






Systematic Review

Microbiota Composition and Probiotics Supplementations on Sleep Quality—A Systematic Review and Meta-Analysis

Daniele Santi ^{1,2,3} , Valentina Debbi ¹, Francesco Costantino ^{1,2}, Giorgia Spaggiari ^{2,3} , Manuela Simoni ^{1,2,3,4} , Carla Greco ^{1,2,*}  and Livio Casarini ^{1,4} 

¹ Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, 41126 Modena, Italy; daniele.santi@unimore.it (D.S.); valentina.debbi@studenti.unimi.it (V.D.); manuela.simoni@unimore.it (M.S.); livio.casarini@unimore.it (L.C.)

² Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, 41126 Modena, Italy

³ Unit of Andrology and Sexual Medicine of the Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria of Modena, 41126 Modena, Italy

⁴ Center for Genomic Research, University of Modena and Reggio Emilia, 41126 Modena, Italy

* Correspondence: carlagreco@unimore.it; Tel.: +39-0593961804

Abstract: The gut microbiota (GM) plays a crucial role in human health. The bidirectional interaction between GM and the central nervous system may occur via the microbiota–gut–brain axis, possibly regulating the sleep/wake cycle. Recent reports highlight associations between intestinal dysbiosis and sleep disorders, suggesting that probiotics could ameliorate this condition. However, data are poor and inconsistent. The aim of this quantitative metanalytic study is to assess the GM composition in sleep disturbances and evaluate probiotics' effectiveness for managing sleep disorders. A systematic review was carried out until July 2022 in online databases, limiting the literature research to human studies and English language articles. No significant GM diversity between patients with sleep disturbances versus healthy controls was found, revealed by α -diversity, while β -diversity is missing due to lack of proper reporting. However, probiotics supplementation significantly reduced the self-assessed parameter of sleep quality and disturbances Pittsburgh Sleep Quality Index (PSQI) score compared with the placebo. No difference in the Epworth Sleepiness Scale (ESS) score was found. While available data suggest that GM diversity is not related to sleep disturbances, probiotics administration strongly improves sleep quality as a subjective perception. However, heterogeneity of data reporting in the scientific literature should be considered as a limitation.

Keywords: microbiome; probiotics; sleep disorders; sleep quality; gut microbiota



Citation: Santi, D.; Debbi, V.; Costantino, F.; Spaggiari, G.; Simoni, M.; Greco, C.; Casarini, L. Microbiota Composition and Probiotics Supplementations on Sleep Quality—A Systematic Review and Meta-Analysis. *Clocks&Sleep* **2023**, *5*, 770–792. <https://doi.org/10.3390/clockssleep5040050>

Academic Editor: Ramin Khatami

Received: 13 November 2023

Revised: 29 November 2023

Accepted: 5 December 2023

Published: 13 December 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The gut microbiota (GM) is a community of intestinal microorganisms, including *bacteria*, *archaea*, and *eukarya*, constituting the intestinal flora [1]. Physiologically, GM shows (i) metabolic properties, being able to produce essential nutrients, (ii) protective functions through the regulation of mucus production, (iii) structural actions, mediating the expression of tight junction proteins, and (iv) neurological properties, interacting with the peripheral and the central nervous system [2]. It is accepted that GM has broad impacts on human health, impacting the colonization and the resistance to pathogens, maintaining the intestinal epithelium, metabolizing dietary and pharmaceutical compounds, and controlling immune function [3]. The GM composition is heterogeneous and represents an individual signature, reflecting dietary habits [4]. In humans, more than two thousand prokaryotic species distributed in 11 different phyla have been recognized [5,6], among which the large dominant phyla are *Firmicutes* and *Bacteroidetes* [7,8]. Derangement of microbiota may impact its metabolic activities, leading to dysbiosis, which, in turn, could lead to several dysfunctions. Therefore, the evaluation of GM composition gathered increasing

relevance [9–13]. GM heterogeneity is described by the α - and β -diversity parameters as measures of species diversity within a community at a local scale and between different communities, respectively [14]. In particular, α -diversity is a measure of microbiome diversity applicable to a single sample, whereas β -diversity quantifies the similarity or dissimilarity between two communities.

In the last decade, the link between GM composition and pathological conditions has gathered increasing interest, suggesting possible connections with infectious and autoimmune diseases, metabolic dysfunctions, neurocognitive disorders, and cancer [15–21]. The mutual relationship between GM and the host is expected to modulate additional physiological processes, such as sleep, which could be perturbed in the case of dysbiosis [22]. Sleep disturbances are classified into major categories, such as insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep–wake disorders, sleep-related movement disorders, and parasomnias [23]. Sleep could be described both quantitatively and qualitatively using multiple tools [24]. Polysomnography (PSG) remains the gold standard approach to quality and quantitatively assess sleep, providing detailed information about brain activity, sleep stages, patterns, oxygen saturation, and eye and leg movements [25]. However, PSG is scarcely used in large-scale investigations due to its cost and invasiveness. Alternatively, actigraphy is based on small wrist-watch digital devices monitoring motor activity data for extended periods [26] and is frequently employed in population-based epidemiologic studies [27]. However, it is not recommended for the routine management of sleep disturbances. Thus, several alternative subjective tools, such as direct observations, sleep diaries, and questionnaires, are largely used as well [28]. In particular, validated questionnaires are common tools because of the advantageous cost/benefit ratio despite the less accurate data collection [29]. Among these, the Pittsburgh Sleep Quality Index (PSQI) is a 19-items questionnaire assessing sleep quality [30], while the Epworth Sleepiness Scale (ESS) is an 8-item self-administered questionnaire evaluating the perceived propensity to fall asleep [31,32]. Finally, the nature and severity of insomnia may be assessed by the Insomnia Severity Index (ISI), determined by a 7-item questionnaire [29].

Several pieces of evidence suggest that GM is essential for the maintenance of normal sleep physiology, modulating the production of metabolites involved in sleep homeostasis, such as interleukin (IL)-1 β , short-chain fatty acids (SCFAs), serotonin (5-HT), γ -aminobutyric acid (GABA), and melatonin [1,33–35]. Experiments in mouse models demonstrated that the SCFA butyric acid modulates the expression of the clock genes *Per2* and *Bmal1*, potentially disrupting circadian rhythms [36,37]. A recent study identified the GM signature of good sleepers, which would be abundant in *Firmicutes*, low in *Prevotella*, and with a high α -diversity index [38]. These data suggest that sleep disorders may be treated by acting on the GM composition using probiotics. They are defined as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host” [39–41] and may be used to treat dysbiosis [39]. Probiotic preparations are largely heterogeneous, and their effects depend, for instance, on dosage, supplementation duration, and bacterial strains [42–44]. However, the possible beneficial impact of probiotics on sleep disorders is a matter of debate. In particular, few pieces of evidence are available so far to apply these compounds in clinical practice.

This systematic review and meta-analytic study has two aims: (i) to evaluate differences in GM composition between subjects with sleep disturbances versus healthy controls and (ii) to investigate the effectiveness of probiotics in treating sleep disorders.

2. Materials and Methods

The systematic review and meta-analysis were performed according to criteria described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2015 Statement. Two separate literature searches were carried out from the first available study on probiotics until July 2022, querying the online databases PubMed (MEDLINE), Embase, the Cochrane Library, and Scopus. Then, two different meta-analyses were performed in sequence.

2.1. Study Selection and Inclusion Criteria

The first literature search evaluated all published articles concerning the relationship between sleep disorders and GM composition, using the following keywords: microbiota OR microbiome OR (gut microbiota) OR (gut microbiome) OR (gut microflora) OR dysbiosis AND sleep OR (sleep disorder) OR (sleep disturbance) OR (sleep problem). Studies were considered eligible when investigating patients with sleep disorders and reporting GM composition. No restrictions on age, sex, study design (i.e., observational or interventional), year of publication, or tool used to evaluate sleep dysfunctions were applied.

The second literature search was designed to identify all studies in which oral daily supplements containing probiotics (live bacteria) or para-probiotics (heat-inactivated/killed probiotic bacteria) were administered to human subjects with sleep disorders. The following search strategy was applied: probiotic AND sleep OR (sleep disorder) OR (sleep disturbance) OR (sleep problem). Interventional studies in which probiotics or para-probiotics were administered together with other substances were excluded to avoid potential biases. A first screening collected all the interventional studies available, but subsequently, only placebo-controlled studies (probiotic treatment versus placebo) were selected. The randomization was not considered an inclusion criterion.

For both literature searches, two authors (FC and VD) independently collected the eligible articles, and conflicts were resolved by a third investigator (DS). A preliminary screening identified potentially relevant studies based on their titles and/or abstracts. The selected studies were systematically screened for inclusion by full text, according to the aforementioned criteria.

2.2. Data Extraction and Analysis

In the first literature search, all extracted data were included in a single dataset, considering authors, year of publication, journal, study design, subjects' age, patient's number, microbiota profiling method, sleep assessment methods, criteria for group subdivision according to sleep disorder, α -diversity, β -diversity, and *Firmicutes* to *Bacteroidetes* ratio, representing a clinical biomarker of dysbiosis [45]. The α -diversity index was considered as the primary endpoint. The main outcome was the comparison of the α -diversity index between subjects with vs. without sleep disorders, as it was the parameter reported across almost all studies, while it was not for β -diversity. When studies reported the median and the interquartile range (IQR) of the index, the corresponding mean \pm standard deviation (SD) was calculated [46,47].

In the second literature search, the following data types were extracted: authors, year of publication, journal, study design, subjects' age and body mass index (BMI), patients' number, microbiota profiling method, sleep assessment methods, intervention(s), probiotic bacteria used and colony forming unit (CFU), placebo treatment, treatment duration, and sleep data (both pre- and post-treatment). Since the most used tool to assess sleep quality was PSQI, it was considered the primary endpoint. The PSQI mean \pm SD before and after treatment was used to quantify the probiotics' effect on sleep quality. When articles reported the standard error of mean (σ), SD was calculated using the following equation:

$$\text{SEM} = \sigma / \sqrt{n}; \sigma = \text{SEM} \times \sqrt{n} \quad (1)$$

where n indicates the number of subjects.

Meta-analyses were performed only when more than three studies were available. The parameter indicating heterogeneity among studies (I^2) was considered as "low," "moderate," and "high" for values of 25, 50, and 75%, respectively [48]. Considering the high heterogeneity expected for the outcomes selected, the random effect model was applied to evaluate the mean difference (MD) among continuous data when available. The Review Manager (RevMan) 5.3 software (Version 5.3.1 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform meta-analyses. When a significant difference was detected by meta-analysis, meta-regression analyses were performed using

“Statistical Package for the Social Science” software for Windows (version 28.0; SPSS Inc., Chicago, IL, USA). Statistical significance was considered for p values < 0.05 .

3. Results

3.1. Overview of Included Studies

The first literature search evaluated the relationship between sleep disorders and GM composition. Among 16846 studies detected, fifty-eight potentially relevant studies were extracted, and eighteen articles were finally included (Figure 1). Table 1 summarizes data from studies analyzed during the first literature search.

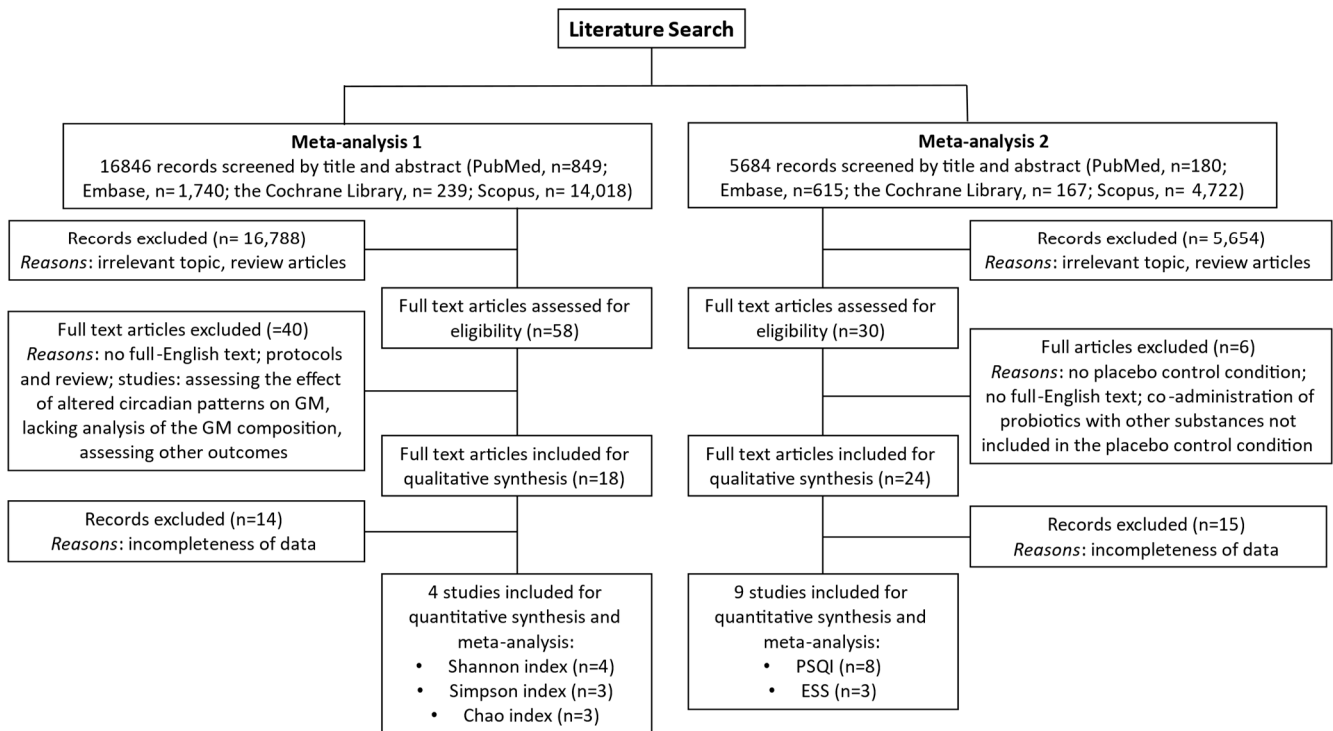


Figure 1. Study flow chart. The relationship between GM composition and sleep disorders (metanalysis 1) and the effect of probiotics on sleep disturbance (metanalysis 2) were assessed.

Table 1. Studies detected during the first literature search.

Authors	Year	Type of Study	Common Features				Study Group (Altered)			Control Group (Healthy)		
			Microbiota Profiling Method	Microbiota Detected	Method (Sleep)	Inclusion Criteria	Number	Age (Years ± SD)	Relative Abundance	Number	Age (Years ± SD)	Relative Abundance
Evans	2017 [49]	CCS	16S rRNA amplicon sequencing (V4 region) using Illumina MiSeq	Phyla Bacteroidetes. Firmicutes. Verrucomicrobia. Actinobacteria. Genera Bacteroides. Faecalibacterium. Prevotella. Roswburia. Akkermansia. Alistipes. Bifidobacterium. Parabacteroides. Blautia. Phascolarctobacterium. Alistipes	PSQI	BD	115	50.2 ± 12.8	Phylum: Faecalibacterium 5.1 ± 4.3% unclassified Firmicutes 0.6 ± 1%	64	48.6 ± 16.6	Phylum: Faecalibacterium 7.7 ± 5.0%; unclassified Firmicutes 1.1 ± 1.2%
Ko	2019 [50]	CCS	16S rRNA pyrosequencing (V3–V4 regions) using Illumina Miseq	Genera Bacteroides. Ruminococcus. Prevotella	PSG	AHI score > 5 health controls	52	NA	NA	61	NA	NA
Collado	2019 [51]	CCS	16S rRNA amplicon sequencing (V3–V4 region) using MiSeq/Illumina protocols	Phylum Tenericutes. Firmicutes. TM7. Lentisphaerae. Fusobacteria. Proteobacteria. Verrucomicrobacteria. Actinobacteria. Bacteroidetes. Porphyromonadaceae. Peptospreptococcaceae and other clostriales	Snoring assessed by interview	Snoring frequency (< or ≥3/week)	27	2.0 ± 0.0	Proteobacteria 1.1%	16	2.0 ± 0.0	Proteobacteria 0.4%
Zhang	2021 [52]	CCS	16S rRNA amplicon sequencing (V4–V5 region) using qIllumina	Phyla Bacteroidetes. Firmicutes. Orders Pasteurellales and Actinomycetes. Families Bacteroidaceae. Prevotellaceae. Porphyromonadaceae. Rikenellaceae. Genera Bacteroides. Prevotella. Parabacteroides. Escherichia. Flavonifractor. Alloprevotella. Parabacteroides. Hungatella	PSQI	MDD diagnosis	36	36.81 ± 13.5	GENUS: Bacteroides 40.0% Prevotella 5.9% Parabacteroides 2.8% Escherichia 2.5% Alistipes 2.2% Alloprevotella 0.5% Tyzzerella 0.3% Paraprevotella 0.2% Haemophilus 0.1% Flavonifractor 0.2% Anaerotruncus 0.1%	45	39.29 ± 11.44	GENUS: Bacteroides 25.0% Prevotella 24.3% Parabacteroides 1.7% Escherichia 0.7% Alistipes 0.8% Alloprevotella 0.18% Tyzzerella 0.2%. Paraprevotella 0.2% Haemophilus 0.2% Flavonifractor 0.1% Anaerotruncus 0.1% Weissella 0.02 Eisenbergiella 0.01

Table 1. Cont.

Common Features						Study Group (Altered)			Control Group (Healthy)			
Authors	Year	Type of Study	Microbiota Profiling Method	Microbiota Detected	Method (Sleep)	Inclusion Criteria	Number	Age (Years ± SD)	Relative Abundance	Number	Age (Years ± SD)	Relative Abundance
Fei	2021 [53]	CCS	16S rRNA pyrosequencing (V4 regions) using Illumina Miseq	Family Ruminococcaceae Erysipelotrichaceae Genera Bacteroides. Oscillospira. Catenibacterium. Prevotella. Dialister	Questionnaire	Sleep length (short ≤ 7 h. normal 7–9 h long ≥ 9 h)	Short 154 Long 248	Short 35.6 ± 6.2 Long 33.6 ± 6.3	GENUS: Streptococcus 0.7% Coprococcus 1.0% Dorea 0.3 Bamasiella 0.9% Intestinibacter 0.1% SPECIES: Blautia_obeum 0.7% Streptococcus_salivarius 0.7% Clostridium_sp 0.1% Dorea_formicigenerans 0.2% Coprococcus_sp 0.2% Ruminococcus_lactaris 0.7%	250	35.7 ± 6.4	NA
Valentini	2020 [54]	CCS	16S rRNA amplicon sequencing	Phyla Bacteroidetes Actinobacteria Firmicutes Bacteroidetes Proteobacteria Families Clostridiaceae Lactobacillaceae Lachnospiraceae Oscillospiraceae Erysipelotrichaceae Coriobacteriaceae Desulfovibrionaceae Enterobacteriaceae Erwiniaceae Enterobacteriaceae. Erwiniaceae Bacteroidaceae Prevotellaceae Lactobacillaceae Prevotellaceae Sutterellaceae Flavobacteriaceae Genera Colinsella. Eubacterium. Faecalibacterium Colinsella Escherichia Klebsiella Clostridium Lactobacillus Oscillobacter Clostridium Ruminococcus Oscillospira Veillonella Klebsiella	Sleep Clinical Record PSG	OSAHS	7	5.0 ± 1.9	NA	8	8.7 ± 3.6	NA

Table 1. Cont.

Authors	Year	Type of Study	Common Features				Study Group (Altered)			Control Group (Healthy)		
			Microbiota Profiling Method	Microbiota Detected	Method (Sleep)	Inclusion Criteria	Number	Age (Years ± SD)	Relative Abundance	Number	Age (Years ± SD)	Relative Abundance
Zhang	2021 [55]	CCS	16S rRNA amplicon sequencing (V3–V4 region) using Illumina	Order Coriobacteriales Class Coriobacteria Family Barnesiaceae. Genera Klebsiella, Barnesiella, Ruminiclostridium, Phoceia, Blautia, Lactococcus, Bilophila	PSG ESS MSLT	NT1	20	19.0	NA	16	26.0	LDA score: More abundant in HC individuals Class Coriobacteriia 2.26%. Order Coriobacteriales 2.26%. Family Barnesiaceae 2.52%. Genus Lactococcus 2.37%. Genus Phoceia 2.39%. Genus Ruminiclostridium 2.00%. Genus Barnesiella 2.46%. Genus Blautia 3.25%. Genus Bilophila 2.00%
Mercado	2021 [56]	CCS	16s rDNA amplicon sequencing (V3–V4 region) using the MiSeq Illumina	Ezakiella, Clostridium sensu stricto, Porphyromonas and Barnesiella (family Porphyromonadaceae). Coriobacteriales Incertae Sedis, Synergistaceae/Synergistales/Synergistia/Synergistestetes, Escherichia-Shigella, Turicibacter	PROMIS-SD	PROMIS-SD, T-score > 55	19 high-occurring symptoms	60.9 ± 16.0	LDA score: More abundant in NT1 individuals Genus Klebsiella 3.19	22 low-occurring symptoms	56.4 ± 7.9	NA
Agrawal	2021 [57]	CCS	16S rRNA amplicon sequencing (V4 region) using Illumina MiSeq	Phyla Firmicutes, Bacteroidetes Order Rhodospirillales Families Acidaminococcaceae, Rikenellaceae, Sutterellaceae, Acidaminococcaceae, Rikenellaceae, Alcaligenaceae, Desulfovibrionaceae, Pseudomonadaceae, Pasteurellaceae Genera Lachnoclostridium, Sutterella, Bilophila, Phascolarctobacterium, Alistipes, Pseudomonas	Sleep length (self-reported)	Sleep length < 6 h short sleepers, 6–8 normal sleepers	16	59.4 ± 7.5	NA	47	62.7 ± 5.8	FIRMICUTES 40% BACTEROIDOTA 36% Lachnoclostridium 1.5% Sutterella 1.25% Alistipes 1.3% Bilophila 0.61% Phascolarctobacterium 0.5% UBA1819 0.13% Paraprevotella 0.29% Pseudomonas 0.06% Eubacterium_siraeum 0.006%

Table 1. Cont.

Authors	Year	Type of Study	Common Features				Study Group (Altered)			Control Group (Healthy)		
			Microbiota Profiling Method	Microbiota Detected	Method (Sleep)	Inclusion Criteria	Number	Age (Years ± SD)	Relative Abundance	Number	Age (Years ± SD)	Relative Abundance
Hua	2020 [58]	CCS	16S rRNA amplicon sequencing using Illumina MiSeq	Phyla Firmicutes. Actinobacteria. Bacteroidetes. Proteobacteria. Verrucomicrobia Genera Faecalibacterium. Agathobacter	CSHQ	CSHQ < 41	60	4.0 ± 0.2	FIRMICUTES 34% BACTEROIDOTA 39%. Lachnoclostridium 0.40% Sutterella 0.38% Alistipes 0.48% Bilophila 0.25%. Phascolarctobacterium 0.20% UBA1819 0.03% Paraprevotella 0.11% Pseudomonas 0.08% Eubacterium_siraeum 0.13%	60	3.9 ± 0.1	Predominant phyla: Firmicutes 43.3%. Actinobacteria 28.3%. Bacteroidetes 20.7%. Proteobacteria 5.6%. Verrucomicrobia 1.3%
Buschart	2018 [59]	CCS	16S and 18S rRNA amplicon sequencing (V4 regions) using Illumina HiSeq	Families Corynebacteriaceae. Lachnospiraceae. Rumnococcaceae. Bacteroidaceae. Prevotellaceae. Porphyromonadaceae. Enterobacteriaceae. Phylobacteriaceae. Streptococcaceae. Comamonadaceae. Moraxellaceae.	ESS PSG	PD or iRBD	97 (76 PD and 21 iRBD)	PD: 68.0 ± 9.7 iRBD: 66.1 ± 7.9	Predominant phyla: Firmicutes 43.15% Actinobacteria 25.88% Bacteroidetes 22.57% Proteobacteria 6.34% Verrucomicrobia 1.62%	78	68.4 ± 6.7	
Zhang	2020 [60]	CCS	16S rRNA gene sequencing (V4 region)	Phyla Actinobacteria. Proteobacteria. Firmicutes. Bacteroidetes Orders Coriobacteriales. Sphingobacteriales Genera Vagococcus. Adlercreutzia. Bifidobacterium. Parascardovia. Metascardovia. Ruminococcus Species Anaerostipes caccae	OSHAS	OSHAS/ OSHAS + cerebral infarction diagnosis		NA	NA	30	NA	NA
Aizawa	2019 [61]	CCS	16S or 23S rRNA-targeted RT-qPCR	Genera Bifidobacterium. Lactobacillus	HAM-D subscale	BD	39	40.3 ± 9.2	NA	58	43.1 ± 12.9	NP

Table 1. Cont.

Authors	Year	Type of Study	Common Features				Study Group (Altered)			Control Group (Healthy)		
			Microbiota Profiling Method	Microbiota Detected	Method (Sleep)	Inclusion Criteria	Number	Age (Years ± SD)	Relative Abundance	Number	Age (Years ± SD)	Relative Abundance
Tang	2022 [62]	CCS	16S rRNA gene sequencing (V3–V4 region)	Phyla Firmicutes. Proteobacteria Genera Escherichia-Shigella. Faecalibacterium. Streptococcus. Haemophilus. Phascolarctobacterium. Oscillibacter	AHI	OSHAS + T2DM	27	47.6 ± 5.2	NP	26	45.6 ± 8.8	NA
Masyutina	2021 [63]	CCS	16S rRNA gene sequencing	Phyla Actinobacteria Genera Faecalibacterium. Prevotella 9. Lachnospira. Blautia. Faecalibacterium. Lachnospira Species Eubacterium hallii	PSQI ISI	CI diagnosis	55	31.6 ± 7.4	NA	50	33.2 ± 6.6	NA
Grosicki	2020 [38]	CCS	16S rRNA gene sequencing (V3–V4 region)	Phyla Firmicutes. Bacteroidetes. Proteobacteria Classes Clostridia. Clostridia. Negativicutes Orders Clostridiales. Bacteroidales Families Bacteroidales. Lachnospiraceae. Ruminococcaceae Genera Blautia. Prevotella. Faecalibacterium. Ruminococcus. Bacteroides	PSQI	PSQI > 5	9	28.8 ± 10	Euryarchaeota 2.41 × 10 ⁴ Actinobacteria 9.06 × 10 ³ Bacteroidetes 3.16 × 10 ¹ Chloroflexi 1.47 × 10 ⁶ Cyanobacteria 1.84 × 10 ³ Elusimicrobia 1.66 × 10 ⁴ Firmicutes 5.99 × 10 ¹ Fusobacteria 1.36 × 10 ⁴ Lentisphaerae 6.21 × 10 ⁵ Proteobacteria 4.19 × 10 ² Spirochaetes 7.35 × 10 ⁷ Synergistetes 6.25 × 10 ⁵ TM7 1.23 × 10 ⁵ Tenericutes 9.26 × 10 ⁴ Verrucomicrobia 3.10 × 10 ² Thermi 2.20 × 10 ⁶	19	30.3 ± 10.8	Phylum Firmicutes 38.0 ± 10.3 Bacteroidetes 34.6 ± 11.8 Proteobacteria 2.8 ± 1.8 Class Clostridia 32.0 ± 9.9 Bacteroidia 34.6 ± 11.8 Negativicutes 2.2 ± 1.5 Order Clostridiales 32.0 ± 9.9 Bacteroidales 34.6 ± 11.8 Family Bacteroidaceae 13.9 ± 9.3 Lachnospiraceae 9.6 ± 4.2 Ruminococcaceae 12.2 ± 5.5 Genus Blautia 2.2 ± 1.1 Prevotella 16.0 ± 19.1 Faecalibacterium 8.7 ± 4.2 Bacteroides 13.9 ± 9.3 Ruminococcus 2.3 ± 2.6

Table 1. Cont.

Common Features				Study Group (Altered)					Control Group (Healthy)			
Authors	Year	Type of Study	Microbiota Profiling Method	Microbiota Detected	Method (Sleep)	Inclusion Criteria	Number	Age (Years ± SD)	Relative Abundance	Number	Age (Years ± SD)	Relative Abundance
Bikov	2022 [64]	CCS	16S rRNA gene sequencing (V3–V4 region)	Phyla Actinobacteria. Proteobacteria Class Gammaproteobacteria Families Prevotellaceae. Lactobacillae Genera Porphyromonas. Lachnospiraceae. Lactobacillus. Roseburia	PSG	OSAHS	19	55 ± 12	Phylum Firmicutes 38.0 ± 10.3 Bacteroidetes 34.6 ± 11.8 Proteobacteria 2.8 ± 1.8 Class Clostridia 32.0 ± 9.9 Bacteroidia 34.6 ± 11.8 Negativicutes 2.2 ± 1.5 Order Clostridiales 32.0 ± 9.9 Bacteroidales 34.6 ± 11.8 Family Bacteroidaceae 13.9 ± 9.3 Lachnospiraceae 9.6 ± 4.2 Ruminococcaceae 12.2 ± 5.5 Genus Blautia 2.2 ± 1.1 Prevotella 16.0 ± 19.1 Faecalibacterium 8.7 ± 4.2 Bacteroides 13.9 ± 9.3 Ruminococcus 2.3 ± 2.6	20	43 ± 16	NA
Cai	2021 [65]		rRNA gene sequencing		PSQI	Healthy controls	157	22.3 ± 2.4	NP			

AHI: Apnea-Hypopnea index; ASD: Autism Spectrum Disorder; BD: Bipolar disorder; CSHQ: Children’s Sleep Habits Questionnaire; CCS: case-control study; CI: chronic insomnia; ESS: Epworth Sleepiness Scale; HAM-D: Hamilton Depression Rating scale; ISI: Insomnia Severity Index; MDD: Major Depressive Disorder; MSLT: Multiple Sleep Latency Test; NA: not available; NR: not reported; NT1: Narcolepsy type 1 OSAHS: Obstructive Sleep Apnea/Hypopnea Syndrome; PD: Parkinson disease; PROMIS-SD: PROMIS Sleep Disturbance; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; T2DM: type 2 diabetes mellitus.

While not statistically quantifiable, visual assessment of the number of GM components reported in studies shows high variability across studies. The mean age of patients considered was 35.7 ± 22.1 years, ranging from a minimum of 2-year-old children [54] to adults of 68.0 years [62] (Table 1). Similarly, high variability in sleep disorders was detected among studies. Indeed, sleep disturbance pattern includes several conditions of different nature, such as insomnia, reduced sleep quantity, obstructive sleep hypopnea/apnoea syndrome (OSHAS) [54,62], and narcolepsy type 1 [55], not allowing clear conclusions about associations between GM and sleep disturbances (Table 1). Relatively high study heterogeneity is also characterized by the tool used to evaluate sleep quality, which includes PSQI [65], sleep clinical record (SCR) [54], PSG [54,55], ESS [55], and multiple sleep latency test (MSLT) [55], while all studies considered the 16S ribosomal subunit mRNA to profile the microbiota (Table 1).

Eighteen eligible studies [38,49–65] were included in the systematic review, accounting for 236 patients with sleep disorders compared with 233 healthy controls. The α -diversity index was assessed in sixteen of them, while the β -diversity index was assessed in thirteen. However, three different α -diversity indexes were used: the “Shannon” index was evaluated in all the studies, while “Simpson” [55,62,65] and “Chao” [54,55,65] indexes were not. Therefore, α -diversity indexes were used for quantitative analyses. The *Firmicutes/Bacteroidetes* ratio is generally reported, although this is not enough to establish clear differences in sleep patterns in all the populations [54,66,67].

The second literature collection included studies describing oral daily supplements of probiotics or para-probiotics administered to individuals with sleep disorders. Among 5684 studies, thirty were evaluated and twenty-four finally included [68–91] (Figure 1). Finally, eight studies were eligible to be quantitatively analyzed for PSQI score [68,71,80,87,88,90,91] and three for ESS [87–89]. Table 2 summarizes data from studies extracted during the second literature search.

Table 2. Studies detected during the second literature search.

Authors	Year	Study Design	Common Features			Study Group (Probiotic)						Control Group (Placebo)		
			Microbiota Profiling Method	Sleep Assessment Method	Inclusion Criteria	Treatment Duration	Participants (n)	Age (y ± SD)	Intervention Treatment	Probiotic Bacteria	CFU	Participants (n)	Age (y ± SD)	Placebo Treatment
Nishida et al. [81]	2017	R/DB/PC/P	NP	PSQI EEG	Healthy 6th-year Japanese medical students	12 weeks	34	25.1 ± 2.37	200 mL Fermented Milk/Day	<i>Heat—inactivated L. gasseri CP2305</i>	1 × 10 ¹⁰	35	25.1 ± 2.4	Milk: high-fructose corn syrup, powdered skim milk, lactic acid, soybean polysaccharide, pectin, sodium citrate, flavors, sweeteners
Kato-Kataoka et al. [82]	2016	R/DB/PC/P	NP	PSQI	Healthy 4th-year medical students undertaking an examination for promotion	6 or 8 weeks	24	23.0 ± 0.4	100 mL Fermented Milk/Day	<i>L. casei strain Shirota</i>	1 × 10 ⁹ /mL	23	22.7 ± 0.4	Milk: similar composition with the addition of lactic acid
Nakakita et al. [83]	2016	NR/DB/PC/CO	NP	EEG, AIS, Sleep journals	Healthy males suffering from sleep challenges (AIS ≥ 6)	10 days	6	53.9 ± 8.8	1 × Capsule/Day	<i>Heat-killed L. brevis SBC8803</i>	NS	8	53.9 ± 8.8	Capsules: caramel pigment, finely powdered silica, calcium stearate, starch, cellulose
Sawada et al. [84]	2017	R/DB/PC/CO	Gene expression analysis	PSQI	Male medical students undertaking the cadaver dissection course	4 weeks	NS	24	1 × Bag/Day	<i>L. gasseri CP2305</i>	1 × 10 ¹⁰	NS	24	Lyophilized powder: skim milk (20%), yeast extract (0.50%)
Yamamura et al. [85]	2009	R/DB/PC/CO	NP	Actigraphy, SHRI	Healthy subjects	3 weeks	14	72.1 ± 21.2	100 g Fermented Milk/Day	<i>L. helveticus</i>	NS	15	70.7 ± 21.9	Artificially acidified milk added with L-lactic acid
Calandre et al. [86]	2021	R/DB/PC/P	NP	ISI	Fibromyalgia patients	12 weeks	28	56.0 ± 7.5	4 × Sachets/Day	<i>S. thermophilus BT01</i> <i>B. breve BB02</i> <i>B. animalis subsp. lactis BL03</i> <i>B. animalis subsp. lactis B104</i> <i>L. acidophilus BA05</i> <i>L. plantarum BP06</i> <i>L. paracasei BP07</i> <i>L. helveticus BD08</i>	4.5 × 10 ¹⁴	35	55.5 ± 8.6	Sachets: maltose, cornstarch, silicon dioxide

Table 2. Cont.

Authors	Year	Study Design	Common Features			Study Group (Probiotic)				Control Group (Placebo)				
			Microbiota Profiling Method	Sleep Assessment Method	Inclusion Criteria	Treatment Duration	Participants (n)	Age (y ± SD)	Intervention Treatment	Probiotic Bacteria	CFU	Participants (n)	Age (y ± SD)	Placebo Treatment
Dhiman et al. [87]	2014	R/DB/PC/P	NP	PSQI, ESS	Cirrhosis patients	24 weeks	16	48.0 ± 1.4	1 × VSL#3 Sachet/Day	<i>L. paracasei</i> DSM 24733 <i>L. plantarum</i> DSM 24730 <i>L. acidophilus</i> DSM 24735, <i>L. delbrueckii bulgaricus</i> DSM 24734) <i>B. longum</i> DSM 24736 <i>B. infantis</i> DSM 24737 <i>B. breve</i> DSM 24732 <i>Streptococcus thermophilus</i> DSM 24731	9 × 10 ¹¹	11	50.1 ± 9.8	Sachets: corn flour
Wong et al. [88]	2015	R/DB/PC/P	NP	PSQI, ESS	IBS	6 weeks	20	53.3 ± 18.6	8 Capsules/Day	<i>L. acidophilus</i> <i>L. casei</i> <i>L. delbrueckii bulgaricus</i> <i>L. plantarum</i> <i>B. longum</i> <i>B. infantis</i> <i>B. breve</i> <i>Streptococcus salivarius</i> <i>thermophilus</i>	1.125 × 10 ¹¹	22	40.9 ± 16.5	Capsules: NS
Majeed et al. [89]	2018	R/DB/PC/P	NP	mESS	MDD and IBS	90 days	20	40.4 ± 10.3	1 × Tablet/Day	<i>B. coagulans</i> MTCC 5856	2 × 10 ⁹	20	43.9 ± 9.8	Tablets: microcrystalline cellulose, starch, sodium starch glycolate, magnesium stearate
Shafie et al. [90]	2022	R/DB/PC/P	NP	PSQI	Post-menopausal women	6 weeks	33	51.8 ± 2.3	100 g Yogurt/Day	<i>B. lactis</i> <i>L. acidophilus</i>	1 × 10 ⁸ C CFU/g	33	52.4 ± 2.4	Yogurt: containing <i>L. bulgaricus</i> and <i>Streptococcus thermophilus</i>

AIS: Athena Insomnia Scale; CO: cross-over design; DB: double blinded; ECG: electrocardiography; EEG: Electroencephalography; ESS: Epworth sleepiness scale; HE: hepatic encephalopathy; HLPCQ: Healthy Lifestyle and Personal Control Questionnaire; IBS: Irritable Bowel Syndrome; ISI: Insomnia Severity Index; MDD: Major Depressive Disorder; mESS: modified Epworth sleepiness scale; MEQ: Morningness-Eveningness Questionnaire; NP: not performed; NR: non-randomized; OSHAS: obstructive sleep apnea; P: parallel design; PC: placebo-controlled; PCR: polymerase chain reaction; PLA: placebo group; PRO: probiotic group; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; R: randomized; SD: standard deviation; SHRI: Sleep-Health Risk Index; VAS: Visual analog scales. Italics are used for bacterial and viral taxa at the level of family and below.

Overall, 274 subjects treated with probiotics were compared with 261 subjects receiving a placebo. Only one study showed a cross-over design, whereas others employed a randomized approach. Five studies recruited healthy individuals [68,71,78,82], one study [87] enrolled cirrhosis patients recovered from hepatic encephalopathy (HE), one employed [88] patients with irritable bowel syndrome (IBS) and sleep complaints, and one [90] recruited post-menopausal women. Moreover, three studies [71,87,88] reported baseline BMI, and one study enrolled patients with overweight (BMI > 25 kg/m²). Regarding the use of probiotics, three studies employed single strains of bacteria [68,78,82] and five multiple strains [71,87,88,90,91] (Table 2). Typically, probiotics were administered within the 10⁸–10¹¹ CFU dose range for a variable duration of 3 [71] to 24 weeks [68,87]. Different media were used to convey the treatment, such as capsules [78,88,91], tablets [68], powder sachets [71,87], fermented milk [82], or yogurt [90], revealing a certain grade of variability among studies for probiotic administration. Compliance with supplementation protocols, if shown, was higher than 95% [82,87,91], except for one study [68], reporting 92%. Thus, as occurred in the first literature search, a high heterogeneity among studies was expected for the aforementioned reasons. Among these, the patient’s compliance with the probiotic consumption protocol should be considered as a further source of heterogeneity. However, none of the studies reported side effects or adverse events, suggesting general good tolerance to the treatment.

3.2. Meta-Analyses

Meta-analysis to compare GM composition between sleep disorders vs. healthy individuals was performed using α -diversity data (Figure 2). α -diversity was not different between patients with and without sleep disorders, considering the Shannon ($p = 0.580$, Figure 2A), Simpson ($p = 0.160$, Figure 2B), and Chao ($p = 0.410$, Figure 2C) indexes. Instead, β -diversity was not considered due to lack of reporting in more than three (i.e., 13) studies.

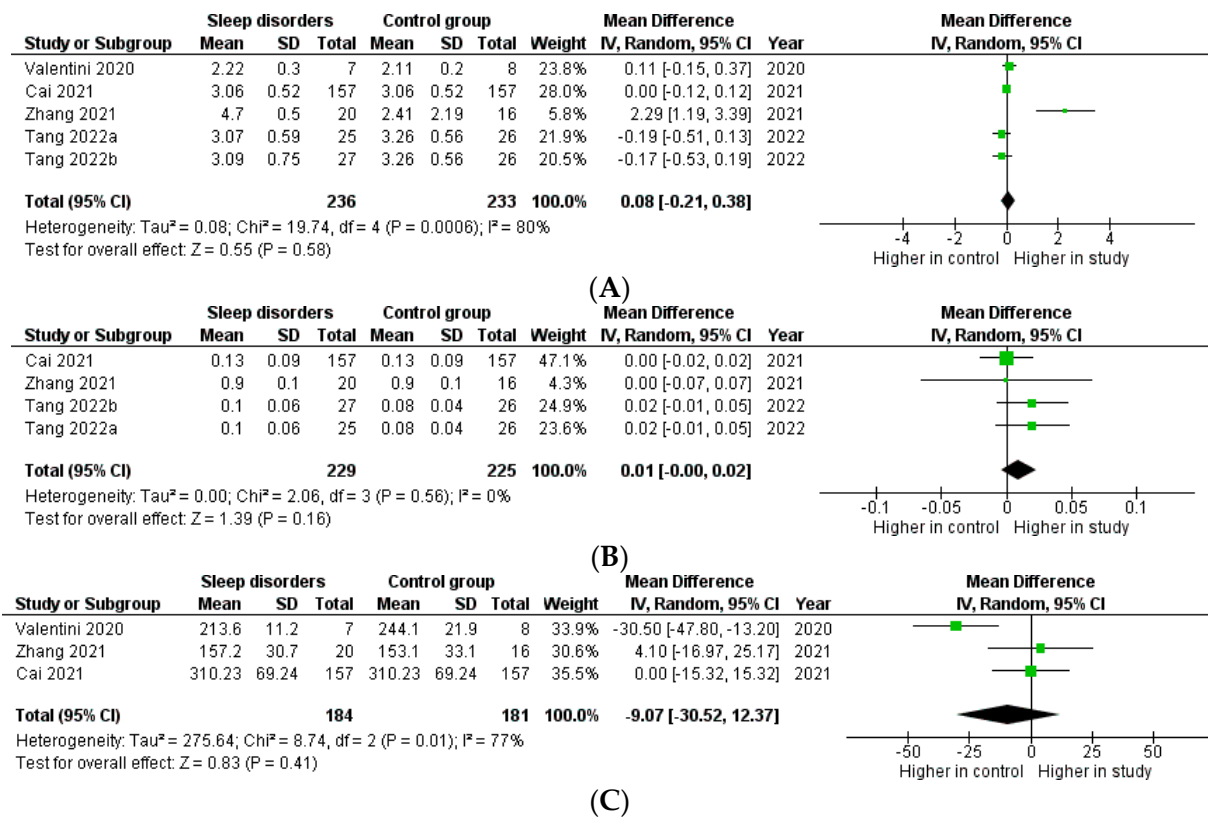


Figure 2. Forest plot for the mean difference of α -diversity. Patients with sleep disorders and healthy controls were compared, considering Shannon (A), Simpson (B), and Chao indexes (C). **References in figure:** Valentini 2020 [54]; Cai 2021 [65]; Zhang 2021 [52]; Tang 2022 [66].

For the meta-analytic investigation of probiotics effectiveness in sleep disorders and health, only PSQI and ESS data were accessible in more than three articles. Other sleep measures were not suitable for meta-analysis. Probiotic consumption significantly reduced PSQI score compared with placebo administration ($p = 0.04$, Figure 3).

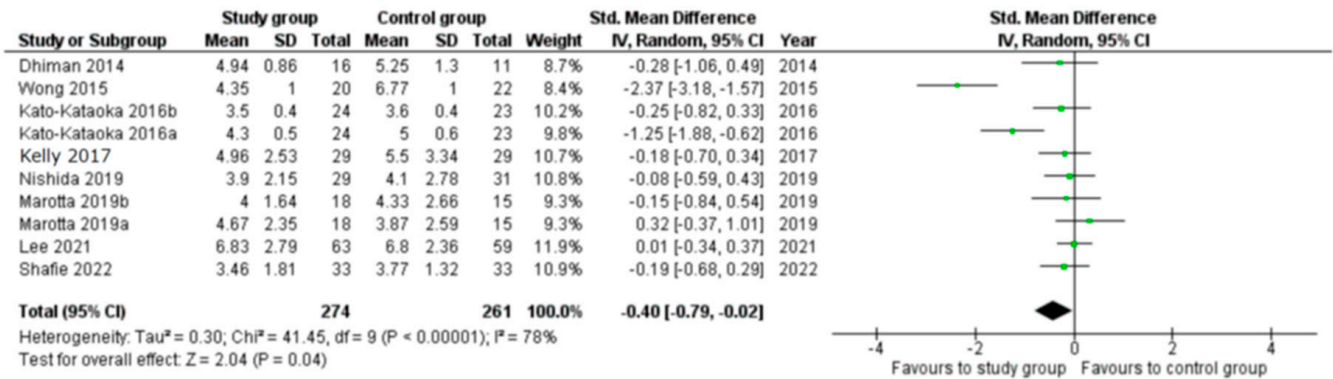


Figure 3. Forrest plot for standard mean difference of PSQI between study (probiotic) and control (placebo) groups. **References in figure:** Dhiman 2014 [87]; Wong 2015 [88]; Kato-Kataoka 2016 [82]; Kelly 2017 [78]; Nishida 2019 [68]; Marotta 2019 [71]; Lee 2021 [91]; Shafie 2022 [90].

Meta-regression analysis was performed using patients’ age as a covariate and the PSQI as the dependent variable. The difference between the study and control group was significantly related to patients’ age (Chi-squared 10.9, $p = 0.012$).

The use of probiotics was linked to ESS score reduction vs. placebo, although it was not statistically significant ($p = 0.070$, Figure 4). Finally, the mean age of subjects did not differ between the study and control groups (-0.06 ; 95%CI: $-0.05, 0.54$ years, $p = 0.850$), excluding the age as a potential source for differences in PSQI score.

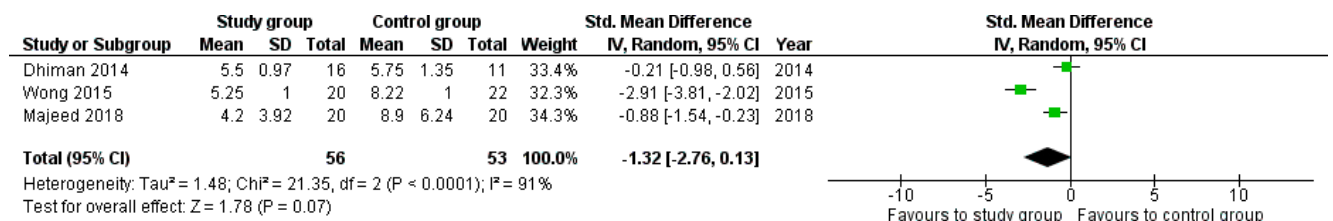


Figure 4. Forrest plot for the standard mean difference of ESS in study vs. control groups. **References in figure:** Dhiman 2014 [87]; Wong 2015 [88]; Majeed 2018 [89].

4. Discussion

This meta-analysis demonstrates that the use of probiotics improves sleep quality, as established by self-assessment questionnaires. However, the self-assessed propensity to fall asleep does not change after probiotics consumption, suggesting that the GM–sleep quality relationship could be only slightly influenced by this therapeutic intervention. Indeed, here we demonstrate that the GM diversity is not different between patients with vs. without sleep disorders, suggesting that there is not a stable substrate on which probiotics could act to improve sleep quality. Results were obtained using α -diversity data, which does not provide a measure of the specific abundance of taxa or species in the gut. Moreover, β -diversity is missing due to a lack of reporting in more than three studies. This is a limitation depending on the heterogeneity of the current literature and precludes the meta-analysis of individual microbiome taxa and/or species. Further, we have considered GM modulation by therapeutic measures on sleep quality as a topic recently explored in a meta-analytic study [92], where authors evaluated the efficacy of probiotic or prebiotic intervention on sleep characteristics. In this study, people with type 2 diabetes mellitus, dementia, and bone

fracture were included, and no improvements in sleep quality (eighteen trials analyzed) and sleep duration (five trials analyzed) were found [92]. These results contrast with our results since we found improvement in sleep quality parameters with probiotics administration versus placebo. This discrepancy could be due to the subject analyzed since only healthy subjects or subjects with specific diseases, such as inflammatory bowel disease and fibromyalgia, were included in the present study. Moreover, the authors considered sleep quality parameters using both standardized questionnaires and self-reported information. In the present work, only PSQI reported significant improvement of sleep disturbances compared with the placebo. ESS score seems to be not significantly different, although it shows a trend similar to what observed by PSQI analysis. Unfortunately, heterogeneity of patient's characteristics with sleep disorders, and wide variability in study experimental settings, make it difficult to generalize further about these results. The role of GM in sleep disorder was recently discussed and converging findings indicated that microbiota could be targeted by interventions aimed at improving sleep [93]. However, we found that sleep disorders could not be associated with GM composition, irrespective to the index used to measure its diversity. On the contrary, PSQI offers the subjective perspective that probiotics administration, obviously influencing GM, improves sleep quality. We may assume that GM could impact sleep behavior, even if possibly weakly, and that this issue requires specific clinical studies with well-selected populations to be addressed.

The scientific interest in the relationship between GM and human functions' homeostasis has been increasing in recent decades [94,95]. In fact, several lines of evidence indicate the existence of a connection between GM and the central nervous system, leading to the definition of the gut-brain axis (GBA) [96]. The bidirectional flow of information between the GM and the central nervous system is poorly understood and probably works through different mechanisms, such as the hypothalamic pituitary adrenal (HPA) axis [2], the immune system [33,97,98], the intestinal neuroendocrine cells [99], the vagus nerve [100] and the enteric nervous system [2]. The GBA influences sleep status in close interaction with emotions, physiological stress, and circadian rhythms [96]. While the existence of these connections is overall clear, the potential impact of GM on sleep physiology has not been completely unraveled. Sleep patterns could be modulated by changes in intestinal permeability, inflammation, immune system activation, energy harvest, and bacterial diversity [101,102]. However, the relationship between either GM composition or the effect of GM changes after probiotics consumption and sleep patterns remains questionable [103]. Our meta-analysis was not able to quantify the relationship between GM composition and sleep disturbance pattern since no differences in α -diversity were found by any indexes used, such as Shannon, Simpson, and Chao. However, taken individually, authors found reduced α - and β -diversity of GM in specific groups with sleep disturbances [38,51,53,54,57,61]. For example, total GM diversity is positively correlated with increased sleep efficiency and total sleep time when otherwise healthy subjects were considered [104]. Thus, we could speculate that the relationship between GM composition and sleep must be considered, evaluating each group of sleep disturbances separately.

The beneficial effect of probiotics supplementation on sleep disturbance seems to be weak but relatively well established, taking the present study into account with previous analyses [105]. In fact, our findings confirmed that probiotics consumption improves the subjective measure of sleep quality in patients with sleep disturbances when compared with placebo groups. Also, in this case, both sleep disturbance patterns and probiotic composition are extremely variable among studies. Despite this heterogeneity, PSQI is statistically different between the two groups considered, suggesting that the beneficial effect of probiotics could be stronger overall than expected, overcoming potential biases, such as selection and detection biases. Moreover, the mean age of participants is similar between the two groups, excluding the role of age in the observed differential composition of microbial community under probiotics administration. Other subjective sleep questionnaires could be less indicative than PSQI of effects obtained upon probiotics administration. For instance, ESS investigates general parameters such as day time sleepiness, instead of

straightly the sleep quality [106]. These considerations might explain why we found no significant improvement in ESS after probiotics administration. However, it is worthy of note that only three studies evaluated ESS [87–89], limiting the statistical power of this subgroup meta-analysis. This is a drawback that may be improved by increasing the number of clinical trials on this specific topic. Interestingly, one study was performed on subjects with bipolar disorder, reporting a negative correlation between *Lactobacillus* count and sleep [61]. This finding, obtained in a specific and limited set of subjects, is suggestive of a possible effect of this bacterial strain on sleep health.

It is intriguing that major benefits on sleep were observed among university students exposed to stressful conditions (e.g., academic examinations or courses), as indicated by some of the studies evaluated [68,71,82]. We may speculate that, in these groups, probiotics mitigate markedly the physiological response to stress exposure, via modulation of glucocorticoid action. A perceived environmental threat, such as a stressful event, triggers the HPA axis to secrete glucocorticoids and the sympathetic nervous system, leading to catecholamine release [107]. Moreover, increasing glucocorticoid levels were detected even in short sleep conditions [103]. Some studies indicated that probiotics administration attenuates the physiological increase in salivary glucocorticoids [82,106], potentially promoting sleep enhancement. This hypothesis suggests a beneficial role of probiotics for the general management of sleep disturbances, although subgroup analyses would be useful to establish firm conclusions.

Gender should be considered among potential determinants for high heterogeneity. Women were enrolled in only one study of those considered [90], whereas other trials included mixed groups of both males and females. Since sex-related differences in the effect of probiotics on sleep were suggested [74,84], we may assume that the heterogeneous gender composition of studies meta-analyzed could be a limitation. According to these studies, we could speculate that better outcomes occurred in men than women after *Lactobacillus gasseri* supplementation, although the limited availability of data prevented more accurate evaluations. Second, the participant's health status varied among trials, including either healthy subjects or individuals affected by different pathological conditions [87,88]. Last, the experimental intervention differed for the type of probiotic bacteria, i.e., species, single vs. multiple strains, dosage, duration of the supplementation, and delivery method. In conclusion, methodological biases should be carefully considered by other studies on this topic.

The present study shows several limitations. The number of trials using the same methodological approach to evaluate sleep disturbance, GM composition, and probiotics type is low. Moreover, studies are highly heterogeneous, including participants with different ages and health statuses and assessment methods to evaluate sleep quality (i.e., subjective or objective measures). In this context, we were not able to collect data useful to adjust the analyses performed. The only available parameter was the patient's age, which, as demonstrated by meta-regression analysis, potentially influenced the final result of the meta-analysis. Moreover, we could collect only α -diversity data, while β -diversity is missing due to lack of proper reporting, limiting the analysis of how individual microbiome taxa or species may contribute to mitigate sleep disturbances. In particular, the variability in Systematic Review patients' ages should be carefully considered since it is well-known that sleep patterns undergo physiological changes with aging [108,109]. In our study, the limited number of studies detected does not allow subgroup analyses based on age and gender. Third, the evaluation of sleep quality by questionnaires is obviously influenced by the subjectivity of these instruments. Although self-reported questionnaires are broadly used for clinical and research purposes, they do not provide objective parameters. Thus, data collected could be less accurate than those obtained by objective sleep assessment tools, such as PSG or actigraphy. Finally, only gut microbial genera/species significantly associated with the outcome are likely to be reported in the literature. This would introduce publication bias and limit the number of included studies. Further clinical trials with

randomized placebo-controlled designs and objective measurements are required to achieve solid conclusions.

In conclusion, the connection between sleep disturbances and GM homeostasis remains to be established since major drawbacks prevent definitive conclusions about this issue. Promising results based on subjective assessment of sleep quality suggested that probiotics could represent an effective clinical intervention to manage sleep disorders targeting GM. The understanding of variables impacting GM, such as diet, physical activity, stress, and pathological conditions, will be crucial to clarify the relationship between intestinal bacteria and sleep.

Author Contributions: All authors included in this article made substantial contributions to the data included, as well as assisted with critical revisions of the writing, and approved the final version for submission for publication. Conceptualization, D.S. and L.C.; Methodology, D.S., V.D., F.C., G.S. and C.G.; Formal Analysis, D.S.; Resources, V.D.; Data Curation, V.D. and G.S.; Writing—Original Draft Preparation, V.D., F.C. and C.G.; Writing—Review and Editing, D.S., V.D., F.C., G.S., C.G. and L.C.; Supervision, M.S. and L.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data reviewed and analyzed during this meta-analysis is available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

List of Abbreviations

BMI, body mass index; CFU, colony forming unit; ESS, Epworth Sleepiness Scale; GABA, γ -aminobutyric acid; GBA, gut–brain axis; GM, gut microbiota; HE, hepatic encephalopathy; HPA, hypothalamic pituitary adrenal; 5-HT, serotonin; IBS, irritable bowel syndrome; IL, interleukin; IQR, interquartile range; MD, mean difference; MSLT, multiple sleep latency test; OSHAS, obstructive sleep hypopnea/apnoea syndrome; PSG, polysomnography; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PSQI, Pittsburgh Sleep Quality Index; SCFAs, short chain fatty acids; SCR, sleep clinical record; SD, standard deviation.

References

1. Cryan, J.F.; O’Riordan, K.J.; Cowan, C.S.M.; Sandhu, K.V.; Bastiaanssen, T.F.S.; Boehme, M.; Codagnone, M.G.; Cusotto, S.; Fulling, C.; Golubeva, A.V.; et al. The Microbiota–Gut–Brain Axis. *Physiol. Rev.* **2019**, *99*, 1877–2013. [[CrossRef](#)] [[PubMed](#)]
2. Santacroce, L.; Man, A.; Charitos, I.A.; Haxhirexha, K.; Topi, S. Current knowledge about the connection between health status and gut microbiota from birth to elderly. A narrative review. *Front. Biosci. (Landmark Ed.)* **2021**, *26*, 135–148. [[CrossRef](#)] [[PubMed](#)]
3. Zhang, S.; Deng, F.; Chen, J.; Chen, F.; Wu, Z.; Li, L.; Hou, K. Fecal microbiota transplantation treatment of autoimmune-mediated type 1 diabetes: A systematic review. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 1075201. [[CrossRef](#)]
4. Fu, J.; Zheng, Y.; Gao, Y.; Xu, W. Dietary Fiber Intake and Gut Microbiota in Human Health. *Microorganisms* **2022**, *10*, 2507. [[CrossRef](#)]
5. Li, J.; Jia, H.; Cai, X.; Zhong, H.; Feng, Q.; Sunagawa, S.; Arumugam, M.; Kultima, J.R.; Prifti, E.; Nielsen, T.; et al. An integrated catalog of reference genes in the human gut microbiome. *Nat. Biotechnol.* **2014**, *32*, 834–841. [[CrossRef](#)] [[PubMed](#)]
6. Hugon, P.; Dufour, J.C.; Colson, P.; Fournier, P.E.; Sallah, K.; Raoult, D. A comprehensive repertoire of prokaryotic species identified in human beings. *Lancet Infect. Dis.* **2015**, *15*, 1211–1219. [[CrossRef](#)] [[PubMed](#)]
7. Khan, I.; Bai, Y.; Zha, L.; Ullah, N.; Ullah, H.; Shah, S.R.H.; Sun, H.; Zhang, C. Mechanism of the Gut Microbiota Colonization Resistance and Enteric Pathogen Infection. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 716299. [[CrossRef](#)]
8. Eckburg, P.B.; Bik, E.M.; Bernstein, C.N.; Purdom, E.; Dethlefsen, L.; Sargent, M.; Gill, S.R.; Nelson, K.E.; Relman, D.A. Diversity of the human intestinal microbial flora. *Science* **2005**, *308*, 1635–1638. [[CrossRef](#)]

9. Johnson, J.S.; Spakowicz, D.J.; Hong, B.Y.; Petersen, L.M.; Demkowicz, P.; Chen, L.; Leopold, S.R.; Hanson, B.M.; Agresta, H.O.; Gerstein, M.; et al. Evaluation of 16S rRNA gene sequencing for species and strain-level microbiome analysis. *Nat. Commun.* **2019**, *10*, 5029. [[CrossRef](#)]
10. Eren, A.M.; Maignien, L.; Sul, W.J.; Murphy, L.G.; Grim, S.L.; Morrison, H.G.; Sogin, M.L. Oligotyping: Differentiating between closely related microbial taxa using 16S rRNA gene data. *Methods Ecol. Evol.* **2013**, *4*, 1111–1119. [[CrossRef](#)]
11. Acinas, S.G.; Marcelino, L.A.; Klepac-Ceraj, V.; Polz, M.F. Divergence and redundancy of 16S rRNA sequences in genomes with multiple *rrn* operons. *J. Bacteriol.* **2004**, *186*, 2629–2635. [[CrossRef](#)] [[PubMed](#)]
12. Liu, W.T.; Marsh, T.L.; Cheng, H.; Forney, L.J. Characterization of microbial diversity by determining terminal restriction fragment length polymorphisms of genes encoding 16S rRNA. *Appl. Environ. Microbiol.* **1997**, *63*, 4516–4522. [[CrossRef](#)] [[PubMed](#)]
13. Pace, N.R.; Stahl, D.A.; Lane, D.J.; Olsen, G.J. The Analysis of Natural Microbial Populations by Ribosomal RNA Sequences. In *Advances in Microbial Ecology*; Marshall, K.C., Ed.; Springer: Boston, MA, USA, 1986; Volume 9. [[CrossRef](#)]
14. Whittaker, R.H.; Whittaker, R.H. Evolution and measurement of species diversity. *Taxon* **1972**, *21*, 213–251. [[CrossRef](#)]
15. Tan, J.; Chen, Y.X. Dietary and Lifestyle Factors Associated with Colorectal Cancer Risk and Interactions with Microbiota: Fiber, Red or Processed Meat and Alcoholic Drinks. *Gastrointest. Tumors* **2016**, *3*, 17–24. [[CrossRef](#)]
16. Zhou, Y.; Zhou, C.; Zhang, A. Gut microbiota in acute leukemia: Current evidence and future directions. *Front. Microbiol.* **2022**, *13*, 1045497. [[CrossRef](#)] [[PubMed](#)]
17. Matzaras, R.; Nikopoulou, A.; Protonotariou, E.; Christaki, E. Gut Microbiota Modulation and Prevention of Dysbiosis as an Alternative Approach to Antimicrobial Resistance: A Narrative Review. *Yale J. Biol. Med.* **2022**, *95*, 479–494.
18. Weiss, G.A.; Hennet, T. Mechanisms and consequences of intestinal dysbiosis. *Cell. Mol. Life Sci.* **2017**, *74*, 2959–2977. [[CrossRef](#)]
19. Gurung, M.; Li, Z.; You, H.; Rodrigues, R.; Jump, D.B.; Morgun, A.; Shulzhenko, N. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine* **2020**, *51*, 102590. [[CrossRef](#)]
20. Nishida, A.; Inoue, R.; Inatomi, O.; Bamba, S.; Naito, Y.; Andoh, A. Gut microbiota in the pathogenesis of inflammatory bowel disease. *Clin. J. Gastroenterol.* **2018**, *11*, 1–10. [[CrossRef](#)]
21. Foster, J.A.; McVey Neufeld, K.A. Gut-brain axis: How the microbiome influences anxiety and depression. *Trends Neurosci.* **2013**, *36*, 305–312. [[CrossRef](#)]
22. Neroni, B.; Evangelisti, M.; Radocchia, G.; Di Nardo, G.; Pantanella, F.; Villa, M.P.; Schippa, S. Relationship between sleep disorders and gut dysbiosis: What affects what? *Sleep Med.* **2021**, *87*, 1–7. [[CrossRef](#)] [[PubMed](#)]
23. Sateia, M.J. International classification of sleep disorders-third edition: Highlights and modifications. *Chest* **2014**, *146*, 1387–1394. [[CrossRef](#)] [[PubMed](#)]
24. Sadeh, A. iii. Sleep assessment methods. *Monogr. Soc. Res. Child Dev.* **2015**, *80*, 33–48. [[CrossRef](#)] [[PubMed](#)]
25. Markun, L.C.; Sampat, A. Clinician-Focused Overview and Developments in Polysomnography. *Curr. Sleep Med. Rep.* **2020**, *6*, 309–321. [[CrossRef](#)]
26. Sadeh, A. The role and validity of actigraphy in sleep medicine: An update. *Sleep Med. Rev.* **2011**, *15*, 259–267. [[CrossRef](#)] [[PubMed](#)]
27. Fekedulegn, D.; Andrew, M.E.; Shi, M.; Violanti, J.M.; Knox, S.; Innes, K.E. Actigraphy-Based Assessment of Sleep Parameters. *Ann. Work Expo. Health* **2020**, *64*, 350–367. [[CrossRef](#)]
28. Zhang, L.; Zhao, Z.X. Objective and subjective measures for sleep disorders. *Neurosci. Bull.* **2007**, *23*, 236–240. [[CrossRef](#)]
29. Morin, C.M.; Belleville, G.; Bélanger, L.; Ivers, H. The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* **2011**, *34*, 601–608. [[CrossRef](#)]
30. Mollayeva, T.; Thurairajah, P.; Burton, K.; Mollayeva, S.; Shapiro, C.M.; Colantonio, A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep Med. Rev.* **2016**, *25*, 52–73. [[CrossRef](#)]
31. Lok, R.; Zeitzer, J.M. Physiological correlates of the Epworth Sleepiness Scale reveal different dimensions of daytime sleepiness. *Sleep Adv.* **2021**, *2*, zpab008. [[CrossRef](#)]
32. Johns, M.W. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* **1991**, *14*, 540–545. [[CrossRef](#)] [[PubMed](#)]
33. Miller, A.H.; Raison, C.L. The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* **2016**, *16*, 22–34. [[CrossRef](#)] [[PubMed](#)]
34. Han, M.; Yuan, S.; Zhang, J. The interplay between sleep and gut microbiota. *Brain Res. Bull.* **2022**, *180*, 131–146. [[CrossRef](#)] [[PubMed](#)]
35. Li, Y.; Hao, Y.; Fan, F.; Zhang, B. The Role of Microbiome in Insomnia, Circadian Disturbance and Depression. *Front. Psychiatry* **2018**, *9*, 669. [[CrossRef](#)] [[PubMed](#)]
36. Leone, V.; Gibbons, S.M.; Martinez, K.; Hutchison, A.L.; Huang, E.Y.; Cham, C.M.; Pierre, J.F.; Heneghan, A.F.; Nadimpalli, A.; Hubert, N.; et al. Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host Microbe* **2015**, *17*, 681–689. [[CrossRef](#)] [[PubMed](#)]
37. Spaggiari, G.; Romeo, M.; Casarini, L.; Granata, A.R.M.; Simoni, M.; Santi, D. Human fertility and sleep disturbances: A narrative review. *Sleep Med.* **2022**, *98*, 13–25. [[CrossRef](#)] [[PubMed](#)]
38. Grosicki, G.J.; Riemann, B.L.; Flatt, A.A.; Valentino, T.; Lustgarten, M.S. Self-reported sleep quality is associated with gut microbiome composition in young, healthy individuals: A pilot study. *Sleep Med.* **2020**, *73*, 76–81. [[CrossRef](#)]

39. Hill, C.; Guarner, F.; Reid, G.; Gibson, G.R.; Merenstein, D.J.; Pot, B.; Morelli, L.; Canani, R.B.; Flint, H.J.; Salminen, S.; et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat. Rev. Gastroenterol. Hepatol.* **2014**, *11*, 506–514. [CrossRef]
40. Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria, October 2001. Available online: <https://www.iqb.es/digestivo/pdfs/probioticos.pdf> (accessed on 4 December 2023).
41. Spaggiari, G.; Brigante, G.; De Vincentis, S.; Cattini, U.; Roli, L.; De Santis, M.C.; Baraldi, E.; Tagliavini, S.; Varani, M.; Trenti, T.; et al. Probiotics Ingestion Does Not Directly Affect Thyroid Hormonal Parameters in Hypothyroid Patients on Levothyroxine Treatment. *Front. Endocrinol.* **2017**, *8*, 316. [CrossRef]
42. McKean, J.; Naug, H.; Nikbakht, E.; Amiet, B.; Colson, N. Probiotics and Subclinical Psychological Symptoms in Healthy Participants: A Systematic Review and Meta-Analysis. *J. Altern. Complement. Med.* **2017**, *23*, 249–258. [CrossRef]
43. Margolis, K.G.; Cryan, J.F.; Mayer, E.A. The Microbiota-Gut-Brain Axis: From Motility to Mood. *Gastroenterology* **2021**, *160*, 1486–1501. [CrossRef]
44. Senok, A.C.; Ismael, A.Y.; Botta, G.A. Probiotics: Facts and myths. *Clin. Microbiol. Infect.* **2005**, *11*, 958–966. [CrossRef]
45. Crovesy, L.; Masterson, D.; Rosado, E.L. Profile of the gut microbiota of adults with obesity: A systematic review. *Eur. J. Clin. Nutr.* **2020**, *74*, 1251–1262. [CrossRef] [PubMed]
46. Luo, D.; Wan, X.; Liu, J.; Tong, T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat. Methods Med. Res.* **2018**, *27*, 1785–1805. [CrossRef]
47. Wan, X.; Wang, W.; Liu, J.; Tong, T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med. Res. Methodol.* **2014**, *14*, 135. [CrossRef] [PubMed]
48. Higgins, J.P.; Altman, D.G.; Gøtzsche, P.C.; Jüni, P.; Moher, D.; Oxman, A.D.; Savovic, J.; Schulz, K.F.; Weeks, L.; Sterne, J.A.; et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ* **2011**, *343*, d5928. [CrossRef] [PubMed]
49. Evans, S.J.; Bassis, C.M.; Hein, R.; Assari, S.; Flowers, S.A.; Kelly, M.B.; Young, V.B.; Ellingrod, V.E.; McInnis, M.G. The gut microbiome composition associates with bipolar disorder and illness severity. *J. Psychiatr. Res.* **2017**, *87*, 23–29. [CrossRef] [PubMed]
50. Ko, C.Y.; Liu, Q.Q.; Su, H.Z.; Zhang, H.P.; Fan, J.M.; Yang, J.H.; Hu, A.K.; Liu, Y.Q.; Chou, D.; Zeng, Y.M. Gut microbiota in obstructive sleep apnea-hypopnea syndrome: Disease-related dysbiosis and metabolic comorbidities. *Clin. Sci.* **2019**, *133*, 905–917. [CrossRef]
51. Collado, M.C.; Katila, M.K.; Vuorela, N.M.; Saarenpää-Heikkilä, O.; Salminen, S.; Isolauri, E. Dysbiosis in Snoring Children: An Interlink to Comorbidities? *J. Pediatr. Gastroenterol. Nutr.* **2019**, *68*, 272–277. [CrossRef]
52. Zhang, Q.; Yun, Y.; An, H.; Zhao, W.; Ma, T.; Wang, Z.; Yang, F. Gut Microbiome Composition Associated with Major Depressive Disorder and Sleep Quality. *Front. Psychiatry* **2021**, *12*, 645045. [CrossRef]
53. Fei, N.; Choo-Kang, C.; Reutrakul, S.; Crowley, S.J.; Rae, D.; Bedu-Addo, K.; Plange-Rhule, J.; Forrester, T.E.; Lambert, E.V.; Bovet, P.; et al. Gut microbiota alterations in response to sleep length among African-origin adults. *PLoS ONE* **2021**, *16*, e0255323. [CrossRef]
54. Valentini, F.; Evangelisti, M.; Arpinelli, M.; Di Nardo, G.; Borro, M.; Simmaco, M.; Villa, M.P. Gut microbiota composition in children with obstructive sleep apnoea syndrome: A pilot study. *Sleep Med.* **2020**, *76*, 140–147. [CrossRef] [PubMed]
55. Zhang, R.; Gao, S.; Wang, S.; Zhang, J.; Bai, Y.; He, S.; Zhao, P.; Zhang, H. Gut Microbiota in Patients with Type 1 Narcolepsy. *Nat. Sci. Sleep* **2021**, *13*, 2007–2018. [CrossRef] [PubMed]
56. González-Mercado, V.J.; Lim, J.; Yu, G.; Penedo, F.; Pedro, E.; Bernabe, R.; Tirado-Gómez, M.; Aouizerat, B. Co-Occurrence of Symptoms and Gut Microbiota Composition Before Neoadjuvant Chemotherapy and Radiation Therapy for Rectal Cancer: A Proof of Concept. *Biol. Res. Nurs.* **2021**, *23*, 513–523. [CrossRef] [PubMed]
57. Agrawal, R.; Ajami, N.J.; Malhotra, S.; Chen, L.; White, D.L.; Sharafkhaneh, A.; Hoffman, K.L.; Graham, D.Y.; El-Serag, H.B.; Petrosino, J.F.; et al. Habitual Sleep Duration and the Colonic Mucosa-Associated Gut Microbiota in Humans-A Pilot Study. *Clocks Sleep* **2021**, *3*, 387–397. [CrossRef] [PubMed]
58. Hua, X.; Zhu, J.; Yang, T.; Guo, M.; Li, Q.; Chen, J.; Li, T. The Gut Microbiota and Associated Metabolites Are Altered in Sleep Disorder of Children with Autism Spectrum Disorders. *Front. Psychiatry* **2020**, *11*, 855. [CrossRef] [PubMed]
59. Heintz-Buschart, A.; Pandey, U.; Wicke, T.; Sixel-Döring, F.; Janzen, A.; Sittig-Wiegand, E.; Trenkwalder, C.; Oertel, W.H.; Mollenhauer, B.; Wilmes, P. The nasal and gut microbiome in Parkinson’s disease and idiopathic rapid eye movement sleep behavior disorder. *Mov. Disord.* **2018**, *33*, 88–98. [CrossRef] [PubMed]
60. Zhang, W.T.; Niu, J.Y.; He, C. Associations of OSAHS complicated by cerebral infarction with intestinal flora, inflammatory factors, homocysteine and adiponectin expression. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 12993–12999. [CrossRef]
61. Aizawa, E.; Tsuji, H.; Asahara, T.; Takahashi, T.; Teraishi, T.; Yoshida, S.; Koga, N.; Hattori, K.; Ota, M.; Kunugi, H. *Bifidobacterium* and *Lactobacillus* Counts in the Gut Microbiota of Patients with Bipolar Disorder and Healthy Controls. *Front. Psychiatry* **2019**, *18*, 730. [CrossRef]
62. Tang, S.S.; Liang, C.H.; Liu, Y.L.; Wei, W.; Deng, X.R.; Shi, X.Y.; Wang, L.M.; Zhang, L.J.; Yuan, H.J. Intermittent hypoxia is involved in gut microbial dysbiosis in type 2 diabetes mellitus and obstructive sleep apnea-hypopnea syndrome. *World J. Gastroenterol.* **2022**, *28*, 2320–2333. [CrossRef]

63. Masyutina, A.A.; Gumenyuk, L.N.; Fatoenko, Y.V.; Sorokina, L.E.; Bayramova, S.S.; Alekseenko, A.I.; Shavrov, Y.V.; Romanova, A.A.; Seydametova, D.I. Changes in gut microbiota composition and their associations with cortisol, melatonin and interleukin 6 in patients with chronic insomnia. *Bull. RSMU* **2021**, *2*, 18–24. [[CrossRef](#)]
64. Bikov, A.; Szabo, H.; Piroaska, M.; Kunos, L.; Szily, M.; Ligeti, B.; Makra, N.; Szabo, D.; Tarnoki, D.L.; Tarnoki, A.D. Gut Microbiome in Patients with Obstructive Sleep Apnoea. *J Appl. Sci.* **2022**, *12*, 2007. [[CrossRef](#)]
65. Cai, H.; Wang, C.; Qian, Y.; Zhang, S.; Zhang, C.; Zhao, W.; Zhang, T.; Zhang, B.; Chen, J.; Liu, S.; et al. Large-scale functional network connectivity mediate the associations of gut microbiota with sleep quality and executive functions. *Hum. Brain Mapp.* **2021**, *42*, 3088–3101. [[CrossRef](#)] [[PubMed](#)]
66. Benedict, C.; Vogel, H.; Jonas, W.; Woting, A.; Blaut, M.; Schürmann, A.; Cedernaes, J. Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals. *Mol. Metab.* **2016**, *5*, 1175–1186. [[CrossRef](#)] [[PubMed](#)]
67. Maki, K.A.; Burke, L.A.; Calik, M.W.; Watanabe-Chailland, M.; Sweeney, D.; Romick-Rosendale, L.E.; Green, S.J.; Fink, A.M. Sleep fragmentation increases blood pressure and is associated with alterations in the gut microbiome and fecal metabolome in rats. *Physiol. Genom.* **2020**, *52*, 280–292. [[CrossRef](#)]
68. Nishida, K.; Sawada, D.; Kuwano, Y.; Tanaka, H.; Rokutan, K. Health Benefits of *Lactobacillus gasseri* CP2305 Tablets in Young Adults Exposed to Chronic Stress: A Randomized, Double-Blind, Placebo-Controlled Study. *Nutrients* **2019**, *11*, 1859. [[CrossRef](#)]
69. Ho, Y.T.; Tsai, Y.C.; Kuo, T.B.J.; Yang, C.C.H. Effects of *Lactobacillus plantarum* PS128 on Depressive Symptoms and Sleep Quality in Self-Reported Insomniacs: A Randomized, Double-Blind, Placebo-Controlled Pilot Trial. *Nutrients* **2021**, *13*, 2820. [[CrossRef](#)]
70. West, N.P.; Hughes, L.; Ramsey, R.; Zhang, P.; Martoni, C.J.; Leyer, G.J.; Cripps, A.W.; Cox, A.J. Probiotics, Anticipation Stress, and the Acute Immune Response to Night Shift. *Front. Immunol.* **2020**, *11*, 599547. [[CrossRef](#)]
71. Marotta, A.; Sarno, E.; Del Casale, A.; Pane, M.; Mogna, L.; Amoroso, A.; Felis, G.E.; Fiorio, M. Effects of Probiotics on Cognitive Reactivity, Mood, and Sleep Quality. *Front. Psychiatry* **2019**, *10*, 164. [[CrossRef](#)]
72. Harnett, J.E.; Pyne, D.B.; McKune, A.J.; Penm, J.; Pumpa, K.L. Probiotic supplementation elicits favourable changes in muscle soreness and sleep quality in rugby players. *J. Sci. Med. Sport* **2021**, *24*, 195–199. [[CrossRef](#)]
73. Quero, C.D.; Manonelles, P.; Fernández, M.; Abellán-Aynés, O.; López-Plaza, D.; Andreu-Caravaca, L.; Hinchado, M.D.; Gálvez, I.; Ortega, E. Differential Health Effects on Inflammatory, Immunological and Stress Parameters in Professional Soccer Players and Sedentary Individuals after Consuming a Synbiotic. A Triple-Blinded, Randomized, Placebo-Controlled Pilot Study. *Nutrients* **2021**, *13*, 1321. [[CrossRef](#)]
74. Nishida, K.; Sawada, D.; Kawai, T.; Kuwano, Y.; Fujiwara, S.; Rokutan, K. Para-psychobiotic *Lactobacillus gasseri* CP2305 ameliorates stress-related symptoms and sleep quality. *J. Appl. Microbiol.* **2017**, *123*, 1561–1570. [[CrossRef](#)] [[PubMed](#)]
75. Moloney, G.M.; Long-Smith, C.M.; Murphy, A.; Dorland, D.; Hojabri, S.F.; Ramirez, L.O.; Marin, D.C.; Bastiaanssen, T.F.S.; Cusack, A.M.; Berding, K.; et al. Improvements in sleep indices during exam stress due to consumption of a. *Brain Behav. Immun. Health* **2021**, *10*, 100174. [[CrossRef](#)] [[PubMed](#)]
76. Patterson, E.; Griffin, S.M.; Ibarra, A.; Ellsiepen, E.; Hellhammer, J. Lpc-37® improves psychological and physiological markers of stress and anxiety in healthy adults: A randomized, double-blind, placebo-controlled and parallel clinical trial (the Sisu study). *Neurobiol. Stress* **2020**, *13*, 100277. [[CrossRef](#)] [[PubMed](#)]
77. Takada, M.; Nishida, K.; Gondo, Y.; Kikuchi-Hayakawa, H.; Ishikawa, H.; Suda, K.; Kawai, M.; Hoshi, R.; Kuwano, Y.; Miyazaki, K.; et al. Beneficial effects of *Lactobacillus casei* strain Shirota on academic stress-induced sleep disturbance in healthy adults: A double-blind, randomised, placebo-controlled trial. *Benef. Microbes.* **2017**, *8*, 153–162. [[CrossRef](#)] [[PubMed](#)]
78. Kelly, J.R.; Allen, A.P.; Temko, A.; Hutch, W.; Kennedy, P.J.; Farid, N.; Murphy, E.; Boylan, G.; Bienenstock, J.; Cryan, J.F.; et al. Lost in translation? The potential psychobiotic *Lactobacillus rhamnosus* (JB-1) fails to modulate stress or cognitive performance in healthy male subjects. *Brain Behav. Immun.* **2017**, *61*, 50–59. [[CrossRef](#)] [[PubMed](#)]
79. Diop, L.; Guillou, S.; Durand, H. Probiotic food supplement reduces stress-induced gastrointestinal symptoms in volunteers: A double-blind, placebo-controlled, randomized trial. *Nutr. Res.* **2008**, *28*, 1–5. [[CrossRef](#)] [[PubMed](#)]
80. Baião, R.; Capitão, L.P.; Higgins, C.; Browning, M.; Harmer, C.J.; Burnet, P.W.J. Multispecies probiotic administration reduces emotional salience and improves mood in subjects with moderate depression: A randomised, double-blind, placebo-controlled study. *Psychol. Med.* **2023**, *53*, 3437–3447. [[CrossRef](#)]
81. Nishida, K.; Sawada, D.; Kuwano, Y.; Tanaka, H.; Sugawara, T.; Aoki, Y.; Fujiwara, S.; Rokutan, K. Daily administration of paraprobiotic *Lactobacillus gasseri* CP2305 ameliorates chronic stress-associated symptoms in Japanese medical students. *J. Funct. Foods* **2017**, *36*, 112–121. [[CrossRef](#)]
82. Kato-Kataoka, A.; Nishida, K.; Takada, M.; Kawai, M.; Kikuchi-Hayakawa, H.; Suda, K.; Ishikawa, H.; Gondo, Y.; Shimizu, K.; Matsuki, T.; et al. Fermented Milk Containing *Lactobacillus casei* Strain Shirota Preserves the Diversity of the Gut Microbiota and Relieves Abdominal Dysfunction in Healthy Medical Students Exposed to Academic Stress. *Appl. Environ. Microbiol.* **2016**, *82*, 3649–3658. [[CrossRef](#)]
83. Nakakita, Y.; Tsuchimoto, N.; Takata, Y.; Nakamura, T. Effect of dietary heat-killed *Lactobacillus brevis* SBC8803 (SBL88™) on sleep: A non-randomised, double blind, placebo-controlled, and crossover pilot study. *Benef. Microbes* **2016**, *7*, 501–509. [[CrossRef](#)] [[PubMed](#)]

84. Daisuke, S.; Tomoko, K.; Kensei, N.; Yuki, K.; Shigeru, F.; Kazuhito, R. Daily intake of *Lactobacillus gasseri* CP2305 improves mental, physical, and sleep quality among Japanese medical students enrolled in a cadaver dissection course. *J. Funct. Food* **2017**, *31*, 188–197. [[CrossRef](#)]
85. Yamamura, S.; Morishima, H.; Kumano-go, T.; Suganuma, N.; Matsumoto, H.; Adachi, H.; Sigedo, Y.; Mikami, A.; Kai, T.; Masuyama, A.; et al. The effect of *Lactobacillus helveticus* fermented milk on sleep and health perception in elderly subjects. *Eur. J. Clin. Nutr.* **2009**, *63*, 100–105. [[CrossRef](#)] [[PubMed](#)]
86. Calandre, E.P.; Hidalgo-Tallon, J.; Molina-Barea, R.; Rico-Villademoros, F.; Molina-Hidalgo, C.; Garcia-Leiva, J.M.; Carrillo-Izquierdo, M.D.; Slim, M. The Probiotic VSL#3 Does Not Seem to Be Efficacious for the Treatment of Gastrointestinal Symptomatology of Patients with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Pharmaceuticals* **2021**, *14*, 1063. [[CrossRef](#)] [[PubMed](#)]
87. Dhiman, R.K.; Rana, B.; Agrawal, S.; Garg, A.; Chopra, M.; Thumburu, K.K.; Khattri, A.; Malhotra, S.; Duseja, A.; Chawla, Y.K. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: A randomized, controlled trial. *Gastroenterology* **2014**, *147*, 1327–1337.e1323. [[CrossRef](#)]
88. Wong, R.K.; Yang, C.; Song, G.H.; Wong, J.; Ho, K.Y. Melatonin regulation as a possible mechanism for probiotic (VSL#3) in irritable bowel syndrome: A randomized double-blinded placebo study. *Dig. Dis. Sci.* **2015**, *60*, 186–194. [[CrossRef](#)]
89. Majeed, M.; Nagabhushanam, K.; Arumugam, S.; Majeed, S.; Ali, F. MTCC 5856 for the management of major depression with irritable bowel syndrome: A randomised, double-blind, placebo controlled, multi-centre, pilot clinical study. *Food Nutr. Res.* **2018**, *62*. [[CrossRef](#)]
90. Shafie, M.; Homayouni Rad, A.; Mohammad-Alizadeh-Charandabi, S.; Mirghafourvand, M. The effect of probiotics on mood and sleep quality in postmenopausal women: A triple-blind randomized controlled trial. *Clin. Nutr. ESPEN* **2022**, *50*, 15–23. [[CrossRef](#)]
91. Lee, H.J.; Hong, J.K.; Kim, J.K.; Kim, D.H.; Jang, S.W.; Han, S.W.; Yoon, I.Y. Effects of Probiotic NVP-1704 on Mental Health and Sleep in Healthy Adults: An 8-Week Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* **2021**, *13*, 2660. [[CrossRef](#)]
92. Gil-Hernández, E.; Ruiz-González, C.; Rodríguez-Arrastia, M.; Ropero-Padilla, C.; Rueda-Ruzafa, L.; Sánchez-Labraca, N.; Roman, P. Effect of gut microbiota modulation on sleep: A systematic review and meta-analysis of clinical trials. *Nutr. Rev.* **2023**, *81*, 1556–1570. [[CrossRef](#)]
93. Wang, Z.; Lu, T.; Chen, W.; Yan, W.; Yuan, K.; Shi, L.; Liu, X.; Zhou, X.; Shi, J.; Vitiello, M.V.; et al. The microbiota-gut-brain axis in sleep disorders. *Sleep Med. Rev.* **2022**, *65*, 101691. [[CrossRef](#)]
94. Morais, L.H.; Schreiber, H.L.; Mazmanian, S.K. The gut microbiota-brain axis in behaviour and brain disorders. *Nat. Rev. Microbiol.* **2021**, *19*, 241–255. [[CrossRef](#)]
95. Sen, P.; Molinero-Perez, A.; O’Riordan, K.J.; McCafferty, C.P.; O’Halloran, K.D.; Cryan, J.F. Microbiota and sleep: Awakening the gut feeling. *Trends Mol. Med.* **2021**, *27*, 935–945. [[CrossRef](#)] [[PubMed](#)]
96. Gong, W.; Guo, P.; Li, Y.; Liu, L.; Yan, R.; Liu, S.; Wang, S.; Xue, F.; Zhou, X.; Yuan, Z. Role of the Gut-Brain Axis in the Shared Genetic Etiology between Gastrointestinal Tract Diseases and Psychiatric Disorders: A Genome-Wide Pleiotropic Analysis. *JAMA Psychiatry* **2023**, *80*, 360–370. [[CrossRef](#)] [[PubMed](#)]
97. Long-Smith, C.; O’Riordan, K.J.; Clarke, G.; Stanton, C.; Dinan, T.G.; Cryan, J.F. Microbiota-Gut-Brain Axis: New Therapeutic Opportunities. *Annu. Rev. Pharmacol. Toxicol.* **2020**, *60*, 477–502. [[CrossRef](#)]
98. Raison, C.L.; Lowry, C.A.; Rook, G.A. Inflammation, sanitation, and consternation: Loss of contact with coevolved, tolerogenic microorganisms and the pathophysiology and treatment of major depression. *Arch. Gen. Psychiatry* **2010**, *67*, 1211–1224. [[CrossRef](#)] [[PubMed](#)]
99. Adak, A.; Khan, M.R. An insight into gut microbiota and its functionalities. *Cell. Mol. Life Sci.* **2019**, *76*, 473–493. [[CrossRef](#)]
100. Fülling, C.; Dinan, T.G.; Cryan, J.F. Gut Microbe to Brain Signaling: What Happens in Vagus. ... *Neuron* **2019**, *101*, 998–1002. [[CrossRef](#)]
101. Poroyko, V.A.; Carreras, A.; Khalyfa, A.; Khalyfa, A.A.; Leone, V.; Peris, E.; Almendros, I.; Gileles-Hillel, A.; Qiao, Z.; Hubert, N.; et al. Chronic Sleep Disruption Alters Gut Microbiota, Induces Systemic and Adipose Tissue Inflammation and Insulin Resistance in Mice. *Sci. Rep.* **2016**, *6*, 35405. [[CrossRef](#)]
102. Kinnucan, J.A.; Rubin, D.T.; Ali, T. Sleep and inflammatory bowel disease: Exploring the relationship between sleep disturbances and inflammation. *Gastroenterol. Hepatol.* **2013**, *9*, 718–727.
103. Matenchuk, B.A.; Mandhane, P.J.; Kozyrskyj, A.L. Sleep, circadian rhythm, and gut microbiota. *Sleep Med. Rev.* **2020**, *53*, 101340. [[CrossRef](#)] [[PubMed](#)]
104. Smith, R.P.; Easson, C.; Lyle, S.M.; Kapoor, R.; Donnelly, C.P.; Davidson, E.J.; Parikh, E.; Lopez, J.V.; Tartar, J.L. Gut microbiome diversity is associated with sleep physiology in humans. *PLoS ONE* **2019**, *14*, e0222394. [[CrossRef](#)] [[PubMed](#)]
105. Haarhuis, J.E.; Kardinaal, A.; Kortman, G.A.M. Probiotics, prebiotics and postbiotics for better sleep quality: A narrative review. *Benef. Microbes* **2022**, *13*, 169–182. [[CrossRef](#)] [[PubMed](#)]
106. Irwin, C.; McCartney, D.; Desbrow, B.; Khalesi, S. Effects of probiotics and paraprobiotics on subjective and objective sleep metrics: A systematic review and meta-analysis. *Eur. J. Clin. Nutr.* **2020**, *74*, 1536–1549. [[CrossRef](#)]
107. Micale, V.; Drago, F. Endocannabinoid system, stress and HPA axis. *Eur. J. Pharmacol.* **2018**, *834*, 230–239. [[CrossRef](#)]

108. Troncoso, C.; Petermann-Rocha, F.; Brown, R.; Leiva, A.M.; Martinez, M.A.; Diaz-Martinez, X.; Garrido-Mendez, A.; Poblete-Valderrama, F.; Iturra-Gonzalez, J.A.; Villagran, M.; et al. Patterns of healthy lifestyle behaviours in older adults: Findings from the Chilean National Health Survey 2009–2010. *Exp. Gerontol.* **2018**, *113*, 180–185. [[CrossRef](#)]
109. Grandner, M.; Mullington, J.M.; Hashmi, S.D.; Redeker, N.S.; Watson, N.F.; Morgenthaler, T.I. Sleep Duration and Hypertension: Analysis of >700,000 Adults by Age and Sex. *J. Clin. Sleep Med.* **2018**, *14*, 1031–1039. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.