REVIEW

Sl- p, circadian rhythm and g t microbiota: alt rations in Alzh im r's dis as and th ir pot ntial links in th pathog n sis

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Introduction

A z e er's sease (AD) s a e e era ve ce ra ervous sys e (CNS) sor er, c arac er ze y a pro ress ve o se o euroco ve sy p o s, c u a es a, ap as a, sor e a o , e c[1] W e e e o o y o AD re a s ar e y u k ow , AD s e era y ea ure y e epos o o β a y o (Aβ) a e o r a o o eu ro r ary a es o au pro e CNS

T e u a o y ar o s a ar e var e y o cr oor a s co u es w c e s ve y erac w os a eac o er rou rec co ac s or e a o es[2] I as o ee pos u a e a u a u cro o a (GM), e co ec o o a cr oor a s co u es e u a es ve rac , o s rea s ca ce o u a ea a sease[3,4] oweve r, o u rece y ave we ee a e o ves a e er co pos o a u c o w e a va ces DNA seque c a e a e o c a ays s ec ques[5] Moreover, ra u ax s (BGA), w c s u es e erac o s e wee GM a CNS, as a e s ca a e o rece years T ere s uc ev e ce s ow a ere GM co pos o severa euro o ca seases, c u a k so 's sease (D) a au s spec ru sor er (ASD)[6–8] C a es GM co pos o a c ess ave a so ee o serve AD pa e s a v ua s w co ve pa r e (MCI),[9,10] su es a po e a ro e o GM ys os s AD pa o e es s

Severa eurode e era ve seases c u AD, D a u o sease (D) ave ee p ca e w s eep s ur a ce a c rca a r y ys u c o[11] W e s eep a c rca a r y s rup o (SCRD) are usua y reco ze as e co seque ces o ese seases, s u es ave repor e e ex s e ce o s eep sor ers o o o re e o se o AD a D, eve y eca es[12–15] Moreover, row ev e ce ca es a s eep s ur a ce a c rca a r y sa e ay co r u e o euro a a o , ow Aβ c eara ce e cacy,

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c ease co ce a o d eac ve oxyge spec es (R S), co po se oo a a e (BBB) a GM ys os s[16–18] owever, e p ese wo k evea e e co e a o e wee SCRD a AD, u o causa y, a u e wo k s ee e o eso ve s ssue

S u es e as ew eca es ave o g exa e co o e e a s d e u a GM, c u g e, e c e a s ess[19,20] Rece gs su gges a ove o e d s eep a c ca a y s ap g a o u a g e co pos o d GM[21] pa ewe e , o e es d ou k ow e ge, o ev ews o a e ave co s e e e poss e co u o s d sy e gs c e ac o s e wee SCRD a GM ys os s o e pa oge es s d AD I s ev ew, we s p ese ece s u es a exa e e GM a e a o s AD a SCRD We su a ze ose gs a co pa e e GM c a ges a o co pos o a a u c o a eve s ac oss s u es We o se e co o a es GM a e a o s d v ua ac e a a u a ous c a ges a u c o a eve e wee AD a SCRD co o s T e d o e, we scuss poss e e ac o s e wee SCRD a GM, w c co u e o AD o se y uc g pe p e a a ce a a o (F gu e 1) We easo a s s ac eve ou g va ous pa ways c u g

Table 1. Summary of studies investigating GM alteration in AD.

Reference	Participant/animal model	GM profiling method	Higher or lower bacterial taxa in AD patients/AD animal models	Other major findings
Human study				
26	43 AD patients and 43 age- and gender-matched HC Location: China	16S rRNA gene seq V3-V4 region	↑ Family: Enterococcaceae, Lactobacillaceae Genus: *Subdoligranulum* Species: *Ruminococcus gnavus* ↓ Family: Lachnospiraceae, Bacteroidaceae, Veillonellaceae Genus: *Lachnoclostridium, Bacteriodes*	
9	30 AD patients, 30 MCI patients, and 30 age- and gender-matched HC Location: China	16S rRNA gene seq V3-V4 region	↑ Family: Lachnospiraceae, Streptococcaceae, Erysiopelotrichaceae, Coriobacteriaceae, Lactobacillaceae, Bifidobacteriaceae Genus: *Akkermansia, Blautia, Dorea, Eggerthella, Streptococcus, Bifidobacterium, Lactobacillus* ↓ Family: Alcaligenaceae, Bacteroidaceae, Porphyromonadaceae, Pasteurellaceae, Rikenellaceae Genus: *Alistipes, Bacteroides, Butyricimonas, Haemophilus, Parabacteroides*	- Similar alteration of gut and blood microbiota in AD and MCI - Increased blood *Staphylococcus, Pseudomonas*, and *Escherichia* in AD and MCI vs. HC - *Dorea, Blautia*, and *Escherichia* as risk factors for AD
10	33 AD patients, 32 aMCI patients, and 32 age- and gender-matched HC Location: China	16S rRNA gene seq V3-V4 region	↑ Family: Enterobacteriaceae, Veillonellaceae ↓ Family: Clostridiaceae, Lachnospiraceae, Ruminococcaceae Genus: *Blautia, Ruminococcus*	- Progressive enrichment of Enterobacteriaceae distinguishes AD from aMCI and HC - Elevated bacterial secretion system and LPS biosynthesis
27	25 AD patients and 25 age- and gender-matched HC Location: USA	16S rRNA gene seq V4 region	↑ Family: Bacteroidaceae, Rikenellaceae, Gemellaceae Genus: *Blautia, Bacteroides, Alistipes, Bilophila, Gemella, Phascolarctobacterium* ↓ Family: Ruminococcaceae, Bifidobacteriaceae, Clostridiaceae, Peptostreptococcaceae, Mogibacteriaceae, Turicibacteraceae Genus: *Bifidobacterium, Dialister, Clostridium, Turicibacter, Adlercreutzia*	
28	40 Amy+ patients, 33 Amy- patients, and 10 HC Location: Italy	Microbial DNA qPCR Assay Kit	Amy+ *vs.* HC ↑ Genus: *Escherichia, Shigella* ↓ Species: *Eubacterium rectale, Bacteroides fragilis*	- Escherichia and Shigella correlate with pro-inflammatory IL-1β, NLRP3 and CXCL2 - Eubacterium rectale correlates with anti-inflammatory IL-10
Animal study				
29	Female APP/PS1 mice Control: female WT mice Age: 3, 6 and 24 months	16S rRNA gene seq V1-V3 region	↑ Family: Erysipelotrichaceae Genus: *Sutterella* ↓ Family: Rikenellaceae Genus: *Ruminococcus, Oscillospira*	- Progressive GM shift in AD mice at 3 months
30	Male SAMP8 mice Control: male SAMR1 mice Age: 6 months	16S rRNA gene seq V3-V4 region	↑ Genus: *Alistipes, Akkermansia, norank_f__Lachnospiraceae, Odoribacter, Streptococcus, Rikenella, Butyricicoccus* ↓ Genus: *Prevotella, Parasutterella, Butyrivibrio, Eubacterium, Ruminococcus, norank_f__S24_7*,	- Altered GM structure with decreased fermentation capacity - Dysregulated lipid, carbon and pyruvate metabolism
31	Male APP/PS1 mice Control: male WT mice Age: 6 months	16S rRNA gene seq V3-V4 region	↑ Family: Verrucomicrobiaceae, Desulfovibrionaceae, Staphylococcaceae, Corynebacteriaceae Genus: *Akkermansia, Staphylococcus, Desulfovibrio, unclassified_f__Erysiopelotrichaceae*, ↓ Family: S24_7, Prevotellaceae, Enterococcaceae Genus: *Faecalibaculum, Ruminococcaceae UCG-01, Alloprevotella, Enterococcus*	- Alleviated AD pathology in AD mice after FMT from WT mice - Increased level of butyrate in FMT-treated AD mice
32	Male SAMP8 mice Control: male SAMR1 mice Age: 7 months	16S rRNA gene seq V3-V5 region	↑ Genus: *uncultured Bacteroidales bacterium* ↓ Family: Clostridiales vadinBB60 group, Family XIII, Christensenellaceae, Ruminococcaceae, Desulfovibrionaceae, Deferribacteraceae Genus: *Mucispirillum, Serratia, Subdoligranulum, Ruminiclostridium, Coprococcus, Oscillibacter*	- Decreased spatial learning and memory function in WT pseudo GF mice after FMT from AD mice
33	Male APP/PS1 mice Control: male WT mice Age: 1, 3, 5–6, 8–12 months	16S rRNA gene seq V3-V4 region	↑ Family: Erysiopelotrichaceae, Verrucomicrobiaceae Species: *Desulfovibrio C21_c20* ↓ Genus: *Ruminococcus, Butyricicoccus* Species: *Butyricicoccus pullicaecorum*	- Lower level of SCFAs in feces and brain of AD mice - Disrupted intestinal structure
34	Male APP/PS1 mice Control: male WT mice Age: 3, 6 and 8 months	16S rRNA gene seq V3-V4 region	↑ Family: Helicobacteraceae, Desulfovibrionaceae, Coriobacteriaceae Genus: *Odoribacter, Helicobacter* ↓ Genus: *Prevotella, Ruminococcus*	- Impaired spatial learning and increased Aβ burden in AD mice

(*Continued*)

GM alterations in AD: from clinical and animal literature

Rece c ca o se va o s avel ou s g ca GM a e a o s o AD a MCI pa e s e e, we su a ze e a e a o s d GM co pos o AD pa e s co pa e o co os Ta e 1 (op) [9,10,26–28] I a , a a o e s a e a so use o e s u es, a e eva s a e su a ze Ta e 1 (o o) [29–36] No e a a sge c ce c u g A / S1, SAM 8, 5xFAD a e e va ves we e e os eque y use AD o e s [3] Su s a ces suc as D ga ac ose, Aβ p o e a popo ysacc a e (S) we e a so use seve a s u es o uce AD pa o o gy [38]

I as ee su gges e a α ve s y a ays s a F cu es/Bac e o e es (F/B) a o, wo e que y use c e a c o o e a ays s, a e o e a e ves ga g e assoc a o e wee GM a e a o a D

SCRD s u \es T e \ gs s owe \ e e r co co r \a ce a g e r axo o c reso u o T e r d o r e, GM a e r a o s a l a y, ge us a \ spec es eve a r e p r ese e \ e l o ow g a es (Ta es 1–5) Ge e r a y, we ave \ e e \ g e r eve d pa o o s a \ owe r eve d e e c a ac e r a o AD pa e s a \ a as (F gu r e 2)

T e p r o a a o y axa *Escherichia* a \ *Shigella* d E e r o ac e r aceae ave o g ee p r o pose \ o co r u e o se r es d gas r o es a \ seases [10] I c r ease \ eve d *E. coli* S as a so ee \ e ec e \ e pos o r e r a sa p es d AD pa e s [40] T e exo ox d *Escherichia* a \ *Shigella* cou \ \ s up e e gy d ep e a ce l u r e r ea \ g o eak y gu a \ l ac a es e r a s oca o d ac e r a o e oo \ [41] *E. coli* a o g w seve r a g r a e ga ve ac e r a possess sys e s l o p r o luc g ac e r a Aβ w c s a e o pe e r a e es a a r r e r a \ BBB a \ a e c r oss see \ g e CNS [42,43] I a \ \ o *Escherichia*, ac e r a Aβ p r o luc g sys e s ave a so ee l ou \ *Staphylococcus*, g g g s po e a r o e co r u g o AD pa o ge e s s [44] A ou g *Staphylococcus* was o \ e ec e \ u a l eca sa p e, s g e r a u \ a ce was l ou \ e oo \ d AD pa e s [9] S u \ es ave r epo r e \ a s r a s d *Ruminococcus gnavus* w c e o g o e l a y ac osp r aceae use e r a uc gyca s o \ e g r a \ e ucus aye r d es a a r r e r [45] I c r ease \ eve d *Ruminococcus gnavus* as ee assoc a e \ w a a o y owe \ s ease, su gges g e po e a r o e d *Ruminococcus gnavus* p r o o g a a o [46]

T e wo l a es Ru ococcaceae a \ C os r \ aceae, ajo r SCFA p r o luc g axa a a a GM, ave ee r epo r e \ o e \ ec r ease \ va r ous e a o ca \ eu r o \ e ge e r a ve \ seases [4] T e r e a ve a u \ a ce d Ru ococcaceae was l ou \ o e pos ve y co r r e a e \ w g e r M e a S a e Exa a o (MMSE) a \ Mo r ea Co g ve Assess e (MoCA) sco r es, w c \ ca es e e r co g ve l u c o s [10] owe r eve d a a a o y axa *Eubacterium rectale* a \ *Bacteroides fragilis* a o g w c r ease \ p r o a a o y cy o k es suc as I 1β, N R 2a \ CXC 8 ave ee a so \ e ec e \ AD pa e s [28] *Lactobacillus* a \ *Bifidobacterium* a r e wo co o p r o o c axa capa e d p r o lu c g eu r o r a s e r ga a a o u y r a e (GABA) w ose e a o s as ee r epo r e \ o e \ s up e \ AD pa e s [48] *Lactobacillus* a \ *Bifidobacterium* p ay a po r a r o e p r o ec g es a ce s a \ luc g a a a o y r espo ses [49,50] S u \ es ave s ow a p r o o c r ea e us g s r a s d *Lactobacillus* a \ *Bifidobacterium* was a e o a e o r a e sy p o s assoc a e \ w AD [51,52]

GM interventions restore the progression of AD

As s a e \ a ove, os s u \ es l ocus g o GM a \ AD p r ese e \ co r r e a o s u o causa r e a o s ps W e r e a sa ope ques o e e \, [53] seve r a s u \ es ave egu o \ e o s r a e ow GM affec AD pa o o gy y s ow g e e e c a effec s r oug GM e r ve o a a o \ e s, cu \ g p r o o c supp e e , [51,52,54–58] a o c r ea e , [59–64] ge r l ee (GF) a as [36,63,65] a l eca c r o o a r a sp a a o (FMT) [31,32,35,36,61,62] T ese success u r as suppo r e r o e d GM \ y os s co r u g o AD pa o ge e s s a \ p r o g r ess o a \ su gges po e a e e s d GM o u a o l o r AD r ea e (Ta e 2) (F gu r e 3)

Sleep, circadian rhythm and GM

A ou g u a gu ecosys e a a s r a e r es e , pe r u r a o y a o cs, g l a l oo \ a \ s r ess cou \ \ a ge es a o eos ass [3,66] T ese k ey \ e e r a s d GM ave ee s u \ e \ ex e s ve y ove r e pas \ eca \ es, u e r o e d s eep a \ c r ca \ a r y r egu a g GM was u \ e r es a e \ [6] Rece s u \ es ave s ow a u a GM \ sp ay \ u r a osc a o a o co pos o a a \ l u c o a eve s [68] I as ee sug ges e \ a SCRD ay ea \ o GM \ y os s r oug seve r a \ \ ec ways, cu \ g \ s up g e r y c uc ua o d GM, ac va g e A ax s, c r eas g l oo \ a \ e e r gy ake, \ ec r eas g p y s ca ac v y a \ \ a ag g gu a r r e r eg y [21,69, 0] I s pa r , we su a r ze r ece p r o g r ess r ega r \ g e co r r e a o e wee SCRD a \ GM \ y os s as we as ow SCRD pac s GM (Ta es 3, 4) k e e \ gs AD, c r ease \ pa o o s a \ \ ec r ease \ e e c a ac e r a we r e \ e e \ SCRD co \ o s o u a a \ a a o \ es

Table 2. Summary of studies investigating GM intervention and AD.

Reference	Participant/animal model	Treatment	Main findings (Exp *vs*. Con)
Probiotic supplement			
51	AD patients Exp: AD patients + probiotic milk Con: AD patients + normal milk	Duration: 12 weeks Probiotic milk contained *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum*, and *Lactobacillus fermentum*	- ↑ cognitive function - ↑ insulin and lipid metabolism
54	AD patients Exp: data after taking Omnibiotic Stress Repair Con: baseline data before probiotic treatment	Duration: 4 weeks Omnibiotic Stress Repair contained 9 strains from *Lactococcus, Lactobacillus*, and *Bifidobacterium*	- ↑ *Faecalibacterium prausnitzii* - ↑ tryptophan metabolism and serum kynurenine
55	Female App^{NL-G-F} mice Exp: AD mice + VSL#3 Con: AD mice + vehicle (water)	Duration: 8 weeks VSL#3 contained 8 strains of lactic acid-producing bacteria	- ↓ intestinal inflammation and gut permeability
52	Male 3xTg-AD mice Exp: AD mice + SLAB51 Con: AD mice + vehicle (water)	Duration: 4 months SLAB51 contained 9 live probiotic strains	- ↓ cognitive impairment and brain damage - ↓ pro-inflammatory cytokines - ↓ Aβ deposition in brain
56	Male ddY mice + intra-hippocampal Aβ injection Exp: AD mice + probiotic supplement/ acetate Con: AD mice + vehicle (water)	Duration: starting 2 days before Aβ injection Probiotic supplement: living, heat-killed or fragmented *Bifidobacterium breve* A1	- ↓ cognitive impairment - Altered gene expression in hippocampus - ↑ plasma acetate by *B. breve* A1 - Partially attenuated behavioral deficit by non-viable *B. breve* A1 and acetate
57	Male Wistar rats + intra-hippocampal Aβ injection Exp: AD rats + probiotic supplement Con: AD rats + vehicle (water)	Duration: 8 weeks Probiotic supplement: *Lactobacillus acidophilus, Lactobacillus fermentum, Bifidobacterium lactis*, and *Bifidobacterium longum*	- ↑ spatial memory - ↓ Aβ deposition in brain - ↓ oxidative stress response
58	Male Sprague-Dawley rats Exp: (1) rats + antibiotic, (2) rats + antibiotic + probiotic Con: rats + vehicle (water)	Duration: 41 days Antibiotic: ampicillin Probiotic: *Lactobacillus fermentum* NS9	- Disrupted GM in (1) and normalized GM in (2) - ↓ colon inflammation in (2) *vs*. (1) - ↑ spatial memory in (2) *vs*. (1)
Antibiotic treatment			
59	Male APP/PS1 mice Exp: AD mice + ABX treatment Con: AD mice + vehicle (water)	Duration: post-natal day 14 to day 21 ABX contained 9 antibiotics	- Altered GM composition - ↓ Aβ deposition in the brain - ↓ glial reactivity at Aβ plaque - ↓ neuroinflammation
60	Male APP/PS1 mice Exp: AD mice + ABX treatment Con: AD mice + vehicle (water)	Duration: lifespan ABX contained 9 antibiotics	- Altered GM composition - ↓ Aβ deposition in the brain - ↓ neuroinflammation and reactive gliosis at Aβ
61	5xFAD mice Exp: AD mice + ABX treatment Con: AD mice + vehicle (water)	Duration: 5 months ABX contained ampicillin, streptomycin and colistin	- ↓ GM abundance - ↓ infiltration of pro-inflammatory Th1 cells and M1 cells into the brain
62	APPPS1-21 mice Exp: (1) male + ABX, (2) female + ABX Con: male/female + vehicle (water)	Duration: lifespan ABX contained kanamycin, gentamicin, colistin, metronidazole and vancomycin	- Sex-specific gut microbiota alteration - (1): ↑ anti-inflammatory cytokines, ↓ Aβ, and ↓ phagocytic microglial at Aβ - (2): ↑ pro-inflammatory cytokines, no change of Aβ deposition, and ↑ phagocytic microglial at Aβ
63	Male 5xFAD mice Exp: AD mice + ABX treatment Con: AD mice + vehicle (water)	Duration: 2 months ABX contained vancomycin, cefoxitin, gentamicin, and metronidazol	- ↑ ceca size and weight - ↓ level of hippocampal Aβ - ↑ cognitive function

(*Continued*)

Table 2. (Continued).

Reference	Participant/animal model	Treatment	Main findings (Exp *vs*. Con)
64	Male APPPS1-21 mice Exp: (1) AD mice + ABX, (2) AD mice + individual ABX Con: AD mice + vehicle (water)	Duration: lifespan ABX contained kanamycin, gentamicin, colistin, metronidazole, and vancomycin	- ↑ ceca size and altered GM composition - ↓ Aβ deposition only in (1)
Germ-free animal			
36	APP/PS1 mice Exp: GF AD mice Con: conventionally raised AD mice	GF mice: embryos were washed with Invitrogen and transferred to GF pseudo-pregnant mice	- ↓ Aβ level and Aβ deposition - ↓ neuroinflammation - ↑ Aβ-degrading enzyme
65	Female APP/PS1 mice Exp: (1) SPF AD mice, (2) GF AD mice Con: (3) SPF WT mice, (4) GF WT mice		- Altered GM composition in (1) *vs*. (3) - ↓ cognitive function in (1)(2) *vs*. WT - ↑ Aβ and neuroinflammation in (1) *vs*. (2) and (3) - ↑ MAPK signaling pathway in (1) *vs*. (2) and (3)
63	Male 5xFAD mice Exp: GF AD mice Con: SPF AD mice	GF mice were generated through embryo transfer	- ↑ ceca size and weight - ↓ Aβ and neuroinflammation - ↑ cognitive function - ↑ Aβ uptake by microglial
FMT and co-housing			
35	Female ADLP^{APT} mice Exp: AD mice + WT FMT Con: AD mice + vehicle (water)	Duration: 16 weeks FMT: oral gavage	- ↓ cognitive impairment - ↓ Aβ, tau pathology, and glial activity - ↓ expression of inflammation-related genes
36	GF APP/PS1 mice Exp: (1) GF AD mice + AD FMT, (2) GF AD mice + WT FMT Con: GF AD mice + vehicle (water)	FMT: oral gavage	- ↑ overall Aβ level in (1) and (2) - Higher level of increased brain Aβ42 in (1) *vs*. (2)
61	WT mice Exp: WT mice co-housed with AD mice Con: WT mice separately housed with AD mice	Duration: 7 months	- ↓ discriminating learning - Similar GM and cytokine expression to AD mice - ↑ infiltrating Th1 cells into brain
61	(1) WT mice + Aβ injection + AD FMT (2) AD mice + WT FMT (3) WT mice + Aβ injection + GV-971-treated AD FMT	FMT: oral gavage	- (1) ↑ Th1 cells and ↓ Th2 cells in brain - (2) ↓ Th1 cells in brain - (3) ↓ Th1 cells in brain
31	Male APP/PS1 mice Exp: AD mice + WT FMT Con: AD mice + vehicle (water)	FMT: oral gavage	- ↓ neuroinflammation - ↓ Aβ deposition and tau phosphorylation - ↓ GM dysbiosis and cognitive deficits
32	Male pseudo GF WT mice Exp: (1) GF mice + SAMP8 FMT, (2) GF mice + SAMP1 FMT Con: GF WT mice + vehicle (water)	Duration: 14 days FMT: oral gavage	- ↓ cognitive function in pseudo GF mice - Restored GM composition in (2) not (1) - ↑ cognitive function in (2) not (1)
62	ABX-treated male APPPS1-21 mice Exp: ABX-treated AD mice + AD FMT Con: ABX-treated AD mice + vehicle (water)	Duration: lifespan FMT: oral gavage	- ↑ Aβ plaque burden - GM profile similar to AD mice - Microglial morphologies similar to AD mice

Note: Exp = experimental group, Con = control group, ABX = antibiotic cocktail, GF = germ-free, SPF = specific pathogen-free, ↑ = increase, ↓ = decrease.

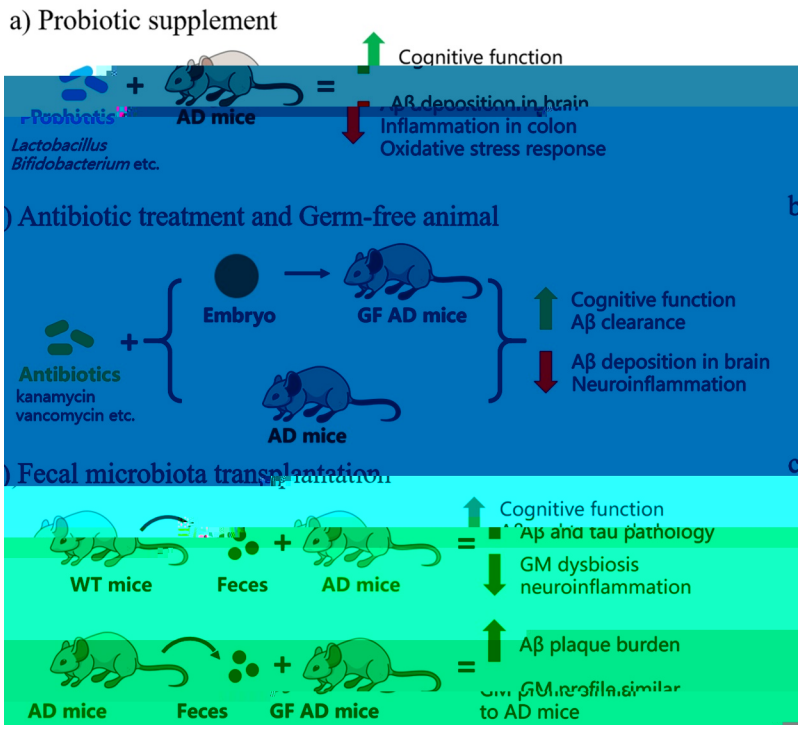

Figure 3. GM intervention studies in AD animal models. (a) Probiotic supplement study: AD mice feed with probiotic strains of *Lactobacillus* and *Bifidobacterium* showed reversed cognitive dysfunction, decreased Aβ deposition in brain and lower level of colon inflammation. (b) Antibiotic treatment and germ-free (GF) animal study: antibiotic treated embryo was transferred to pseudo-pregnant mice to generate GF mice. Both GF AD mice and AD mice feed with antibiotic display improved cognitive function, increased Aβ clearance and alleviated neuroinflammation. (c) Fecal microbiota transplantation (FMT) study: FMT from healthy wild-type (WT) donor could restore GM dysbiosis, ameliorate Aβ and tau pathology, and downregulate neuroinflammation in AD mice, whereas GF AD mice receiving FMT from AD mice show aggravated Aβ burden and GM profile similar as observed in AD mice.

Sleep disturbance and GM alterations

GM a e a o s u a a l a a o le s cause l y seep l su a ce o f e a e l o s eep qua y a e p ese e l Ta e 3 (op) [1– 4] a l Ta e 3 (o o), [5–80] espec ve y To la e, o y a ew s u l es exp o e l e effec s d s eep pac g o GM u a s, es c g e l ocus o e assoc a o e wee spec c ac e a axa a l s eep qua y ase l o s u g s eep qua y dex (SQI) o s eep p y s o o gy Two s u l es co pa e l e GM d l v lua s a e s o e s eep lep va o w ase e la a co ec e l d o e lep va o [1,81] Bu e f l gs a e a g e y co s s e , k ey ow g o l s c expe f e a les g s a l seve a u co o e l va a es, c u l g la y l ea y a l e e gy ak e d e su jec s T e d o e, l ew co o a es GM c a ges ca e co c u le l o u a su l es I co as, u pe a a ase l expe f e a su l es a l ocus o e pac s d o g e f s eep lep va o a l ag e a o o GM co pos o ave ee co luc e l, w a g e y le ca esu s d GM a e a o s

Increased bacterial taxa by sleep disturbance

I u a s, pa a s eep lep va o a l poo f s eep qua y esu e l o e a u la E y s ope o f c aceae, evo e aceae a l Co o ac e aceae a l a y eve (Ta e 3, op) S eep lep va o a l ag e a o a as co f u e l o GM ys os s l ea u e l y c ease l Ru ococcaceae, ac osp aceae, E y s ope o f c aceae, E e o ac e aceae a l S ap y ococcaceae a l a y eve , a l *Ruminococcus, Prevotella, Escherichia* a l *Shigella* a ge us eve (Ta e 3, o o)

evo e aceae s a so a u oge c ac e a axo g y coa e l y IgA [82] I as a so ee sugges e l a spec es d evo e aceae cou l luce es a a a o , s ow e

Table 3. Summary of studies examining the impact of sleep disturbance on GM and correlation between sleep quality and bacterial taxa.

Reference	Participant/ animal model	GM profiling method	GM alterations by sleep disturbance/correlated with poor sleep quality	Other major findings
Human study				
71	9 healthy males Partial SD *vs.* NS Location: Sweden	16S rRNA gene seq V4 region	↑ Family: Coriobacteriaceae, Erysiopelotrichaceae	- Increased insulin resistance and fasting insulin level
72	28 healthy adults PSQI for sleep measuring Location: USA	16S rRNA gene seq V4 region	+ Genus: *Prevotella* - Family: Lachnospiraceae Genus: *Blautia, Ruminococcus*	
73	37 adults aging from 50 to 85 PSQI for sleep measuring Location: USA	16S rRNA gene seq	- Phylum: Verrucomicrobia, Lentisphaerae	- Better Stroop and Color-Word performance were associated with better sleep quality
74	22 healthy males Actiwatch for sleep measuring Location: USA	16S rRNA gene seq V4 region	+ Family: Lachnospiraceae Genus: *Blautia, Lachnospiraceae UCG-004, Oribacterium* - Genus: *Lachnospiraceae ND3007*	
Animal study				
75	Male C57BL/6 J mice Chronic SF *vs.* NS	16S rRNA gene seq V4 region	↑ Family: Lachnospiraceae, Ruminococcaceae ↓ Family: Lactobacillaceae, Bifidobacteriaceae	- Increased food intake, VWAT, inflammation, insulin resistance, and gut permeability - Enhanced inflammation in GF mice after FMT from SF mice
76	Male C57BL/6 J mice Short SD *vs.* NS	16S rRNA gene seq V3-V5 region	↑ Family: Lachnospiraceae Genus: *Moryella* ↓ Genus: *Oxobacter*	- Subtle GM alteration by short period of SD
77	Male Wistar-Kyoto rats SF *vs.* NS	16S rRNA gene seq V4 region	↑ Genus: *Escherichia, Shigella, Enterococcus, Lachnospiraceae UCG-008* ↓ Genus: *Butyrivibrio, Oscillospira, Eubacterium, Dorea* Species: *Eubacterium ruminantium*	- Increased mean arterial pressure
78	Male C57BL/6 N mice SD *vs.* NS	16S rRNA gene seq V4 region	↓ Family: Bifidobacteriaceae, Lactobacillaceae, Turicibacteraceae Genus: *Bifidobacterium, Lactobacillus, Turicibacter*	- Reduced fecal bile acid and triterpenoids
79	Sprague Dawley rats Acute SF (ASF) *vs.* NS Chronic SF (CSF) *vs.* NS	Distal ileum (D), cecum (C), and proximal colon (P) samples 16S rRNA gene seq	ASF ↑ Family: Enterobacteriaceae (D), S24-7 (D), Ruminococcaceae (C) Genus: *Oscillospira* (C), *Bacteroides* (C), *Prevotella* (C) ↓ Family: Lactobacillaceae (D) Genus: *Lactobacillus* (P) CSF ↑ Family: Staphylococcaceae (D), Clostridiaceae (D)(P), Erysipelotrichaceae (P), Ruminococcaceae (P) Genus: *Prevotella* (P), *Clostridium* (P) ↓ Family: Lactobacillaceae (D)	- Increased microbial invasion - Altered intestinal structure but not gut barrier integrity - Increased KC/GRO level
80	Male Wistar rats Paradoxical SD *vs.* NS	16S rRNA gene seq	↑ Genus: *Parabacteroides, Ruminococcus, Aggregatibacter, Phascolarctobacterium* ↓ Genus: *Akkermansia, Oscillospira*	- Depression-like behavior - Increased CRH, ACTH, and CORT and pro-inflammatory cytokines IL-6, TNF-α, and CRP - Decreased arginine, proline, and pyruvate metabolism

Note: NS = normal sleep, SD = sleep deprivation, SF = sleep fragmentation, PSQI = Pittsburgh Sleep Quality Index, FMT = fecal microbiota transplantation, GF = germ free, ↑ = increase, ↓ = decrease, + = positively correlated, – = negatively correlated.

leve op e d ucus aye a la e vo ve
va ous es a seases c u g IBD a
co s[8] No e a a oug s eep s u a ce
c ease a u la ce d Ru ococcaceae a
ac osp aceae u e su jec s, s a y
lue o c ease oo a e as o a es a e
g y e e a ve ac e a u z g e p a
le ve e a po y sacc a es c ow oo [5]

Decreased bacterial taxa by sleep disturbance

I u a s u es, a lec e e e a ve
a u la ce d *Ruminococcus* s co e a e w
poo s eep qua y (Ta e 3, op) I a a
su jec s, ac o ac acea, B o ac e aceae,
Tu c ac e aceae a o a y a ge us
eve , o ge e w *Eubacterium* a
Akkermansia a ge us eye , ex e s g
ca lec ease a e s eep lep va o (Ta e 3,
o o)

Eu ac e aceae a o g w C os aceae,
ac osp aceae a Ru ococcaceae a e po
a SCFAs

Table 4. Summary of research studying the impact of circadian rhythm disruption on GM.

Reference	Participant/ animal model	GM profiling method		GM alterations by circadian rhythm disruption	Other major findings
Human study					
87	10 healthy males Night shift *vs.* day shift Location: Turkey	16S rRNA gene seq	↑	Family: Coriobacteriaceae, Erysipelotrichaceae, Prevotellaceae, Lachnospiraceae Genus: *Dorea, Coprococcus* Species: *Ruminococcus torques, Ruminococcus gauvreauii*	
			↓	Species: *Faecalibacterium prausnitzii*	
68	2 healthy individuals After jet lag *vs.* before jet lag	16S rRNA gene seq V1-V2 region	↑ ↓	Phylum: Firmicutes Phylum: Bacteroidetes	- Human GM showed diurnal oscillation - FMT from jet-lagged individual into GF mice caused weight gain and body fat accumulation
88	22 healthy adults Acute sleep-wake cycle shift After shift vs. before shift Location: China	16S rRNA gene seq V4 region	↑ ↓	Family: Pasteurellaceae, Fusobacteriaceae Genus: *Dialister, Escherichia, Shigella* Family: Peptostreptococcacea, Desulfovibrionaceae Genus: *Ruminococcaceae UCG-013*	- Acute sleep-wake cycle shift had limited impact on GM
Animal study					
89	Male C57BL/6 J mice Inverted light (IN) *vs.* LD	16S rRNA gene seq V4 region	↑ ↓	Genus: *Barnesiella, Clostridium, Lactobacillus* Genus: *Turicibacter*	- Increased weight gain, inflammation, and insulin resistance - Disrupted gut barrier by fecal water of IN mice
90	Male C57BL/6 J mice LL *vs.* LD	16S rRNA gene seq	↑ ↓	Species: *Ruminococcus torques* Genus: *Subdoligranulum* Species: *Lactobacillus johnsonii, Eubacterium plexicaudatum*	- Increased LPS synthesis and decreased SCFAs and indole metabolism - Disrupted gut barrier integrity
91	Male rats LL *vs.* LD DD *vs.* LD	16S rRNA gene seq V3-V4 region	LL ↑	Family: Erysiopelotrichaceae, Bacteroidaceae, Prevotellaceae, Lactobacillaceae Genus: *Blautia, Prevotella, Lactobacillus, Faecalibacterium*	- Increased anxiety and activity
			LL ↓	Family: Ruminococcaceae, Porphyromonadaceae Genus: *Parabacteroides*	
			DD ↑	Family: Erysiopelotrichaceae, Prevotellaceae, Lactobacillaceae Genus: *Blautia, Prevotella, Lactobacillus, Faecalibacterium*	- Decreased activity - Decreased DA and NE in urine
			DD ↓	Family: Ruminococcaceae, Porphyromonadaceae Genus: *Parabacteroides, Bacteroides, Ruminococcus*	
68	WT mice Jet lag *vs.* LD	16S rRNA gene seq V1-V2 region	↑ ↓	Family: Prevotellaceae, Rikenellaceae Family: Christensenellaceae, Anaeroplasmataceae Genus: *Lactococcus, Dorea, Lactobacillus, Ruminococus*	- Mice GM exhibited diurnal oscillation - Disrupted diurnal rhythmicity of GM by jet lag

Note: LD = normal light cycle, LL = constant light, DD = constant dark, FMT = fecal microbiota transplantation, GF = germ free, ↑ = increase, ↓ = decrease.

Faecalibacterium was e o y s e ac e a axa cause y c ca a y s up o a ge us eve *Faecalibacterium prausnitzi*, e so e spec es d ge us *Faecalibacterium*, s o e d e os a u a ac e a u a GM ep ese g o e a 5% d ac e a popu a o es e[96] I ac s as a po a SCFA u y a e p o uc g axo , s a o o e e s *Ruminococcaceae* a y[9] Mo eove , s u es ave epo e a ega ve assoc a o d *Faecalibacterium prausnitzi* w va ous a a o y owe s eases c u g C a CD, sugges g a cou e a ea ca o[96]

Linking GM, sleep, circadian and AD

GM and AD – causal or coincidental?

W a s e o e d GM ys os s AD? I e a s e a a e w e e GM ys os s p ays

as causa of

Table 5. Summary of the trend of GM alteration in AD and SCRD.

Taxonomic level	Trend	Implication in health and disease

w e a ayz g e ove app g d GM a e a o s
ffe e co o s, we co uc sepa a e eva ua
o s u a s a fo e s I u a s, SCFAs
p o uc g Ru ococcaceae a a y o ge us
eve s s ow o e s g ca y owe e e
co o , w e eas g y u og c ac e a
c u g E ys ope o c aceae a
Co o ac e aceae a a y eve a e s ow o e

s g ca y g e eac co o Mos o e
GM co po e s a e co s s e e wee ffe e
co o s, so e es ue o o e eva a a
ava a e a p ese (Ta e 5) I a a o e s,
s a e s a e o se ve seve a ac e a
v ua s e wee ffe e co o s Fo exa p e,
e e c a ac e a c u g ac o ac aceae,
B o ac e aceae, Tu c ac e aceae a

[illegible]

s g ca y ec ease x9qAB5xx eep s u a ce a /o c ca a s up o , a o e pa s d pa o o s a e u o y c ease , w e excep o d Ru ococcaceae As s a e a ove, 0x450Bcases Ru ococcaceae u g s eep s

[illegible]

Nex , we e uc a e e po e a o e d GM ys os s e eve op e d AD y p ov g e ev e ce d ow GM e ve o s, c u g p o o cs, a o cs, ge ee ea e a FMT, es o e co g ve u c o s a a ev a e AD pa o o y (Ta e) (F gu e) A ou g va ous A6 o s o u a e GM co pos o , e e g g ev e ce as ca e a SCRD cou s u GM a ea o GM ys os s Mos u a s u es e e y ves ga e e co e a o e wee SCRD a GM ys os s, w e a a s u es p ov e o e s g s o GM a e a o s u e ffe e SCRD co o s

spec c c a ges ce a spec es S g ca y, e e oge e y d e o lo o ges app e l o ge e c a e a ex ac o , DNA seque c g e l es y e d su jec s a l e o s l o l a a a ays s cou l co p o se e esu s a o g l ffe e s u l es a l ea l o co s s e cy, w c cou l e expec e l u a s u l es We sugges a l u e wo k s ee le l o specl y e a e a o d GM a spec es a l eve s a eve , a l co po a e e a o c a l l u c o a a ays s o eyea poss e ec a s s k gGM ys os s a l l seases us gs a la l ze l expe e a les g a l l a a a ays s

Phylogenetic

ea g o e co s s e a a e g g e o e d ac osp aceae ea a sease

Akkermansia muciniphila (*A. muciniphila*) s a o e po a SCFA p o uce a u zes uc as ca o sou ce [110] owe ve , e uce a u a ce d *A. muciniphila* as ee assoc a e w a a o y owe seases a e eva e a a o [85] Seve a ev ews ave a so sug es e *A. muciniphila* as a p o s g p o o c ea g e a o c so e s a o ua g u e espo ses [111,112] D ffe e o e uc e g a g axa, *A. muciniphila* was a so ou o p o o e uc p o uc o , esp e s a y o ea ow ucus aye [113] Neve e ess, c ease eve d *A. muciniphila* was ou D pa e s a so e oppos e effec s ave ee epo e [6,85]

Controlling variables in human studies

A co pos o a eve , a weak co ec o d GM c a ges e wee u a a a su es ca e es a s e s ce u a a u e a o s a ye s c c oo ga s s, a ou g a s a e e d GM a e a o s was o se ve a u c o a eve owe ve , co pa e o u a , a a o e s ex e o e co s s e GM a e a o s o AD a SCRD s u es T s sc epa cy s a y ue o e e su es ava a e, e e o ge eous sa p es a ffe e e o oo ges app e u a su es

I a a su es, ce a fa s we e o w e ca ge e c ad g ou , ouse co s a e v o e a e w u e oo , a va a es a cou co p o se e su y ave ee ca d u y co o e as poss e W e eas u a su es, u pe ac o s c u g face, a o a y, cu u e ad g ou a e uca o ay ave su s a a pac s o e es y e, a y e a ea g a d pa c pa s, w c ec y affec GM co pos o [114] Fo exa p e, pa c pa s d e ve AD pa e s s u es we ave scusse a ove we e o ee co e s w ve se cu u e ad g ou I as ee epo e a e pays a u a e a o e ea a s a key e e a d GM [115,116] Wes e sy e e, g a a p o e , sug a a a a ow ve ge a es, a vo s e g ow d Bac e o e es, espec a y *Prevotella*, w c as ee assoc a e w co o ca ce a seve a owe seases [11] Me e a ea e, ea u e y u , pa e a u sau a e a, s s GM owa o e a u a *Akkermansia, Bifidobacterium* a *Lactobacillus* [11] A so, oo c e a y e a ca o y a es p o o es e g ow d g y e e ave ac e a suc as ac osp aceae, ac o ac aceae a Ru ococcaceae e p y u F cu es [9] T us, e ve se e a y cou co u e o e scepa GM a e a o s AD pa e s o ffe e cou es Mo eove, e va e expe e a es g s a e e o ge eous e o s, cu g eca sa p e acqu e e , DNA ex ac o a seque c g as we as e c e a e e g co g ve u c o a seep qua y, ake cu o co c u e a co s s e e d GM a e a o s o ffe e su es

T e d o e, see s p ope o co pa e GM a e a o s u a su es so e y ase o ow eve p y o ge e c a ays s, w c ca e eas y affec e y e a ove e o e ac o s owe ve , we o se ve a co e e e y ak g e pe spec ve d e a o s a u c o s (Ta e 5, F gu e 4)

Conclusion

Base o e eva ua o s o ffe e su es o GM a o co pos o a a u c o a eves, s ev ew sug es s a poss e k e wee SCRD a AD y GM We p opose a o g e SCRD ay ec y ea o c o c GM ys oss y a e g ea g a , es ye, e a o s , ec SCRD a GM ys os s cou wo k sy e gs ca y o co u e o e o se a p o g ess o d AD (F gu e 5) owe ve , e co u o d s a e a ve pa way e eve op e d AD e a s u ce a a equ es u e e uc a o , s ce e e oo gy d spo a c AD va es o pe so o pe so [118] A so, o e su es a e ee e o u e e o s a e espec c ec a s s d ow SCRD ea s o GM ys oss a ow p o o ca a o c ea e a e o a e AD pa oo gy, as we as e po e a p ca o s d pa o o s suc as E ys ope o c aceae a Co o ac e aceae ea a sease

Disclosure statement

No po e a co c d e es was epo e y e au o s

ORCID

Yo g g p //o c o g/0000 000 1066 54 1

References

1 As a GM, Ta asov VV, C u a ev MACA, Av a Ro guez VN, Bac u M, A ev G S T e poss y d a ec ous e o og y d a z e e sease Mo Neu o o 019;56(6) 44 9–4491 o 10 100 /s1 035 018 1 88 y

Se e R, Fuc s S, M o R Rev se es a es o e u e d u a a ac e a ce s e o y oS B o 016;14(8) e100 53 o 10 1 1/jou a p o 100 53

Ze e g , B e ow , e a Gu c o o e a e a o s A z e e s ease Sc Rep 201 ; o 10 1038/s41598 01 13601 y

28 Ca a eo A, Ca a e N, Ga uzz S, ovas S, op zzo N, Fes a C, Fe a C, Gue a , ag e a B, Musc o C, e a Assoc a o d a a y o oss w p o a a o y gu ac e a axa a pe p e a a a o a e s cog vey pa e e e y Neu o o Ag g 201 ;49 60–68 o 10 1016/j eu o o a g g2016 08 019

29 Baue C, Co a o MC, D az Cuevas A, V a J, e ez Ma ez G S s gu c o o a co pos o a A / SS1 a sge c ouse o e d A z e e s s ease u g espa e App M c o o 2018;66 (6) 464–4 1 o 10 1111/ a 12888

30 e gW, Y , Ya gJ, Xu , Wa gY, Z a gZ, ua gS, Wa gZ, Z a gC Assoc a o d gu c o o a co pos o a u c o w a se esce ce acce e a e ouse o e d A z e e s D sease us g 16S RNA ge e a e age o c seque c g a ayss Ag g (A a y NY) 2018;10(12) 4054–4065 o 10 1863 / ag g 10169

31 Su J, JX X, g Y, Fy W, Ty G, Cw Y, Sq Y, y Y, D W, ZQ S, e a Feca c o o a a spa a o a ev a e A z e e s ease ke pa oge es s A / S1 a sge c ce T a s syc a 2019;9 o 10 1038/s41398 019 0525 3

32 Z a GF, Ya gN, S, ua gNN, Fa gX, Z a gJ, Z u B, Ya g , Ya gC, uo A A o a gu c o o a co pos o co u es o cog ve y u c o SAM 8 ce Ag g s 2018;10(6) 1225 –1236 o 10 1863 /a g g 101464

33 Z a g , Wa gY, X a XY, S C , C e W, So gN, Fu XJ, Z ou R, Xu YF, ua g , e a A e e gu c o o a a ouse o e d A z e e s ease J A z e e s D s 201 ;60(4) 1241–1245 o 10 3 /Ja 1 00820

34 S e , u , J F A z e e s ease s oogca a e av o a a es a o s a sge c ce co e a e w spec c gu c o o e sa e J A z e e s D s 201 ;56(1) 85–90 o 10 3 /Ja 160884

35 MS, Y, C o , W, a S, ee D, D, J, C o , yu DW, e a T a s e d a ea y c o o a e uces a y o a au pa o ogy a A z e e s ease a a o e Gu 2020;69(2) 283–294 o 10 113 6/ gu j 2018 1 4 1

36 a ac T, Ma u gua gN, Du eu N, C ea a V, Mc Coy D, F so G, Ne e JJ, Fa k F, Juc e M, asse T, e a Re uc o d A eaa y o pa oogy A S1 a sge c ce e a se ce d gu c o o a Sc Rep 201 ; o 10 1038/s ep41802

37 owas k , Ba a Gu M c o o a MA Ax s A z e e s ease J Neu ogas oe e o 2019;25 (1) 48–60 o 10 5056/j 1808

38 T c es A, Ta a C, Nouve e A, a B, au e a F, Mesc T Gu c o o a, cog ve a y a e a o e v ua s a sys e a c ev ew C I e v Ag g 2018;13 149 –1511 o 10 14 / C a S1 916

39 Ge a S, Mo aje M C a ges d co o c ac e a co pos o a so 's ease a o e eu o e ge e a ve seases Nu e s 2018 10 o 10 390/ u10060 08

40 Z ao Y , Co g , Ja e V, u w WJ M c o o e e ve popoysacc a e e c e e pe uc ea e go d A z e e s ease a F o I u o 201 8 o 10 389/ u 201 01064

41 o g J, We s J, Ca D, Ga c a Ro e as C , MacDo a T, Me ce e A, W y e J, T oos F, B u e RJ u a es a a e u c o ea a ease C T a s Gas oe 2016 o 10 1038/c g2016 54

42 Ga oway S, Ta k ec R, MMS G, D a wa SS, Ma o JC A y o e a co oca zes w apo pop o e B a so p ve ce s d es a es e p s ea D s 2009 8 o 10 1186/14 6 511x 8 46

43 o qv s S, C u a , Bousse , A k , W, Bjo u T, Wa g ZY, Roy o , Me k R, JY D ec ev e ce d a so pa oogy sp ea i o e gas o es a ac o e a as Ac a Neu opa o 2014;128(6) 805–820 o 10 100 / s00401 014 1343 6

44 s o a o F, Ca o SS, E o I, Ve a a MM, G a pe e F, Ba o M Roe d gu c o o a a u e s a y o o a o a pa oge ess d A z e e ease Nu Rev 2016; 4(10) 624–634 o 10 109 / u / uw023

45 C os E , Ta o E, Mo es e M, Swa ed D, e ssa B, C oss a C, Juge N T e uc eg a a o s a eg d Ru ococcus g avus e po a ce d a o ecu a a s s a ases Gu M c o es 2016; (4) 02 –12 o 10 1080/194909 6 2016 1186334

46 Sc e e M, Ga e e A, V a k s , Xav e RJ M c o a ge es a pa ways a a o y owe ease Na Rev M c o o 2019;1 (8) 49 –511 o 10 1038/s415 9 019 0213 6

47 Nguye TT, a away , osc o e k T, g R, Jes e DV Gu c o o e se ous e a esses a sys e a c ev ew a c ca eva ua o Sc zop Res 2019 o 10 1016/j sc es 2019 08 026

48 VDR D , Fo e za AS, Fo e za V Re eva ce d gu c o o a cog o , e av ou a A z e e s ease a aco Res 2018;136 29– 4 o 10 1016/j p s 2018 0 00

49 R v e e A, Se a k M, a D, e oy F, De Vuys B o ac e a a uy a e p o uc g co o ac e a po a ce a s a egies o e s u a o e u a gu Fo M c o o 2016; 9 9 o 10 389/ i c 2016 009 9

50 Y A, eog JB, C i o M o o cs, p e o cs, sy o cs a su se s v y Nu Res Rev 2018;31 (1) 45–51 o 10 101 /S0954422411 00018x

51 A a E, Ase Z, Da es va a k R, Ba a F, ouc k E, Ta aj R, a GA, Sa a M Effec

d o o c supp e e a o o co g ve u c o a \ e a o c s a us A z e e s D sease a a lo ze , lou e \ a \ co o e \ a F o Ag g Neu osc 2016;8 256 lo 10 89 ag 2016 00256

5 Bo , Ceca V, Be a \ S, Sca po a S, Suc o lo s JS, Nasu C, F o D, Boa e MC, Ross G, E eu e AM M c o o a o u a o cou e ac s A z e e s \ sease p o g ess o ue c g eu o a p o eo ys s a \ gu o o esp as a eve s Sc Rep 201 ; (1) 4 6 lo 10 1038/s41598 01 0258

5 I z a RF, Go e TE, e a MT, Rea \ ea \ B Do ec o s ave a o e e pa oge ess d A z e e \ sease? Na Rev Neu o 2020;16(4) 19 –19 lo 10 1038/s41582 020 0 9

54 e u e F, S e e , Sc ue z B, Fuc s D, Gos e JM o o c supp e e a o pa e s w A z e e s e e a a exp o a ve e ve o s u y Cu A z e e Res 2018;15(1) 1106–111 lo 10 1 4/ 1389200219666180813144834

55 au , Naga o o Co s , Go ov o S, Go ov o MY, u g MG, Co s C o o c s a e o a e es a pa op ys oogy a ouse o e d A z e e s \ s ease Neu o o Ag g 2020;9 114–134 lo 10 1016/j eu o o ag g 2020 04 009

56 o ayas Y, Suga a a S a a , M suya a E, u a a T, Yasuda A, o lo T, A e , Xao JZ T e apeu c po e a d B lo ac e u eve s a A1 o p eve g cog ve pa e A z e e s \ sease Sc Rep 201 lo 10 1038/s41598 01 13368

5 Az SAN, Djazaye A, Sa a M, Aza , A a va \ B, Sa ag za a F, S a i za e M, Va a M ac o ac a \ lo ac e a a e o a e e o y a \ ea g e c s a \ ox a ve s ess e a a y o \ (1 4) jec e \ a s App ys o Nu Me 2018;43( ) 18– 6 lo 10 1139/ap 201 0648

58 Wa g T, u X, a g S, W, Wu X, Wa g , J F ac o ac us e e u NS9 es o es e a o c luce \ p ys oogca a \ psyc oogca a o a es a s Be d M c o es 2015;6 0 – 1 lo 10 389 0/ B 2014 01

59 M e MR, e e e R, Me se M, Z a g C, eo e V, Z a g XQ, y e Cas o , Z a g X , Musc MW, S e X , e a A o c luce \ pe u a o s c o a \ ve s y u g pos a a leve op e a e s a y o \ pa oogy a age \ A (SWE)/ S1(De a E9) u e o le d A z e e s \ sease Sc Rep 201 ; lo 10 1038/ s41598 01 1104 w

60 M e MR, Z a g C, eo e V, R gus D , Z a g XQ, y e Cas o , Musc MW, ao F, Wa \ JF, o z a DM, e a A o c luce \ pe u a o s gu c o a \ ve s y ue ces eu o a a o a \ a y o loss a u e o le d A z e e s \ sease Sc Rep 2016;6 lo 10 1038/ s ep 00 8

61 Wa g XY, Su GQ, Fe g T, Z a g J, ua g X, Wa g T, Xe ZQ, C u X , Ya g J, Wa g , e a So \ u o g o a a e e apeu ca y e o le s gu c o o a a \ supp esses gu ac e a a o ac s s ape \ eu o a a o o A z e e s \ sease p o g ess o Ce Res 2019;29(10) 8 –80 lo 10 1038/s41422 019 0216 x

6 Do \ ya B, u z T, S a SM, Bau e \ C, e ow z J, Z a g X , Go e N, Z a g XQ, Bu ovs y , G e JA, e a Sex spec c effec s d c o o e pe u a o s o ce e a A e a a yo loss a \ c o g a p e o ypes J Exp Me 2019;216( ) 154 –1560 lo 10 1084/je 2018 86

6 Mezo C, Dc a s N, Mossa \ , S aszews , Neu e J, Y az B, Sc epi D, De Ag ue o MG, Ga a Vo a u g SC, Macp e so AJ, e a D ffe e effec s d co s uve a \ luce \ c o o a o u a o o c o g a a ouse o le d A z e e s \ sease Ac a Neu opa o Co 2020;8 lo 10 1186/s404 8 020 00988 5

64 B oa \ ea \ MJ, Bo o C, A c as , Bez S, Z u F, Goff F, Ny J, D o a a , Gu Moo e F, G a SGN, e a Sy e g s c lepe o d gu c o a co so a, u o \ v lua a o cs, e luces a y o los s A S1 1 A z e e s a sge c ce Sc Rep 2020;10 lo 10 1038/s41598 020 64 9 5

65 Z, Z u , Guo YX, Du X , Q C Gu c o o a e gu a e co g ve le c s a \ a y o \ epos o a o le d A z e e s \ sease J Neu oc e 2020 lo 10 1111/j c 150 1

66 Wa e AW, I ce J, Du ca S , We se M, o op G, Ze X , B ow D, S a es MD, Sco , Be ge a A, e a Do a a \ \ e espo s ve g oups d ac e a w e u a coo c c o o a Is e J 2011;5( ) 200– 0 lo 10 1038/Is ej 2010 118

6 u XF, Cao SQ, Z a g XW Mo u a o d gu c o o a a axs y p o o cs, p e o cs, a \ e J Ag Foo C e 2015;63(6) 885– 895 lo 10 1021/acs ja c 5 0 404

68 T ass CA, Zeev D, evy M, Z e a Sc ap a G, Suez J, Te ge e AC, A a so , a z MN, o e T, Z o a N, e a T a s g lo co o d c o o a \ u a osc a o s p o o es e a o c o eos ass Ce 2014;159 ( ) 514–529 lo 10 1016/j ce 2014 09 048

69 a a SG, a s ed A, C eese a JF o e a o e o o e gu c o o a o u a g os c ca \ a y s a \ e a o c ea M c oo ga s s 2019 lo 10 390/ c oo ga s s 0 0041

0 ue ge JM, pp MR S ep a \ c o es I Rev Neu o o 2016;13 20 – 5 lo 10 1016/ s 2016 0 00

1 Be e c C, Vo ge , Jo as W, Wo g A, Bau M, Sc u a A, Ce e aes J Gu c o o a a \ guco e a o c a e a o s espo se o ecu e pa a s ep ep va o o a we g you g \ v lua s Mo Me a 2016;5(12) 11 5–1186 lo 10 1016/j o e 2016 10 003

Gos d GJ, Re a B , Fa AA, Va e o T, us ga e MS Sei epo e e s ep qua y s assoc a e \ w gu c o o e co pos o you g ea y \ v lua s a p o su y S ep Me 2020; 6–81 lo 10 1016/j s eep 2020 04 013

3 A leso JR, Ca o I, Azca a e MA, Roc e e AD, e g J, ea C, S effe , Ma le o M, M c e J, Gu s a J A p e a y exa a o d gu c o o a, seep, a cog ve ex y ea y o le a u s S eep Me 201 ;38 104–10 o 10 1016/j s eep 201 0 018

4 S R , Easso C, y e SM, apoo R, Do e y C , Dav so EJ, a k E, opez JV, Ta a J Gu c o o e ves y s assoc a e w seep p ys oo gy u as os e 2019 14 o 10 1 1/jou a po e 0222394

5 o oyk o VA, Ca e as A, ayla A, ayla AA, eo e V, e s E, A e os I, G ees e A, Qao Z, u e N, e a C o c seep s up o a es gu c o o a, uces sys e c a a pose ssue a a o a su ess a ce ce Sc Rep 2016;6 o 10 1038/s ep 5405

6 E A y S, Bo s us G, Rave F, ave es R A d pe o d seep ep va o ea s o su e c a ges ouse gu c o o a J Seep Res 2019 o 10 1111/js 12920

Mak A, Bu e A, Ca k MW, Wa a a e C a a M, Swee ey D, Ro d Rose la e E, G ee SJ, F k AM S eepl ag e a o c eases oo p essu e a s asso c a e w a e a o s e gu c o o e a eca e a o o e as ys o Ge o cs 2020;52 ( ) 280–292 o 10 1152/p ys o ge o cs 00039 2020

8 Bowe s SJ, Va gas F, Go za ez A, e SN, Ja g , Do es e C, g R, W g , owy CA, F es e M, e a Repea e seep s up o ce ea s o pe s se s s e eca c o o e a e a o o e os e 2020;15 o 10 1 1/jou a po e 0229001

9 T pe J, E s D, B a od A, Ro e s E, I g a , e ez E, S o A, B ow D, u zey V, We C, e a Te po a a eg o spec c effec s d seepl ag e a o o gu c o o a a es a o p oogy Sp ague Daw ey as Gu M c o es 2020;11 (4) 06– 20 o 10 1080/19490976 2019 1 01 52

80 Ma W, So g J, Wa g , S F, Z ou N, Ja g J, Xu , Z a g , a g , Z ou M C o c pa a ox ca seep ep va o uce ep ess o k e e av o , e egy e a o s a c o a c a ges as e Sc 2019;225 88–9 o 10 1016/j s 2019 04 006

81 Z a g S , Ba , Goe N, Ba ey A, Ja g CJ, Bus a FD, Mee o , D ges DF, Se ga A u a a a gu c o o e co pos o s a a e o ow g seep es c o Na Aca Sc SA 201 ;114(8) E1564–E 1 o 10 10 /p as 1620 6 114

82 a NW, e Zoe e MR, Cu e TW, Ba y NA, S d a ows J, ao M, Deg a , u JZ, e e I, Z a g W, e a I u og o u A coa g e es co o ge c ac e a a a o y owe s ease Ce 2014;158(5) 1000–1010 o 10 1016/j ce 2014 08 006

83 Ja k sso E, Ro guez e o AM, Sc u e A, E u A, Boyse , Be a k M, So e F, Bad e F, a sso GC, Jo a sso MEV T e co pos o d e gu c o o a s apes e co o ucus a e E o Rep 2015;16(2) 164–1 o 10 15252/e 2014 9263

84 Sc e M, S ee k e s S , V a k s , Jae ge M, os g M, F a zosa EA, Te o s R, Ja se T, Jaco s , MJ B, e a k g e u a gu c o o e o a a o y cy d e p o uc o capac y (vo 16 , pg 11 5, 2016) Ce 2016;16 ( ) 189 o 10 1016/j ce 2016 11 046

85 De e M, Be ze C, e Vos WM Ak e a s a uc p a a s o e eg ua g os u c o s M c o a ge es s 201 ;106 1 1–181 o 10 1016/j cpa 2016 02 005

86 Vo g RM, Fo sy CB, G ee SJ, E ge A, C ca a A R y a e gu c o o e I Rev Neu o o 2016;131 193–205 o 10 1016/ s 2016 0 00

8 Mo as , B c S, a ak a T T e c ca a s up o d g wo k a e s gu c o o a co sse w e eva e sk o u e e a o ca gas o es a pa oogy C o o o I 2020 o 10 1080/0 4205 8 2020 1 8 1

88 u Z, We Z , C e J, C e , Mao X, u Q, Su , Z a g Z, Z a g , Da Z, e a Acu e seep wa e cyc e s esu s co u y a e a o d u a gu c o o e Sp e e 2020;5 o 10 1128/Sp e e 00914 19

89 ayla A, oyk o VA, Qao Z, G ees e A, ayla AA, Ak a pou M, A e os I, Fa e R, Goza D Exoso es a e a o c u c o ce expose o a e a g a k g cyc es d g g s l wo k sc e ues F o ys o 201 ;8 88 o 10 389/p ys 201 0088

90 Deave JA, Eu S , To o k M C ca a s up o c a ges gu c o o e axa a u c o a ge e co pos o F o M c o o 2018;9 o 10 389/ c 2018 00

91 a M, Ba o sy e ova EG, u es RA, G yaeva E , ou ova E , os ova TA, u yav seva AV, o k aya MV, as u o VA, as a ov AS, e a T e effec s d esy c o oss o e gu c o o a co pos o a p ys oogica pa a e e s d as B c M c o o 2019;19 o 10 1186/s12866 019 1535

92 Vacca M, Ce a o G, Ca a ese FM, o casa , Go e M, De A ges M T e co ove s a o e d u a gu ac osp aceae M c oo ga s s 2020 8 o 10 390/ c oo ga s s80405

93 g CW, e S , G se a S, Zoe e la EG, McSwee ey CS, Sy I, McGud MA, F o T Muco y c ac e a w c ease p eva e ce IBD ucosa aug e v o u za o d uc y o e ac e a A J Gas oe e o 2010;105(11) 2420–2428 o 10 1038/aj g 2010 281

94 C os E , Ta a o E, e Ga G, Fo s M, e ssa B, Juge N sa o d uc gyca s y e u a gu sy o u ococcus g avus s s a lepe e os e 2018 8 o 10 1 1/jou a po e 00 6341

Mo u a o d e gu c o o a as y ug a q gz a es u g e ea e d g a e uce o a co o c a y ve sease x Me Ce o gev 2018;2018 261619 o 10 1155/2018/ 261619

96 M que S, Ma R, Ross , Be u ez u a a G, C a e JM, Sok o , T o as M, We s JM, a ge a Faeca ac e u p aus z a u a es a ea Cu p M c o o 2013;16(3) 255–261 o 10 1016/j 2013 06 003

9 opez S es M, Du ca S , Ga c a G J, Ma ez Me a M Faeca ac e u p aus z a o c o o ogy o ag os cs a p og os cs Is e J 201 ;11 (4) 841–85 o 10 103 8/ s ej 2016 1 6

98 e eg C, A o o , Co ucc R, B a zz C, Fo a M I e pay a o gu c o o a, es a ucosa a e a e c eu o u e sys e a co o pa o eu o ege e a ve seases? Ac a Neu opa o 2018;136 (3) 345–361 o 10 100 /s00401 018 1856 5

99 Seo D , o z a DM Gu c o o a o e o ga o a po e a key p aye e pa o ogy d A z e e s sease J Ge o o A B o Sc Me Sc 2020; 5( ) 1 –1 41 o 10 109 /ge o a/gz 6

100 Ngu ye T A, Ve a S va S, s o A, Raes J ow o a ve s e ouse o u a gu c o o a esea c ? D s Mo e Mec 2015;8(1) 1–16 o 10 1 4 / 01 400

101 Te c a EM, 'Ro a J, Ga a CGM, D a TG, C ya JF W e y s ee e ues c ca a e ac o s w e c o o a gu a ax s Ce Me a 2020;31(3) 448–4 1 o 10 1016/j c e 2020 0 008

10 Ma ge F, Go e a M, Gau e , Zazue a A, eso a S, Nava e , Ba a u u a R T e cu es/ ac e o e es a o a e eva a e d gu ys os s o ese pa e s? Nu e s 2020;12 (5) 14 4 o 10 390/ u12050514 4

103 asca e A, Ma c es N, Govo S, Coppo a A, Gazza uso C T e o e d gu c o o a o es y, a e es e us, a effec d e o ew s g s o o seases Cu p a aco 2019;49 1–5 o 10 1016/j cop 2019 03 011

104 a se N, Vo ge se F , Va De Be g FW, N e se DS, A ease AS, e e se B , A Sou WA, So e se SJ, a se , Ja o se M Gu c o o a u a a u s w ype a e es ffe s o o a e ca u s os e 2010;5( ) e9085 o 10 1 1/jou a po e 0009085