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Systematic Literature Review of Microbiota Transfer Therapy for the Management of Autism Spectrum Disorder in children

Proyecto de Investigación

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RESUMEN

El trastorno del espectro autista (TEA) es una afección del desarrollo neurológico que tiene un mecanismo etiológico biológico poco claro. La literatura sugiere una relación estrecha entre la microbiota intestinal y el desarrollo del sistema nervioso central, neuroinmune y neuroendocrino. Las nuevas teorías y estrategias para el manejo del TEA se han enfocado en el eje cerebro-intestinos a través de la terapia de transferencia de microbiota. Se realizó una revisión sistemática de la literatura sobre la eficacia y la seguridad de la terapia de transferencia de microbiota para el tratamiento de los síntomas en niños con TEA. La búsqueda se realizó el 19 de abril de 2018 en cinco bases de datos. Se identificó un documento que incluía 18 pacientes tratados, que presentaron mejoras clínicas significativas en los síntomas gastrointestinales y relacionados con el TEA. La causalidad y la correlación de la intervención y los resultados esperados no pueden asumirse con la evidencia actual. Además, no se pueden hacer recomendaciones sobre la efectividad o seguridad de la terapia de transferencia de microbiota en niños con TEA. Se requieren ensayos clínicos aleatorios, controlados con placebo, doble ciego y protocolos clínicos para esta intervención.

Palabras clave: terapia de transferencia de microbiota, trastorno del espectro autista (TEA), microbioma, revisión sistemática de la literatura.

ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental condition that has an unclear biological etiologic mechanism. Literature suggest a close relation between the gut microbiota and the central nervous system development, neuroimmune and neuroendocrine systems. New theories and strategies target the management of ASD, by focusing on the brain-gut axis through microbiota transfer therapy. We conducted a systematic literature review on the efficacy and safety of the microbiota transfer therapy for the management of symptoms in children with ASD. The search was conducted on the 19th of April 2018 in five databases. One paper was identified that included 18 patients treated, with significant clinical improvements in the gastrointestinal and ASD related symptoms. The causality and correlation of the intervention and the expected outcomes cannot be assumed with the current evidence. Moreover, recommendations about effectiveness or safety of microbiota transfer therapy in children with ASD cannot be made. Randomized, placebo-controlled, double-blind control trials and clinical protocols for the intervention are needed.

Key words: microbiota transfer therapy, autism spectrum disorder (ASD), microbiome, systematic literature review.

PREFACIO

Este trabajo de titulación tiene la intención de ser un producto publicable, por lo que su estructura y extensión siguen las recomendaciones de guías internacionales de revisiones sistematicas de la literatura.

TABLA DE CONTENIDO

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impaired communication, impaired reciprocal social interaction, and restricted, repetitive patterns of behavior or interests (Faras, Al Ateeqi, & Tidmarsh, 2010). The symptoms of ASD are typically observed in the early childhood, and as ASD is a *spectrum*, the manifestations vary greatly depending on the chronological age, the developmental level, and the severity of the patient's condition (American Psychiatric Association, 2013). Today, the ASD term replaces the previous term *"pervasive developmental disorder"*, and does not use the subtypes of Asperger's disorder, Rett's disorder and childhood disintegrative disorder (Ousley & Cermak, 2014). Currently, ASD includes specifiers to indicate the type of impairment and the severity level and encompasses disorders previously referred as childhood autism, Kanner's autism, high-functioning autism, early infantile autism, among others [2](American Psychiatric Association, 2013). In the past couple of decades, the prevalence of ASD has increased, reaching 1%~2%, partially because of changes in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) diagnostic criteria and patients being diagnosed at a younger age (Park et al., 2016). Standardized research assessment tools have been designed following the DSM-IV criteria. Such tools include the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) (Lyall et al., 2017).

Etiologic theories of ASD have changed over the years. It is currently accepted that ASD is not a single disorder, though a multi-factorial disorder that has genetic and non-genetic risk factors involved. Causes related to genetics are estimated to be present in 10% to 20% of patients with ASD (Park et al., 2016). Researchers suggested that ASD is the result

of a complex interaction between genetic and environmental risk factors. The specific neural mechanism remains unclear, although literature suggest a close relation between the gut microbiota and the central nervous system development, neuroimmune and neuroendocrine systems (Cani & Knauf, 2016)(Martin & Mayer, 2017). This evidence has led to the development of new theories and strategies for the management of ASD, by focusing on the brain-gut axis through *microbiota transfer therapy* (Choi & Cho, 2016)(Yang, Tian, & Yang, 2018). Children with ASD have been targeted as a relevant interventional group for using microbiota transfer therapy. They tend to present an impaired gut microbiota (*dysbiosis*), gastrointestinal symptoms that are related to the severity of the ASD, an increased use of antibiotics and often different diets in comparison with neurotypical individuals (Yang et al., 2018)(Cryan & Dinan, 2012).

The gut-brain axis has been described to be a bidirectional communication of the gut microbiota and the central nervous system (Falsaperla et al., 2017). The gut of humans is populated by $1x10^{13}$ to $1x10^{14}$ microorganisms belonging to more than 1000 species (Yang et al., 2018). Their molecular communication includes an endocrine pathway with cortisol, an immunologic pathway with several cytokines and a neural pathway with the vagus and enteric nervous system (Kennedy et al., 2016)(Yang et al., 2018). These bidirectional pathways control the permeability and barrier function of the gut, therefore, the composition of the microbiota. Although, the probiotic agents, defined as a living being that positively influence health when ingested, and the gut microbiota can alter the concentration of cytokines and short-fatty acids (SCFA) which have a direct action in the brain function (Cryan & Dinan, 2012). Other studies support the genomeceutical theory, which propose that some compounds are able to affect gene expression in cells and the gene products, such as proteins and RNA (Brudnak, 2001). Ultimately, the genomeceutical compounds increase the

expression of dipeptidyl peptidase-IV, a molecule that has shown to be downregulated in ASD and it is even used for ASD diagnosis. Furthermore, the gut-associated lymphoid tissue (*GALT*) has been described as one of the elements involved in the pathophysiology of autism, through molecular mechanisms not completely identified yet (Felice & O'Mahony, 2017)(Brudnak, 2001).

In the past years, *microbiota transfer therapy* has gathered interest from researches and efforts to develop a novel intervention for the management and clinical improvement of different pathologies, including ASD (Colman & Rubin, 2014). Microbiota transfer therapy aims to restore the gut microbiota of the receiver through the infusion of donor feces to the gastrointestinal tract via oral capsules, endoscopic stomach, duodenum, jejunum, ileum, coecum or sigmoid infusions or rectal enema infusions (Rossen, 2015)(Choi & Cho, 2016). Recent evidence suggests that the microbiota transfer therapy affects the pathophysiology of several brain disorders, such as ASD, Parkinson disease, chronic pain, and disorders in mood and affect (Martin & Mayer, 2017)(Yang et al., 2018). Microbiota transfer therapy has shown to be a durable engraftment of the donor microorganisms and increases the number of species present in the receiver's gut microbiota (Kelly et al., 2015). There is already evidence showing its efficacy for different gastrointestinal diseases, such as inflammatory bowel disease, metabolic syndrome, irritable bowel syndrome, and *Clostridium difficile* infection (Rossen, 2015). As a novel therapy, there is still no protocol for using microbiota transfer therapy for the management of the different pathologies. However in 2010, a workgroup with several societies proposed a protocol for the treatment of *Clostridium difficile* infection with microbiota transfer therapy, including the indications, donor selection criteria, recipient exclusion criteria, means of administering stool, and the evaluation of the success (Bakken et al., 2011). There are still questions about the safety of the microbiota transfer therapy, as it

has the possibility of transmitting infectious agents (Choi & Cho, 2016). Therefore, arduous screening tests should be performed before the procedure is done, and a strict selection criterion for the donor. There are potential adverse events in microbiota transfer therapy, that can be divided in minor events and serious events (Hefazi et al., 2017)(Choi & Cho, 2016).

Until now, no systematic literature review of clinical trials, assessing the use of microbiota transfer therapy in children with ASD has been conducted. The aim of this study is to perform a systematic literature review on the efficacy and safety of the microbiota transfer therapy for the management of symptoms in children with Autism Spectrum Disorders.

METHODOLOGY

This study was made following the 27 items of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement to report a systematic review. No preview review protocol was found for Microbiota Transfer Therapy for the Management of Autism Spectrum Disorder in children. This systematic literature review and the protocol was not registered before the start of the study. This type of study has excepted from the review of an ethics committee.

SEARCH STRATEGY

Searches peer-reviewed were performed in five different databases, MEDLINE via PubMed, LILACS IBECS via BVS, EMBASE via Ovid, Scopus and Cochrane Library. The search was conducted on the 19th of April 2018 for all the databases. A list of search terms was used for each database (Appendix 1). A cross-reference was conducted in the paper

identified in this systematic literature review. Finally, a hand search of reference listings was conducted.

STUDY ELIGIBILITY

To be included, the papers had to meet the following selection criteria. Study design, with randomized controlled trials, quasi-randomized control trials or control trials. Population, with children with autism spectrum disorder (age limitation according to each study). Intervention, with microbiota transfer therapy. Study Outcome, with efficacy or safety outcomes. And no language limitation.

DATA EXTRACTION AND ANALYSIS

The application *EndNote*® was used to extract the information of the manuscripts. An automatic deduplication was made. Two reviewers (P.D.E and L.E.G) independently assessed the titles and abstracts of the database using the selection criteria. Discrepancies about the assessment were solved with discussion until a consensus was reached between P.D.E. and L.E.G. If the information of the database was not enough to use the selection criteria, the full manuscript was retrieved.

QUALITY ASSESSMENT

To assess the risk of bias in estimates of the comparative effectiveness of the study in the included in this systematic literature review, the Risk Of Bias In Non-randomized Studies – of Interventions *(ROBINS-I)* was used (NCBI, n.d.)(Sterne et al., 2016).

RESULTS

Five thousand two hundred ninety-seven papers were identified after automatic deduplication (PRISMA flowchart, *Figure 1*). From those papers, 104 were identified as duplicates, 4,422 were not the study type of interest, 106 papers were not about humans, 621

were not about children with ASD, and 30 were not about microbiota transfer therapy. This exclusion criteria left 14 papers to be included for the full text review. From those 14 papers, 12 of them were not the study type of interest and one was not about children with autistic spectrum disorder. One study was included in the final review. No additional studies were identified along with the hand searches.

The study identified is an open-label trial to investigate the safety, tolerability and efficacy of microbiota transfer therapy for gastrointestinal and behavior symptoms in children with ASD. The study was published in 2017 (Kang et al., 2017). A total of 18 children participated, between ages of seven to 16 years old that presented moderate to severe gastrointestinal problems. Twenty neurotypical children were used as control group. The protocol used for the microbiota transfer therapy was a 14 days of oral vancomycin initial treatment, then a 12 to 24 hours of fasting, followed by a high initial dose of standardized human microbiota in oral or rectal infusions. Subsequently, a maintenance oral dose with a gastric protector was given for seven to eight weeks. Eight weeks later a follow up was made after the end of the treatment. In total, 18 weeks was the time required for the study including the treatment and the follow up.

In the study retrieved, assessment of the gastrointestinal symptoms was made through the Gastrointestinal Symptom Rating Scale and the daily stool records. While the assessment for the autism and related symptoms was made through the ADI-R interview, the Parent Global Impression III (PGI-III), among other scales. After the microbiota transfer therapy intervention, children with ASD showed that their bacteria diversity in the gut was significantly increased compared with their baseline and continued like that for the eight weeks of follow up. These assessments showed substantial changes in gastrointestinal

symptoms, such as constipation, diarrhea, abdominal pain and indigestion. ASD symptoms showed significant improvements during the treatment and no reversion of the effects during the follow up. The score on CARS *(Childhood Autism Rating Scale)* that rates ASD symptoms, showed a decreased of 22% when the treatment was over, and 24% after eight weeks of no treatment. Using other scales, like the SRS (*The Social Responsiveness Scale)* and the ABC *(The Autism Behavior Checklist)*, the improvements in the participants scores was found. The average developmental age was found to be increased in 1.4 yeas with a $p<0.001$ with the VABS-II *(Vineland Adaptive Behavior Scale II)* score. No significant difference was found in the clinical outcomes related if the first dose of the microbiota transfer therapy was given rectally or orally. Other findings include that microbiota transfer therapy was a safe and well tolerated intervention, with some transitory adverse effects, including hyperactivity and aggression during the first phase of vancomycin treatment.

The risk of bias of the study identified was made by the ROBINS-I *(Risk Of Bias In Non-randomized Studies - of Intervention)* assessment tool (Sterne et al., 2016). The risk of bias judgement can be considered low, moderate, serious, critical or no information. The risk of bias due to confounding was considered serious. Although the risk of bias in selection of participants into the study, in classification of interventions, due to deviations from intended interventions, and due to missing data was considered low. Moreover, the bias in measurement of outcomes was considered moderate. An overall bias of the study was considered low, with a predicted direction of bias for this outcome to be favours experimental.

DISCUSION

To date, this is the only systematic literature review on microbiota transfer therapy on children with ASD. After the screening, one study was identified. The study had 18 children for the intervention and 20 neurotypical children as a control group. Significant clinical improvements were found in the children after the microbiota transfer therapy, in the gastrointestinal and ASD related symptoms (Kang et al., 2017). These results were maintained on the eight follow up weeks after the end of the treatment. An update of this study was recently published in April 2019, following up the results of this first study (Kang et al., 2019). All 18 participants with ASD were re-evaluated, showing a significant improvement in both gastrointestinal and ASD behavior symptoms since the end of the treatment. Two years after the intervention, the changes in the microbiota persisted with relative abundances of *Bifidobacteria* and *Prevotella (Kang et al., 2019)*. In a published observation, two children showed improvement in their ASD symptoms after fecal microbiota therapy and five children after several weeks of receiving cultured *Bacteroidetes* and *Clostridia* every day (Aroniadis & Brandt, 2013).

The brain-gut axis involves complex communication and metabolic mechanisms that are still not fully understood. Several pathophysiologic pathways have been proposed, hypothesizing the relation between the microbiota composition with different neurological conditions, nevertheless still needs further evidence to clarify the function of this axis. Taking in consideration that children with ASD present a pattern of dysbiosis, the microbiota transfer therapy has raised attention as a novel intervention for the management of ASD patients. However, it is still not clear if there is a direct relation between ASD and the alteration in their gut microbiota and therefore, if the change in the microbiota directly influences the different gastrointestinal and clinical symptoms of ASD. Besides, microbiota transfer

therapy is a growing field in medicine for management of several diseases. It is not a new therapeutically modality however it has received public attention from the media in the past years. The first report of fecal material given to patients with gastroenterological illness was in China by Ge Hong (Aroniadis & Brandt, 2013). The use of fecal enemas was reported in 1958 as an adjunct treatment of pseudomembranous enterocolitis (Eiseman, Silen, Bascom, & Kauvar, 1958). Today, microbiota transfer therapy is extensively used for *Clostridium difficile* infection, inflammatory bowel disease, and irritable bowel syndrome management (Sha et al., 2014). The evidence is growing around fecal microbiota therapy and its applications in other fields of medicine, including ASD patients. Efficacy and safety data have been recorded mainly in adults, while in children it has not been studied so widely.

The study identified in the systematic review was assessed by the ROBINS-I risk of bias assessment tool. The biggest risk of bias was due to confounding, as the study was open label and did not explain an appropriate analysis method for controlling all the important confounding domains. The other items assessed for bias were scored low or moderate, giving a low overall risk of bias.

LIMITATIONS

Reporting the efficacy and safety of microbiota transfer therapy in children with ASD is limited by the absence of randomized clinical trials in the field. Only one open label study reported to date (Kang et al., 2017). Even though the intervention has been described as effective and safe in the study found, the 18 children of this study are not enough to make recommendations for future application of the microbiota transfer therapy intervention in

ASD children. The causality and correlation of the intervention and the expected outcomes cannot be assumed with the current evidence.

CONCLUSIONS

This systematic literature review shows that the evidence is not strong enough to make recommendations about effectiveness or safety of microbiota transfer therapy in children with ASD. Randomized, placebo-controlled, double-blind control trials and clinical protocols for the intervention are needed. Although, at the moment, three clinical trials have been identified related to microbiota transfer therapy with ASD patients. One that will target ASD and gastrointestinal disorders in children ("Efficacy, Safety, and Tolerability Study of Oral Full-Spectrum MicrobiotaTM (CP101) in Subjects With Autism Spectrum Disorder and Associated GI Symptoms (SPROUT) - Full Text View - ClinicalTrials.gov," n.d.), another one with adults ("Microbiota Transfer Therapy for Adults With Autism Spectrum Disorder (ASD) Who Have Gastrointestinal Disorders - Full Text View - ClinicalTrials.gov," n.d.) and the other one in children and young adults ("The Gut-Brain Study - Full Text View - ClinicalTrials.gov," n.d.).

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FIGURES

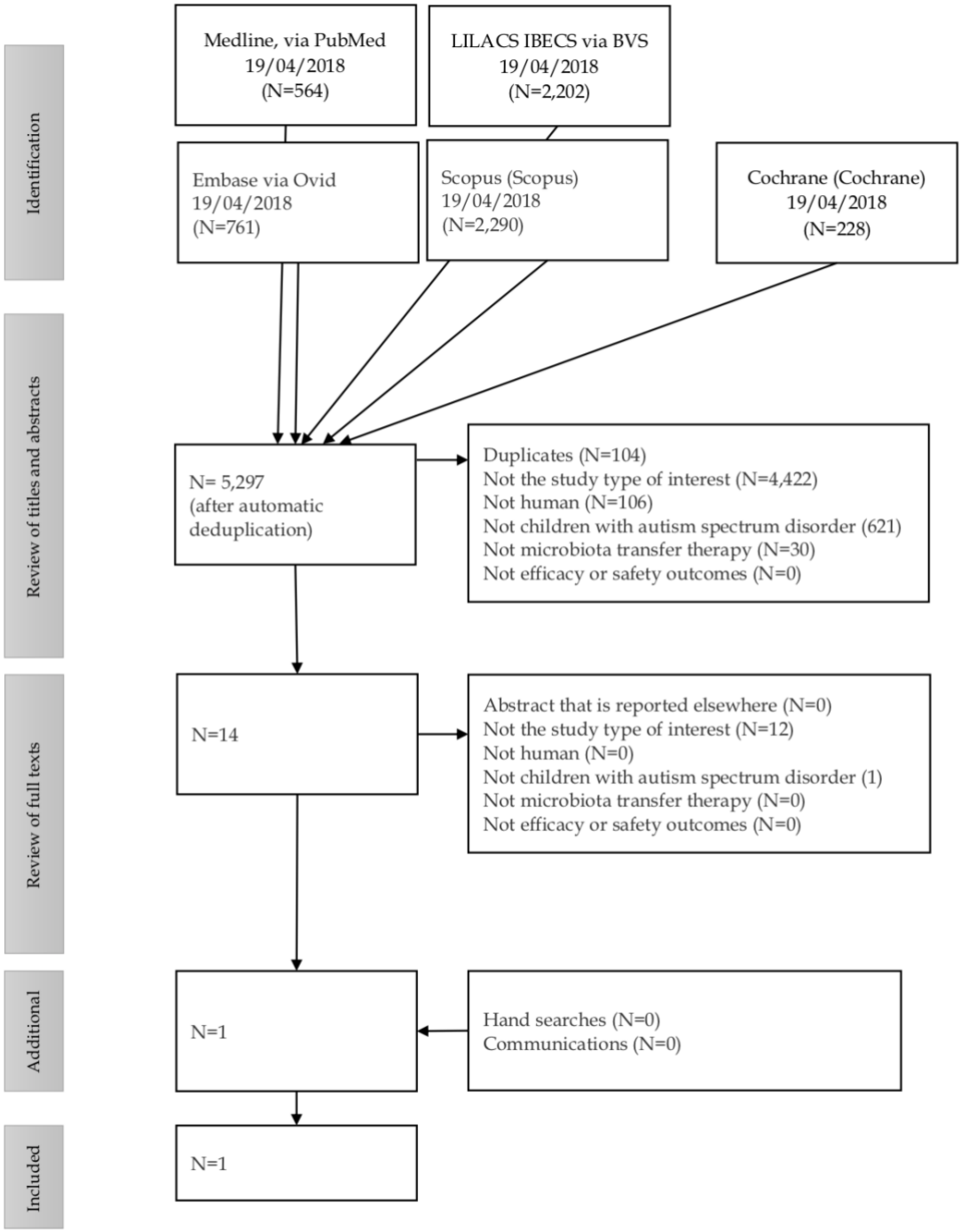

Figure 1

PRISMA Diagram. Identification, screening, eligibility and inclusion of studies

ANNEX A: SEARCH TERMS FOR EACH DATABASE

Search terms_MEDLINE via PUBMED		
Items	*#*	*Search terms*
Population_children	#1	Child[MeSH] OR Infant[MeSH] OR pediatrics[MeSH]
	#2	infant[TIAB] OR infant*[TIAB] OR newborn[TIAB] OR newborn*[TIAB] OR neonat*[TIAB] OR baby[TIAB] OR babies[TIAB] OR child[TIAB] OR child*[TIAB] OR schoolchil*[TIAB] OR preschoo*[TIAB] OR toddler[TIAB] OR toddler*[TIAB] OR girl[TIAB] OR girl*[TIAB] OR boy[TIAB] or boy*[TIAB] OR pediatri*[TIAB] OR paediatri*[TIAB]
	#3	#1 OR #2
Population_austism	#4	"Child Development Disorders, Pervasive"[MeSH] OR "Intellectual Disability"[MeSH] OR "Mental Disorders"[MeSH]
	#5	autis*[TIAB] OR "pervasiv*"[TIAB] OR PDD[TIAB] OR "language"[TIAB] OR speech[TIAB] OR schizophren*[TIAB] OR kanner[TIAB] OR kanner*[TIAB] OR asperge*[TIAB] OR cogniti*[TIAB] OR behavio*[TIAB] OR neurobehavio*[TIAB]
	#6	#4 OR #5
Population_total	#7	#3 AND #6
Intervention_faecal	#8	Microbiota[MeSH] OR Feces[MeSH]
	#9	faecal[TIAB] OR fecal[TIAB] OR stool[TIAB] OR gut[TIAB] OR microbio*[TIAB] OR feces[TIAB] OR microflor*[TIAB] OR bacteri*[TIAB]
	#10	#8 OR #9
intervention_transplant	#11	transplants[MeSH] OR transplantation[MeSH]
	#12	infusio*[TIAB] OR transplan*[TIAB] OR transfer[TIAB] OR therap*[TIAB] OR graft*[TIAB] OR graft[TIAB]
	#13	#11 OR #12
intervention_faecal transplant	#14	"Fecal Microbiota Transplantation"[MeSH]
intevrention_total	#15	(#10 AND #13) OR #14
Total	#16	#7 AND #15

Search_LILACS_IBECS via BVS		
Items	*#*	*Search terms*
Population_children	#1	mh:("^dniño" OR "^dniño preescolar" OR "^drecién nacido" OR Child OR Infant OR pediatrics)
	#2	tw:(nin$ OR "recien nacido" OR "recien nacidos" OR bebe OR bebes OR chico OR chicos OR chica OR chicas OR infant OR infant$ OR newborn OR newborn$ OR neonat$ OR baby OR babies OR child$ OR child OR schoolchil$ OR preschool$ OR toddler OR toddler$ OR girl OR girl$ OR boy OR boy$ OR pediatric OR pediatric$ OR paediatric OR paediatric$)
	#3	#1 OR #2
Population_austism	#4	mh:("^dtrastornos del lenguaje" OR "^dTrastorno Autístico^sgenet" OR "^dtrastorno autístico^sterap" OR "^dtrastorno autístico^spsicol" OR "^dtrastorno autístico^sdiag" OR "^dtrastorno del espectro del autismo^sterap" OR "^dtrastorno del espectro del autismo^spsicol" OR "^dtrastorno del espectro del autismo^sdiag" OR "^dTrastorno Autístico^sgenet" OR "Child Development Disorders, Pervasive" OR "Intellectual Disability" OR "Mental Disorders")
	#5	tw:(desenvolv$ OR idom$ OR OR habla OR lenguaje OR esquizofre$ OR comportamient$ OR autis$ OR pervasiv$ OR PDD OR language OR speech OR schizophren$ OR kanner$ OR kanner OR asperge$ OR cogniti$ OR behavio$ OR neurobehavio$)
	#6	#4 OR #5
Population_total	#7	#3 AND #6
Intervention_faecal	#8	mh: ("^dmicrobiota^sfisiol" OR "^dHeces" OR "^dmicrobiota^sinmunol" OR "Heces/microbiología" OR Microbiota OR Feces OR "Heces/microbiología")
	#9	tw:(faecal OR fecal OR stool OR intesti$ OR gut OR microbio$ OR feces OR heces OR microflor$ OR bacteri$)
	#10	#8 OR #9
intervention_transplant	#11	mh:(transplants OR transplantation OR "Trasplante" OR "^dtrasplante de órganos^smétodos" OR "^dtrasplante")
	#12	tw:(trasplan$ OR infusio$ OR transpla$ OR transfer OR transfer$ OR therap$ OR terapi$ OR graft OR graft$ OR injerto OR injerto$)

	#13	#11 OR #12
intervention_faecal transplant	#14	mh:("Fecal Microbiota Transplantation" OR "Trasplante de Microbiota Fecal" OR "Diarrea/terapia")
intevrention_total	#15	(#10 AND #13) OR #14
Total	#16	#7 AND #15

Search terms_EMBASE via Ovid		
Items	*#*	*Search terms*
Population_children	#1	Child/ OR Infant/ OR pediatrics/
	#2	(infant OR infant* OR newborn OR newborn* OR neonat* OR baby OR babies OR child OR child* OR schoolchil* OR preschoo* OR toddler OR toddler* OR girl OR girl* OR boy or boy* OR pediatri* OR paediatri*).ab,ti
	#3	1 OR 2
Population_austism	#4	"Intellectual impairment"/ OR "Mental disease"/ OR autism/ OR "infantile autism"/ OR "pervasive developmental disorder not otherwise specified"/
	#5	(autis* OR "pervasive developmental disorder*" OR PDD OR "language" OR speech OR schizophren* OR kanner* OR asperger* OR cogniti* OR behavio* OR neurobehavio*).ab,ti
	#6	4 OR 5
Population_total	#7	3 AND 6
Intervention_faecal	#8	Microflora/ OR Feces/ OR "feces microflora"/
	#9	(faecal OR fecal OR stool OR gut OR microbio* OR feces OR microflor* OR bacteri*).ab,ti
	#10	8 OR 9
Intervention_transplant	#11	transplantation/ OR infusion/
	#12	(infusio* OR transplan* OR transfer OR therap* OR graft* OR graft).ab,ti
	#13	11 OR 12
Intervention_faecal transplant	#14	"Fecal Microbiota Transplantation"/
Intervention_total	#15	(10 AND 13) OR 14
Total	#16	7 AND 15

Search terms_SCOPUS via SCOPUS		
Items	*#*	*Search terms*
Population_children	#1	TITLE-ABS-KEY (infant OR infant* OR newborn OR newborn* OR neonat* OR baby OR babies OR child OR child* OR schoolchil* OR preschoo* OR toddler OR toddler* OR girl OR girl* OR boy or boy* OR pediatri* OR paediatri*)
Population_austism	#2	TITLE-ABS-KEY (autis* OR "pervasiv*" OR PDD OR "language" OR speech OR schizophren* OR kanner OR kanner* OR asperge* OR cogniti* OR behavio* OR neurobehavio*)
Intervention_faecal	#3	TITLE-ABS-KEY (faecal OR fecal OR stool OR gut OR microbio* OR feces OR microflor* OR bacteri*)
Intervention_transplant	#4	TITLE-ABS-KEY (infusio* OR transplan* OR transfer OR therap* OR graft* OR graft)
Total	#5	#1 AND #2 AND #3 AND #4

Search_COCHRANE via COCHRANE		
Items	*#*	*Search terms*
Population_children	#1	MeSH descriptor: [Child] explode all trees
	#2	MeSH descriptor: [Infant] explode all trees
	#3	MeSH descriptor: [pediatrics] explode all trees
	#4	(infant OR infant* OR newborn OR newborn* OR neonat* OR baby OR babies OR child OR child* OR schoolchil* OR preschoo* OR toddler OR toddler* OR girl OR girl* OR boy or boy* OR pediatri* OR paediatri*):ab,ti
	#5	#1 OR #2 OR #3 OR #4
Population_austism	#6	MeSH descriptor: ["Child Development Disorders, Pervasive"] explode all trees
	#7	MeSH descriptor: ["Intellectual Disability"] explode all trees
	#8	MeSH descriptor: ["Mental Disorders"] explode all trees
	#9	(autis* OR "pervasiv*" OR PDD OR "language" OR speech OR schizophren* OR kanner OR kanner* OR asperge* OR cogniti* OR behavio* OR neurobehavio*):ab,ti
	#10	#6 OR #7 OR #8 OR #9
Population_total	#11	#5 AND #10
Intervention_faecal	#12	MeSH descriptor: [Microbiota] explode all trees

	#13	MeSH descriptor: [Feces] explode all trees
	#14	(faecal OR fecal OR stool OR gut OR microbio* OR feces OR microflor* OR bacteri*):ab,ti
	#15	#12 OR #13 OR #14
Intervention_transplant	#16	MeSH descriptor: [transplants] explode all trees
	#17	MeSH descriptor: [transplantation] explode all trees
	#18	(infusio* OR transplan* OR transfer OR therap* OR graft* OR graft):ab,ti
	#19	#16 OR #17 OR #18
Intervention_faecal transplant	#20	MeSH descriptor: ["Fecal Microbiota Transplantation"] explode all trees
Intervention_total	#21	(#15 AND #19) OR #20
Total	#22	#11 AND #21