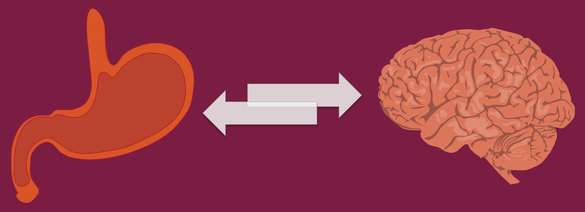

The Gut-Brain Connection: Association Between Multiple Sclerosis and Gut Microbiota

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INTRODUCTION

Background

- The human gut contains approximately 1000 bacterial species, comprising nearly 2 million genes
- Rapid advances of technology in microbiology has led to the emergence of the study of the gut microbiota in health and disease

- Multiple Sclerosis (MS) is an autoimmune disease characterized by demyelination. It is estimated to affect 2.5 million people worldwide and has increased in frequency in recent years
- Despite decades of research, the cause and cure remains unknown
- Gut microbiota alterations have been associated with MS in recent studies

Research Question

- Is there an association between gut microbiota composition and the pathogenesis of Multiple Sclerosis among adults aged 18 years or older?

METHODS

Study Design

- Structured Literature Review

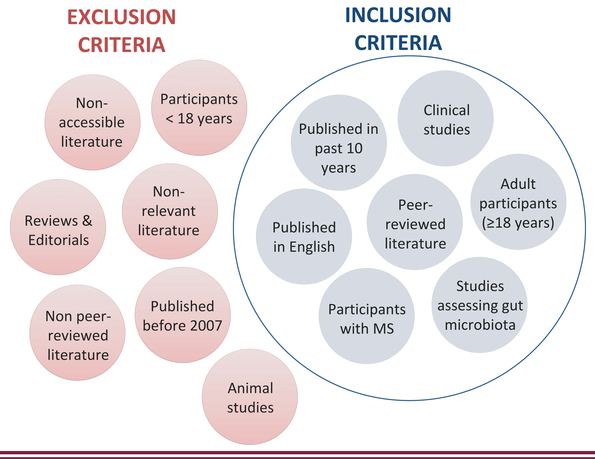
Search Strategy

- Keywords searched: "Multiple Sclerosis" AND "gut microbiota" OR "gut bacteria" OR "gut microbiome" OR "dysbiosis"

Databases Searched

- PubMed and Scopus

Figure 1. Inclusion and Exclusion Criteria



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METHODS

Figure 2. PRISMA Flowchart

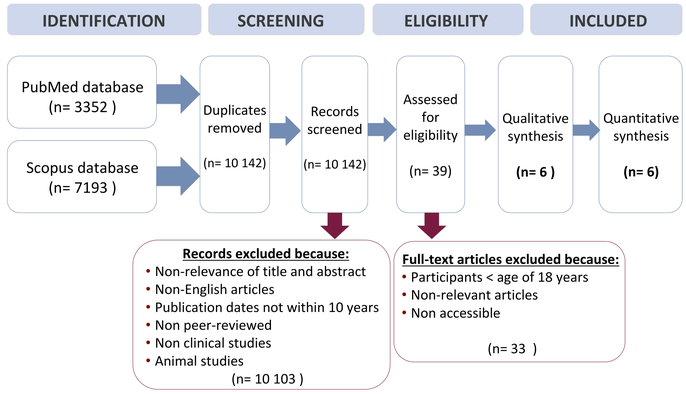

Table 1. Newcastle-Ottawa Quality Assessment Scale For Case-Control Studies

STUDY (YEAR)	SELECTION	COMPARABILITY		EXPOSURE	TOTAL
		Age & Sex	AB* & DMD*		
Berer et al. (2017)	4	2		3	**9**
Cantarel et al. (2015)	1	2		2	**5**
Cekanaviciute et al. (2017)	3	1		2	**6**
Chen et al. (2016)	3	1		2	**6**
Jangi et al. (2016)	2	2		2	**6**
Miyake et al. (2015)	2	2		2	**6**

*AB: Antibiotics
*DMD: Disease-Modifying Drugs

RESULTS

Table 2. Summarized Results of Studies: Differential Abundance of Gut Bacteria Among MS Patients

PHYLUM	INCREASED ABUNDANCE	DECREASED ABUNDANCE
ACTINOBACTERIA	• *Eggerthella lenta*[6]	• *Aldercreutzia*[4] • *Collinsella*[4]
BACTEROIDETES	• *Pedobacter*[4]	• *Bacteroides**[6] (Family= Bacteroidaceae) • *Bacteroidaceae**[2] • *Butyricimonas*[5] • *Parabacteroides**[3,4] • *Prevotella**[4,6]
FIRMICUTES	• *Ruminococcus**[2] *(Class = Clostridia)* • *Streptococcus thermophilus*[6] • *Blautia*[4] • *Dorea*[4]	• *Clostridia**[6] (14 species) • *Lactobacillus*[4] • *Anaerostipes*[6] • *Faecalibacterium**[2,6]
PROTEOBACTERIA	• *Acinetobacter*[3] • *Mycoplana*[4] • *Pseudomonas*[4]	• *Sutterella wadsworthensis*[6]
VERRUCOMICROBIA	• *Akkermansia**[1,2,3,5]	*No findings*

*Red: Concordant between multiple studies
*Blue: Potential conflicting results

RESULTS

Table 3. Summarized Results of Studies: Overall Findings

STUDY	POPULATION	METHOD	OUTCOME

Berer et al. (2017)	34 monozygotic twin pairs discordant for MS	16S rRNA sequencing and shotgun metagenomic sequencing of stool samples	• **Twin siblings:** No significant differences (SD)
			• **Untreated cases vs. controls and vs. treated cases:** Several taxa were significantly ↑ ($p<0.05$)
			• Gut bacteria of discordant twin pairs resembled each other more than that of:
			  • unrelated paired cases ($p<0.033$)
			  • unrelated paired controls ($p<0.013$)
			  • unrelated discordant pairs ($p<0.019$)

Cantarel et al. (2015)	7 MS patients and 8 controls	16S rRNA microarray of stool samples	• **Cases vs. controls**: No SD in overall bacterial diversity and richness • **Cases vs. controls:** SD in abundance of specific bacterial taxa • **Untreated cases vs. treated cases:** SD in overall diversity and richness ($p=0.007$)
Cekanaviciute et al. (2017)	71 untreated RRMS* patients and 71 controls	16S rRNA sequencing of stool samples	• **Cases vs. controls:** No SD in overall microbial diversity and richness • **Cases vs. controls:** SD in abundance at the individual taxa level (25 bacterial genera and 247 species) • **Untreated cases vs. controls:** SD in abundance at the individual taxa level
Chen et al. (2016)	31 RRMS patients and 36 controls	16S rRNA sequencing of stool samples	• **Cases vs. controls:** No SD in overall microbial richness and diversity • **Cases vs. controls:** SD in abundance of 35 individual taxa ($p<0.001$) • **Cases with active disease vs. cases in remission:** No SD in overall diversity and richness ($p=0.1$) • **Cases with active disease vs. cases in remission:** SD in abundance of certain individual taxa
Jangi et al. (2016)	60 RRMS patients and 43 controls	16S rRNA sequencing of stool samples	• **Cases vs. controls**: No SD in overall bacterial diversity and richness • **Cases vs. controls:** SD in abundance of individual bacterial taxa • **Untreated vs. treated cases**: SD in abundance of individual bacterial taxa
Miyake et al. (2015)	20 RRMS patients, 40 controls and 18 controls (providing longitudinal stool samples)	16S rRNA sequencing of stool samples	• **Cases vs. controls**: No SD in overall richness and diversity • **Cases vs. controls**: SD in abundance of 21 species ($p<0.05$) • **Cases vs. longitudinal controls:** Validated SD in abundance of 21 species

*All studies were case-control design; *RRMS = Relapsing-Remitting Multiple Sclerosis

CONCLUSION & DISCUSSION

- In general, there was no significant difference in overall gut bacterial richness and diversity between cases and controls
- Most studies found significant enrichment or depletion of specific bacterial taxa in MS subjects compared to controls
- However, the specific bacterial taxa differences were not always concordant between studies and were sometimes conflicting

Limitations of My Methodology

- Limited to only 2 databases
- Limited to articles published in English
- Limited to 6 studies: new research interest
- Comparability between studies: analyzed microbiome at different taxonomic ranks, different subtypes of MS studied, different geographical regions

Limitations and Biases of Studies

- Small sample sizes
- Cross-sectional nature
- Effect of confounders: age, sex, MS treatment, diet, genetics, geographic location, weight, etc.
- Stool samples: fecal microbiota might not reflect gut microbiota
- Not controlling for different MS subtypes and for active or remission phases
- Cannot infer causation: could be the outcome of disease

The findings suggest there may be an association between altered gut microbiota composition and the pathogenesis of MS. However, because of the limitations stated, such as small sample sizes and confounding effects, it is not possible to definitively conclude an association between the two. Further studies are needed.

Future Suggestions

- Larger-scale, longitudinal studies
- Stratification or controlling for potential confounders
- Gut-directed interventional studies using treatments such as dietary modification or fecal transplantation

Acknowledgments

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