treatment effect on LTM was found in the clinical (Cohen's *d* = -0.34, *Z* = 1.35, *p* = 0.18 95% CI [-0.82; 0.15]) than in the community sample (Cohen's *d* = -0,17, *Z* = 0.56, *p* = 0.58, 95% CI [-0.63; 0.18]). However these findings were not significant. A significant difference in effect sizes was observed between the two samples ($Q(8) = 52.51$, $p < 0.00001$). A small non-significant effect was established both in trials less than 10 weeks (Cohen's *d* = -0.20, *Z* = 1.10, *p* = 0.27, 95% CI [-0.56; 0.16]) and more than 10 weeks (Cohen's *d* = -0.23, *Z* = 0.89, *p* = 0.37, 95% CI [-0.75; 0.28]). A significant difference between groups was observed when participants were stratified by length of treatment ($Q(8) = 52.51$, $p < 0.0001$). There was no longer a significant heterogeneity between the different studies with a treatment duration of less than 10 weeks ($Q(1) = 0.13$, $p = 0.72$). A small effect in favor of probiotics was found for trials including participants younger than 65 (Cohen's *d* = -0.33, *Z* = 1.14, *p* = 0.25, 95% CI [-0.89; 0.24]) but not for trials older then 65 years (Cohen's *d* = 0.01, *Z* = 0.8, *p* = 0.94, 95% CI [-0.29; 0.32]). These findings were not significant. A significant difference in effect sizes was observed between the two groups ($Q(8) = 52.51$, $p < 0.00001$). No significant heterogeneity was yet observed between the studies with a mean age over 65 ($Q(2) = 0.02$, $p = 0.99$). When stratified by strains of flora, the largest treatment effect on LTM was observed in the

administration of *LB plantarum* (Cohen's d = -0.55, Z = 1.21, p = 0.23, 95% CI [-1.44; 0.34]). A medium effect was observed in the *LB plantarum* group (Cohen's d = -0.55, Z = 1.21, p = 0.23, 95% CI [-1.44; 0.34]) and a small effect in the *LB breve* (Cohen's d = -0.18, Z = 0.31, p = 0.76, 95% CI [-1.35; 0.99]). Although none of the observed effects were statistical significant. A significant difference in effect sizes was observed between the different bacterial strains (Q(6) = 47.68, p < 0.00001) and eventually no longer significant heterogeneity was observed between the studies using *LB helveticus* as an intervention (Q(1) = 0.01, p < 0.91).

Regarding the effect of probiotics on STM, further analyses were conducted to see if moderators could explain the heterogeneity. Analyses were conducted for type of sample, mean age and strains of flora. A small effect (Cohen's d = -0.46, Z = 1.11, p = 0.27, 95% CI [-1.28; 0.36]) in the clinical group was observed when stratified by type of sample. No effect was found in the community group (Cohen's d = -0.08, Z = 0.80, p = 0.42, 95% CI [-0.27; 0.11]) and both effects were not statistical significant. There was a significant difference in effect sizes between the two sample types (Q(7) = 15.68, p = 0.03) but no significant heterogeneity between studies was observed in the community-sample (Q(5) = 5.14, p = 0.40). When stratified by mean age, a small effect in favor of probiotics was found for trials including participants younger than 65 (Cohen's d = -0.22, Z = 1.22, p = 0.22, 95% CI [-0.58; 0.13]) but not for trials older then 65 years (Cohen's d = 0.01, Z = 0.8, p = 0.94, 95% CI [-0.29; 0.32]). These effects were however not statistical significant. A significant difference in effect sizes was observed between younger and older groups (Q(7) = 15.68, p = 0.03) and no significant heterogeneity between studies was established in the plus 65 years group (Q(2) = 0.68, p = 0.71) . Regarding the stratification by strains of flora was the largest effect observed in *LB breve* (Cohen's d = -0,35, Z = 0.65, p = 0.52, 95% CI [-1,39; 0.70]), a small effect in *LB plantarum* (Cohen's d = -0,19, Z = 1,29, p = 0.20, 95% CI [-0.47; 0.10]) and a small effect in favor of the placebo condition in *LB helveticus* (Cohen's d = 0,14, Z = 0.64, p = 0.52, 95% CI [-0.30; 0.59]). However, as it was the case with LTM, none of the observed effects were statistical significant. A significant difference in effect sizes was established between the types of bacterial strains (Q(5) = 15.48, p = 0.009). No significant heterogeneity was observed between de studies using *LB plantarum* (Q(1) = 0.79, p = 0.37) and *LB helveticus* (Q(1) = 0.03, p = 0.87).

Although various subgroup analyses were conducted to indicate a potential moderator, both for the LTM and STM, at least one subgroup in each stratification reported a significant heterogeneity between the included studies.

Table 3

Summary of meta-analyses and subgroup analyses on LTM and STM

Subgroup	Number of trials	N	Estimated effect	Test of heterogeneity		P^b
				P^a	I^2	
Probiotics vs Control (LTM)	9	686	-0,23 (-0,63- 0,18)	<0.00001	85%	0.27
Subgroup by type of sample (LTM)						
Clinical	3	231	-0,34 (-0,82- 0,15)	0.03	70%	0.18
Community	6	455	-0,17 (-0,75- 0,42)	<0.00001	85%	0.58
Subgroup by length of treatment (LTM)						
< 10 weeks	2	120	-0,20 (-0,56- 0,16)	0.72	0%	0.27
> 10 weeks	7	566	-0,23 (-0,75- 0,28)	<0.00001	89%	0.37
Subgroup by mean age (LTM)						
< 65 years old	6	522	-0,33 (0,89- 0,24)	<0.00001	90%	0.25
> 65 years old	3	164	0,01 (-0,29- 0,32)	0.99	0%	0.94
Subgroup by strains of flora (LTM)						
LB plantarum	3	255	-0,55 (-1,44- 0,34)	<0.00001	92%	0.23
LB helveticus	2	72	-0,01 (-0,47- 0,46)	0.91	0%	0.98
B. breve	2	196	-0,18 (-1,35- 0,99)	<0.0001	94%	0.76
Probiotics vs Control (STM)	8	626	-0,17 (-0,42- 0,07)	0.03	55%	0.17
Subgroup by type of sample (STM)						
Clinical	2	171	-0,46 (-1,28- 0,36)	0.008	86%	0.27
Community	6	455	-0,08 (-0,27- 0,11)	0.40	3%	0.42
Subgroup by mean age (STM)						
< 65 years old	5	462	-0,22 (-0,58- 0,13)	0.006	72%	0.22
> 65 years old	3	164	-0,08 (-0,38- 0,23)	0.71	0%	0.62
Subgroup by strains of flora (STM)						
LB plantarum	2	195	-0,19 (-0,47- 0,10)	0.37	0%	0.20
LB helveticus	2	79	0,14 (-0,30- 0,59)	0.87	0%	0.52
B. breve	2	196	-0,35 (-1,39- 0,70)	0.0004	92%	0.52

Note. Numbers in parenthesis are 95% confidence intervals.

P^a for heterogeneity: $p < 0.1$ was considered to indicate significant heterogeneity across studies.

I^2 for heterogeneity: $I^2 > 50\%$ was considered to indicate significant heterogeneity across studies.

P^b for meta-analysis: $p < 0.05$ was considered to indicate a significant effect of probiotics on cognition by using a random-effects model.

B = Bifidobacterium; LB = Lactobacillus; LTM = Long term memory; N = Number of participants; STM = Short term memory

Publication bias assessment

Due to high ($Q(8) = 52.51$, $p < 0.00001$) and moderate ($Q(7) = 15.68$, $p = 0.03$) heterogeneity between the different studies regarding the effect of probiotics on LTM and STM, random effect models were appropriate. Funnel plots and more specifically a Duval & Tweedie's trim-and-fill analysis (Duval & Tweedle, 2000) was however not performed as the number of available (<10) studies were too small (Higgins & Green, 2011) to determine a visual and reliable quantitative assessment of the publication bias.

Discussion

This is the first known study that examines the effect of pre- and probiotics on human memory as a cognitive function domain. This relates to both the qualitative systematic review and the quantitative meta-analysis. The current review did not determine a significant difference in effect between pre- and probiotics and placebo on human memory. The effects of probiotics on LTM and STM were small in favor of the treatment but statistically insignificant. The effects of prebiotics on LTM and STM could not be calculated because of insufficient data. Two out of three studies examining the effect of prebiotics however reported no beneficial or adverse effects of the treatment. Therefore, the hypothesis that both pre- and probiotics could lead to beneficial or adverse effects could not be confirmed.

However no cognitive cost was determined in this study, there was also no evidence of a benefit. Because of previous promising research in rodents (Athari Nik Azm et al., 2018; Ho et al., 2019; Yang et al., 2020), the results in this study are surprising. Even early studies in humans showed promising results on general cognition and memory (Allen et al., 2016; Chung et al., 2014). A recent small meta-analysis, which specifically focused on the effect of probiotics on humans with Alzheimer's disease (AD), observed a medium effect on general cognition (Deng et al, 2020). Although it's not clear which contribution memory has in this effect due to the limited use of memory scales, their results are promising and suggests the potential effects in AD. One included study (Xiao et al., 2020) in MCI-patients supports these findings and reports an improvement on both LTM and STM. Their findings report the contribution *B. breve A1* has regarding positive changes of the hippocampus, since this strain suppresses the hippocampal expressions of immun-reactive genes and inflammation that are caused by amyloid-β (Kobayashi et al., 2017). The samples of the other two included studies (Lew et al., 2018; Kim et al., 2021) reporting a beneficial effect on respectively LTM and STM, are however community based. Nevertheless it's likely that the community based dwelling older adults in Kim et al. (2021) endure the same structural changes of the brain (Fjell & Walhovd, 2010), oxidative stress (Tsay et al., 2000) and inflammation (Franceschi et al., 2000) which are common in the elderly. Research shows however that probiotics can improve hippocampal plasticity and brain mitochondrial function by reducing inflammation (Chunchai et al., 2018). In addition they can reduce oxidative stress and levels of pro-inflammatory markers such as TNF-α, IL-6 and IL-1β (Wallace & Milev, 2017; Zhao et al., 2018) and increase anti-inflammatory cytokine production (Messaouidi et al., 2011). The relationship with increased levels of BDNF in Kim et al (2020) supports the critical role of the protein in memory development. The results of the only study

reporting a beneficial effect of prebiotics, more specifically FOS-enriched inulin, on LTM and STM (Smith et al., 2015) are not in line with preclinical investigation in rodents. Savignac (2013) concluded that GOS triggered a stronger reaction on NMDAR (N-methyl-D-aspartate receptor) signaling than FOS, making it appear that GOS has a stronger potential proliferative effect on microbiota. Research results such as these cast doubt on whether the potential effects of certain prebiotic compounds in rodents can simply be extended to humans. Although the neurophysiological mechanisms of the gut microbiome, pre- and probiotics and its relation with the (aging) central nervous system are extensively reviewed (Allen et al., 2016; Quigley, 2017; Lin et al., 2018; Komanduri et al., 2019), the overall conclusions of the meta-analysis in this research are not in line with these reviews. This can be caused by the dominance of included studies with healthy community samples and samples with neurological and psychiatric disorders screened out. In addition, the power to determine significant effects may be limited, both in terms of the limited number of included studies and the limited number of participants in some these studies.

There are almost no remarkable shared characteristics in the three included studies reporting effects on memory in favor of probiotics. They (Lew et al., 2018; Xiao et al., 2020; Kim et al., 2021) all report a different mean age, use a different sample, apply a different probiotic strain and use a different scale. The only common characteristic relates to the length of treatment, since all three studies report a therapy duration of over 12 weeks. The ideal duration of probiotic treatment is however poorly understood thus more research is needed to better determine the best duration of therapy (Floch et al., 2016). Only one study (Smith et al., 2015) reported a beneficial effect of prebiotics on LTM and STM but only after 4 hours. Because evidence regarding time courses of emergence of effects is limited (Sarkar et al., 2016), it's recommended to investigate the time points at which memory effects could emerge. By extension it's important to investigate the long-term effects of both pre- and probiotics. All studies measured at the end of therapeutic treatment did not include a follow-up measurement several months to years later. In this way, a potential long term therapeutic effect of pre- and probiotics could not be measured. Previous research on infant rats showed for example benefits in spatial memory 1 year after prebiotic administration (Oliveros et al., 2016). Future research in humans should investigate the long term effects, alongside structural changes in the brain and microbiome ecosystem.

Subgroup analysis based on type of sample, length of treatment, mean age and strains of flora showed no significant effects of probiotics on LTM and STM. None of these factors can explain the source of heterogeneity. The hypothesis that individuals with a diagnosis and individuals over

the age of 65 experience more positive effects than individuals without a diagnoses and under the age of 18, could not be confirmed. Despite the small number of included trials and the large heterogeneity between studies, there might be different moderators. These may relate to the development of the microbiota across lifespan. It is known that it's composition is influenced by source of nutrition (breastfeeding or formula feeding) (Neu, 2016; Cong et al., 2016), mode of delivery (natural birth or cesarean section) (Jakobsson et al., 2014; Dogra et al., 2015) and the usage of antibiotics (Vangay et al., 2015; Diaz Heijtz, 2016). Although the effects of these factors on human memory are unknown, there is consensus that their impact on the development of the brain are significant (Sharon et al., 2016; Dinan & Cryan, 2017). Examining these factors in future research may give more insight in the effects of pre- and probiotics. The results of this study are, as in prebiotics, not in line with the positive results of previous rodent studies (Athari Nik Azm et al., 2018; Ho et al., 2019; Yang et al., 2020). This suggests that the beneficial effects of probiotic strains cannot be extended to human research. More fundamental and experimental research in humans is necessary to determine the underlying processes and effects before being recommended for consumption.

This research is accompanied by several limitations. No meta-analysis on the effects of prebiotics could be done due to limited research data. In addition, there were also limited studies regarding the effect of probiotics by which no funnel plot could be calculated (Higgins & Green, 2011). Therefore no statements could be done with respect to publication bias and reliability of the synthesized results. Another limitation is the variation of memory scales across the included studies. Most studies used validated scales such as VLT, DST, CERAD-K, RBANS and subscales from the NIH Toolbox. However some studies didn't include the name or description of the used scale (Smith, 2005; Smith et al., 2015) or didn't add references to validation studies (Chung et al., 2014; Rudzki et al., 2019; Xiao et al., 2020). Next, all included studies which reported the usage of prebiotics, used compounds which are internationally accepted as prebiotics (Markowiak & Śliżewska, 2017). This relates to inulin, FOS and GOS. However there are several candidate prebiotics such as xylooligosaccharides, isomaltooligosaccharides, β-Glucans and polyphenols (Floch et al., 2016), which are not included. Especially with regards to polyphenols, a complex group of metabolized phytochemicals from a variety of food sources (Floch et al., 2016), a lot research has been published recently. A recent systematic review of 12 studies showed that polyphenols increased cognitive performance, mostly STM and LTM (Travica et al., 2020). It is recommended that the group of polyphenols be further investigated so that they potentially meet the criteria of prebiotics in the

future as well. Next, no trials were included regarding the effect of pre- and probiotics in children and adolescents (< 18 years old), by which the potential effect related to development could not be analyzed. However it's certain that infancy is an essential period for microbiota- and neuronal development (Dinan & Cryan, 2017). More research is needed to establish the effect of altered microbiota composition in early life on neuropsychological functioning and development in humans (Yang et al., 2016). Finally, a lot of research have been focusing on BDNF as a neuronal substrate of memory improvement (Burokas et al., 2017; Chung et al., 2014; Desbonnet et al., 2008; Hwang et al., 2019; Kim et al., 2021; Sanborn et al., 2020; Savignac et al., 2013; Vázquez et al., 2015; Williams et al., 2016). However more research is needed regarding the favorable effects of inflammation reduction. With systemic inflammation being the potential general underlying factor (Komanduri et al., 2019; Wallace & Milev, 2017), the way is open for mind-body techniques that support and augment the effects of pre- and probiotics through a multicomponent intervention.

Conclusion

This is the first systematic review and meta-analysis regarding the effect of pre- and probiotics on human memory. However the differences between the individual studies are large, the results of this meta-analysis suggest that the efficacy of probiotics in ameliorating human memory is insignificant and insufficient. No statement could be made about the effect of prebiotics. There is a need for both more qualitative RCT's and research concerning the underlying mechanisms of memory development. The use of pre- and probiotics in improving memory is not recommended as long as more qualitative research showing a significant positive effect in health or disease is not available.

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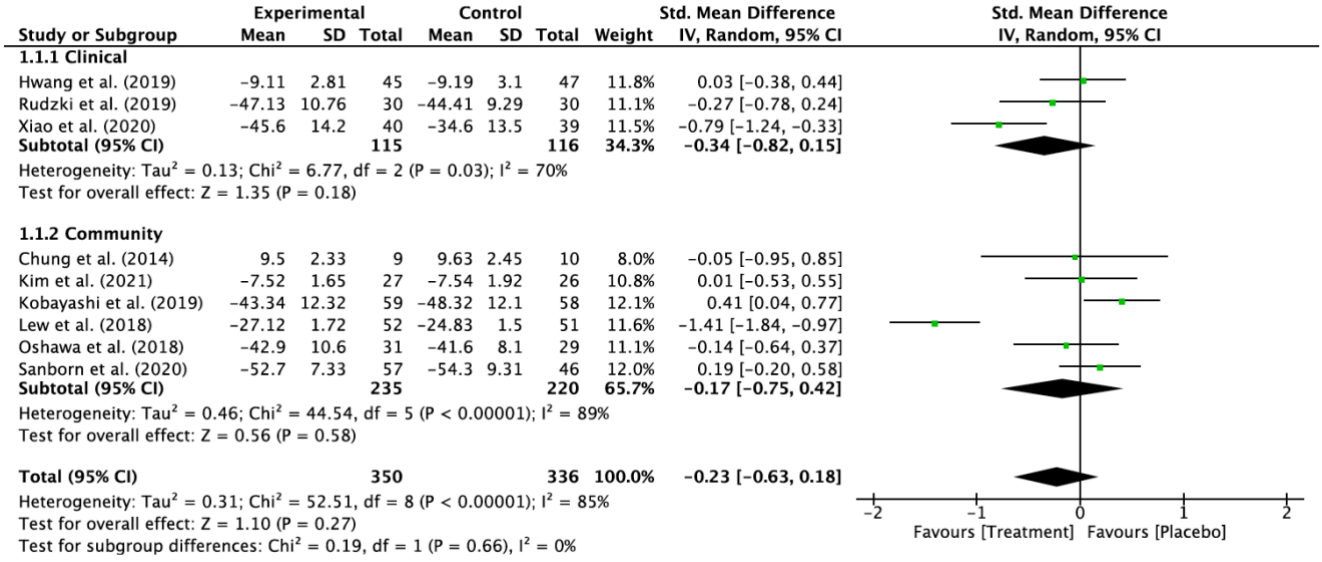
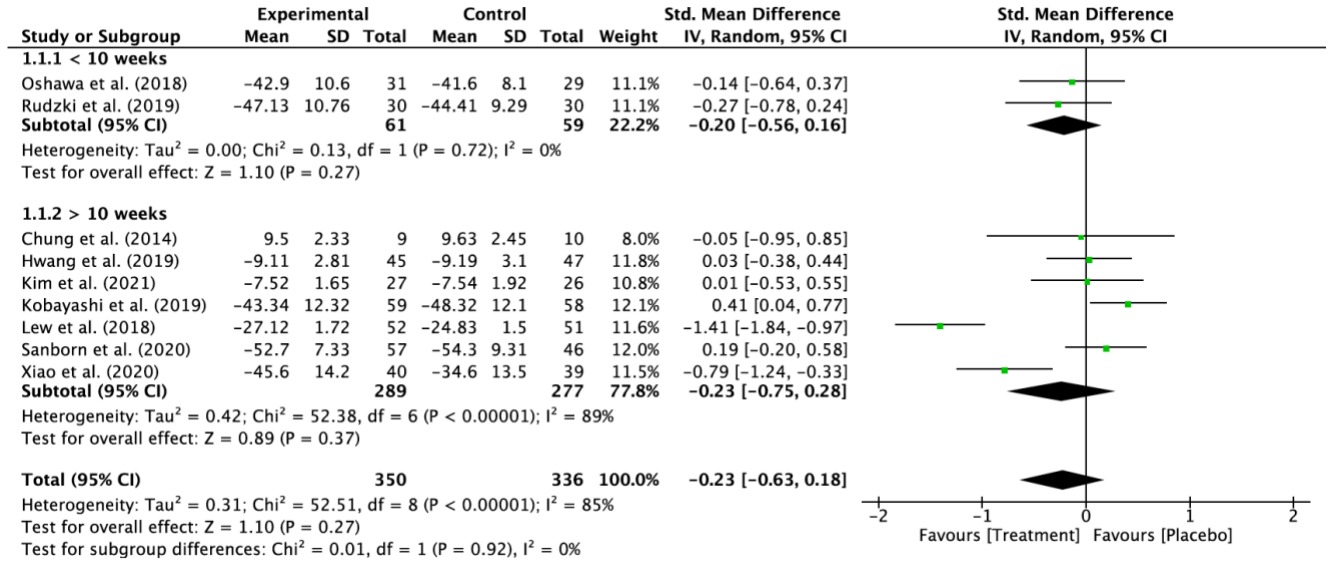
Appendix

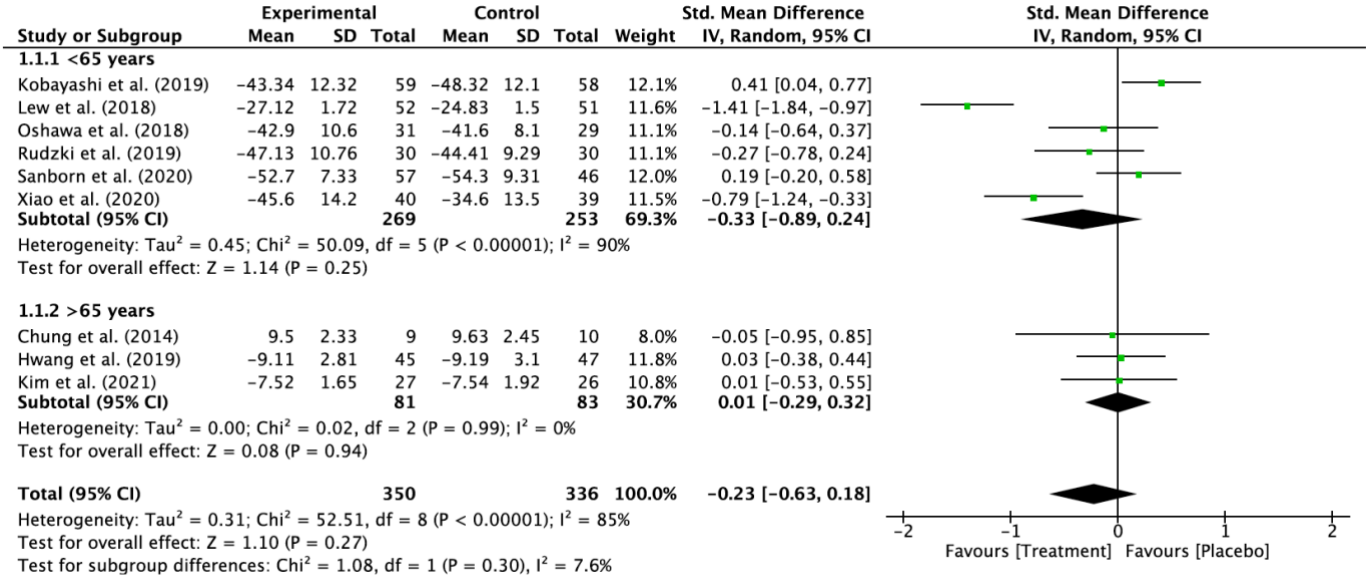
Moderator analysis subgroup by type of sample (LTM)



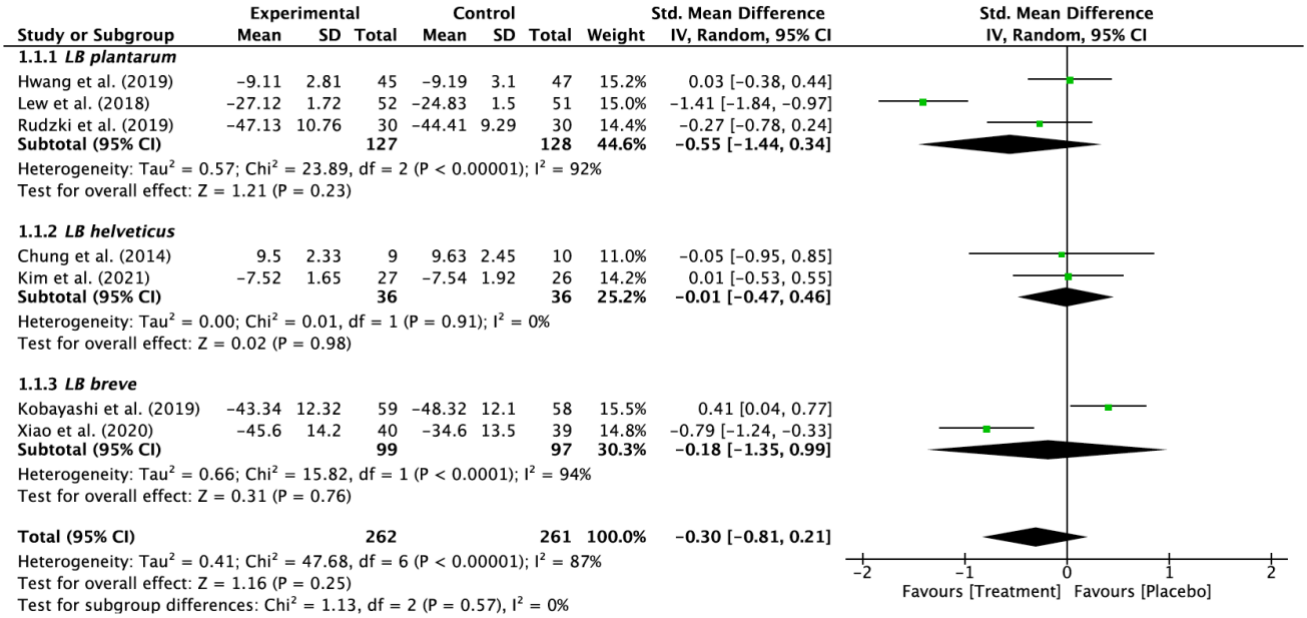
Moderator analysis subgroup by length of treatment (LTM)



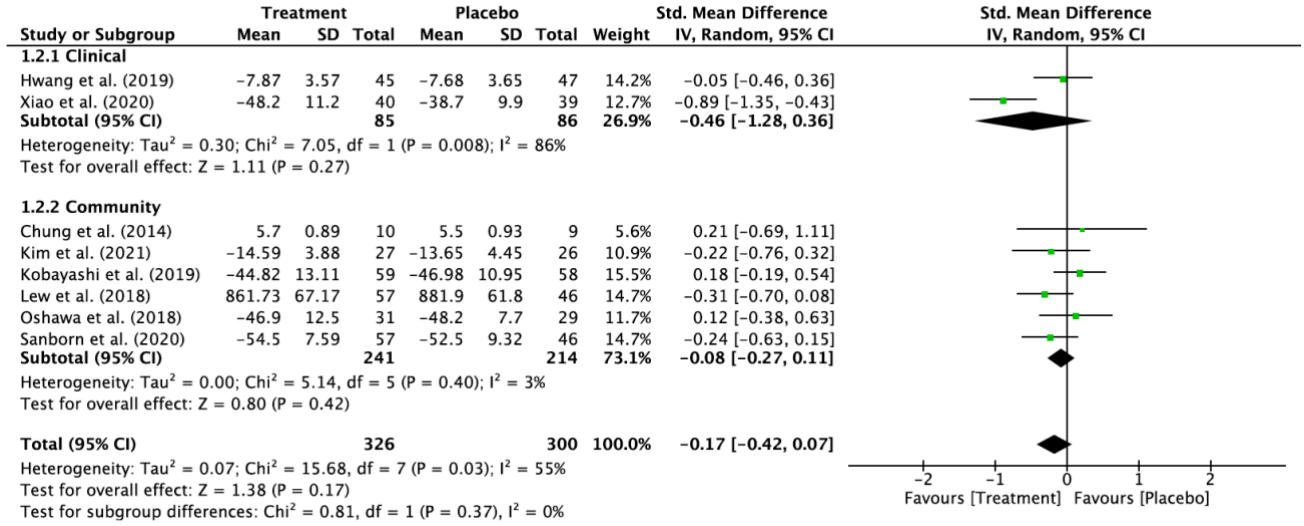
Moderator analysis subgroup by mean age (LTM)



Moderator analysis subgroup by strains of flora (LTM)



Moderator analysis subgroup by type of sample (STM)



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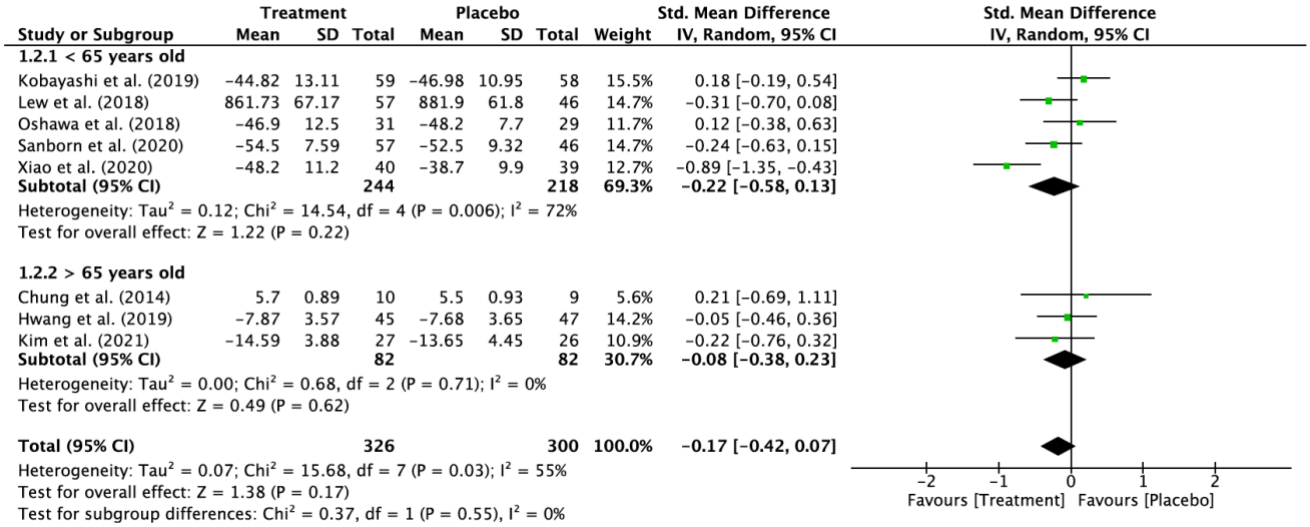

Moderator analysis subgroup by strains of flora (STM)