CJ 바이오사이언스

사람의 생애주기와 장내 마이크로바이옴

CJ 바이오사이언스
김남일 박사

2022.04.15

[목 차]

CORPORATE IDENTITY

› 100,000 SAMPLES

Human microbiome big data

PRECISION TAXONOMY DISCOVERY PLATFORM

Microbiome Bio-digital platform

LIVE BIOTHERAPEUTIC PRODUCTS

Drug development through microbiome therapeutic strains

CJ CHEILJEDANG + CHUNLAB Microbiome for you

CJ BIOSCIENCE

Global No.1 Microbiome Company

150 COUNTRIES

Number of countries using EzBioCloud

NEW BUSINESS DEVELOPMENT

Establishment of all business areas in the microbiome field

OPEN INNOVATION

Pure outsourcing / Licensing / Collaboration / Open source

마이크로바이옴 정밀 분류 플랫폼 기반 비즈니스

마이크로바이옴이란?

마이크로바이옴 (MICROBIOME)이란?

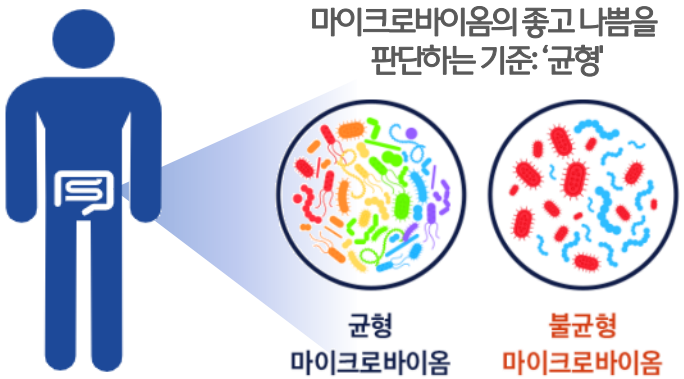
■ 마이크로바이옴 (Microbiome)이란 미생물 (Microbe)과 생태계 (Biome)가 합쳐진 말로, 미생물 환경을 뜻함

Microbiome
Microbe
biome

미생물 생태계

마이크로바이옴의 특징

- 생태계 균형
- 변할 수 있음
- Personal (개인적) → 개인 맞춤

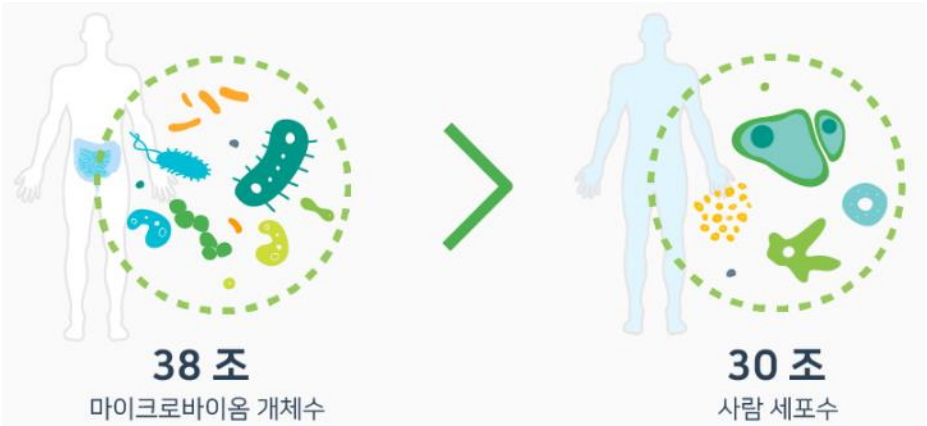


GMI

(Gut Microbiome Index)
장내 마이크로바이옴
건강지수

장내 마이크로바이옴

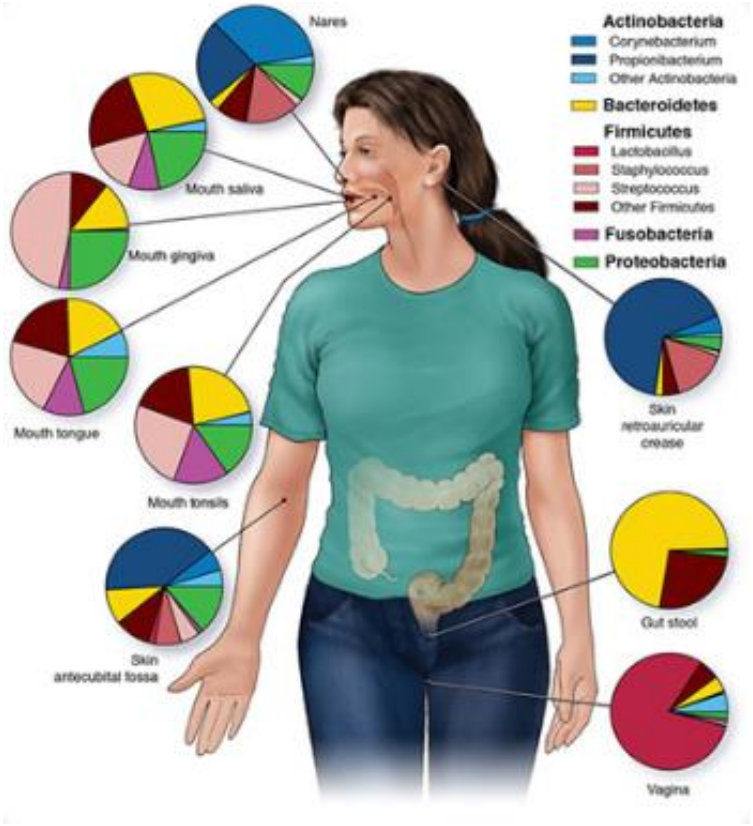
- 인체에는 38조 개의 미생물이 살아가고 있으며,
  이 중 95%가 대장에 모여 살고 있음
- 대장의 경우 100~1000종의 세균이 존재

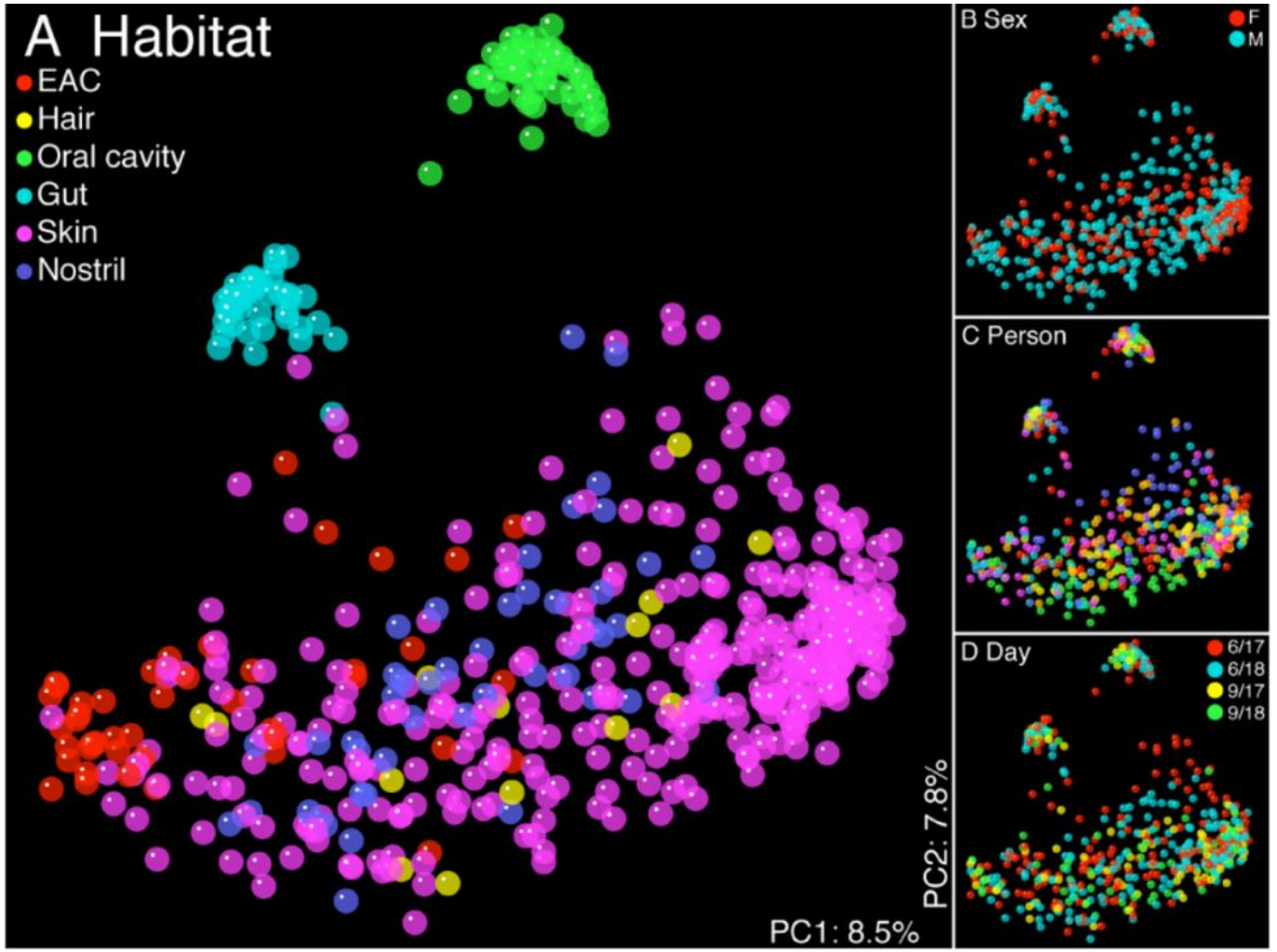


신체 부위별 마이크로바이옴

■ 마이크로바이옴은 인간의 여러 부위에 공생하는 미생물의 생태계

■ 신체 부위별로 마이크로바이옴의 특징이 구분됨

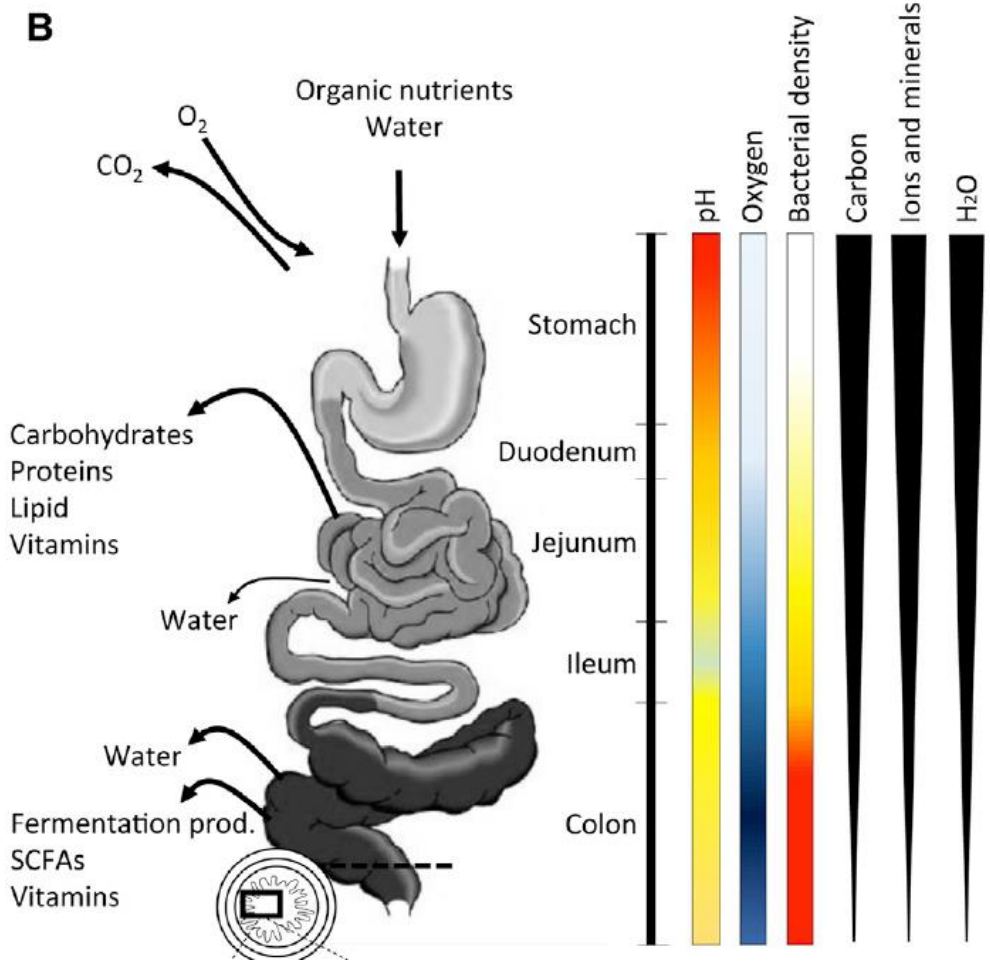


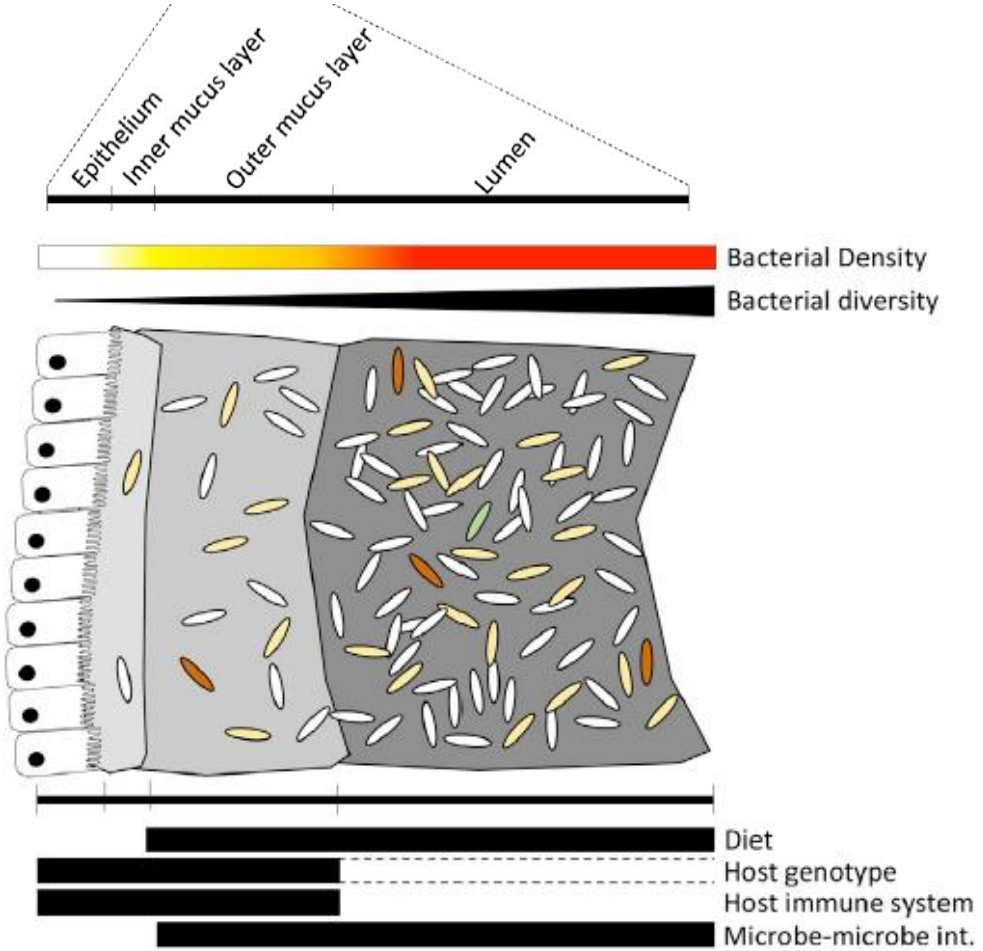


Costello et al. (2009) Science

사람의 소화기관별 환경특징 및 미생물 분포

- pH: 위 pH1.5-5 / 소장 pH 5-8 / 대장 pH 5-7
- 산소: 장은 혐기성 환경 (anaerobic condition)으로 fermentative metabolism에 적합 (SCFAs 생성)
- 온도: 변화가 크지 않음





Hacquard et al. (2015) Cell Host Microbe

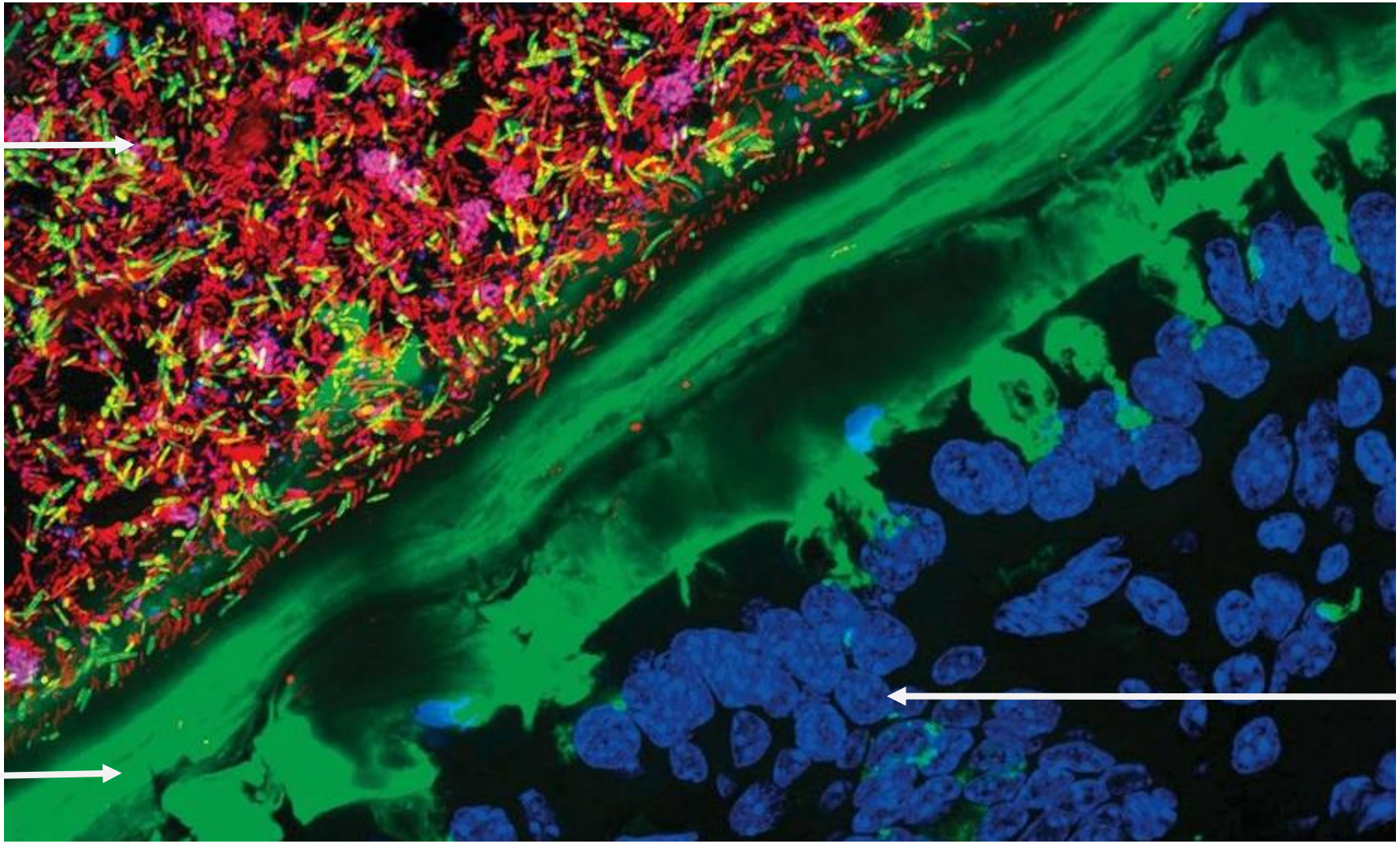
장내 마이크로바이옴

■ 장내 마이크로바이옴은 소화, 흡수뿐만 아니라 면역체계 유지, 뇌와 간에 필요한 물질 생성 및 전달 등 생태계를 형성

- 사람은 식물의 세포벽을 분해하는 효소를 만들지 못함

마이크로바이옴

세균(bacteria)이 〉99%



점막 (Mucus)

70% 이상의 조절면역세포 (helper T cell) 가 장에 있음

장 세포

Tropini et al. (2017) Cell Host Microbe

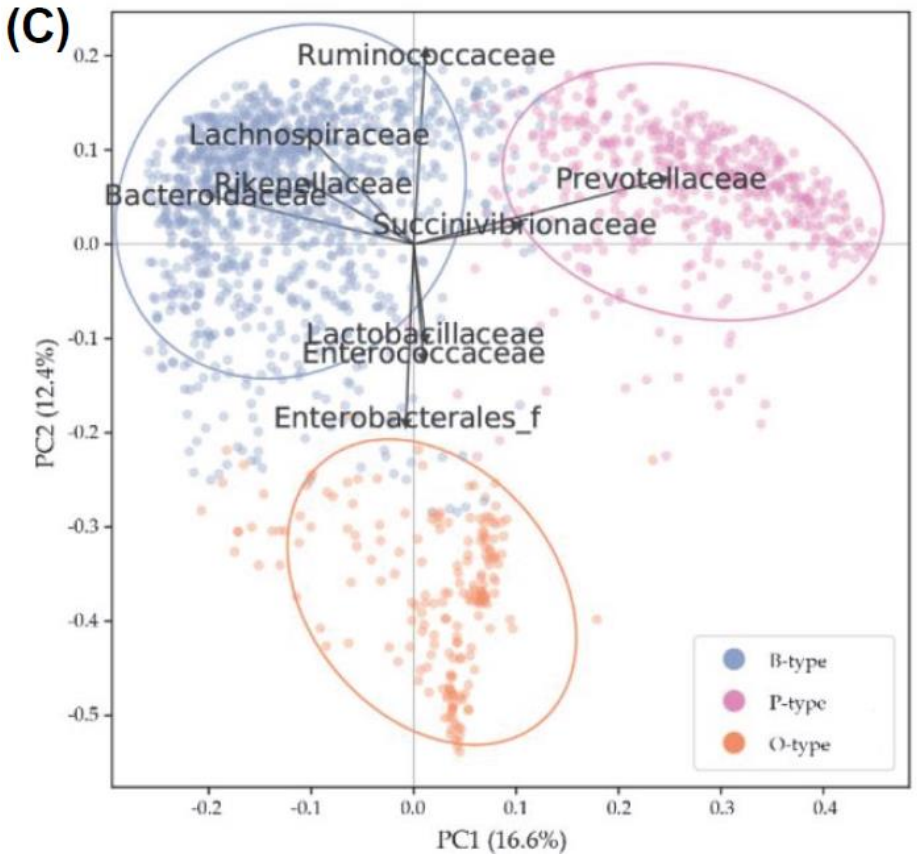
장내 마이크로바이옴

■ 장 유형 (Enterotype)은 크게 3가지로 구분 가능: P type, B type, O type

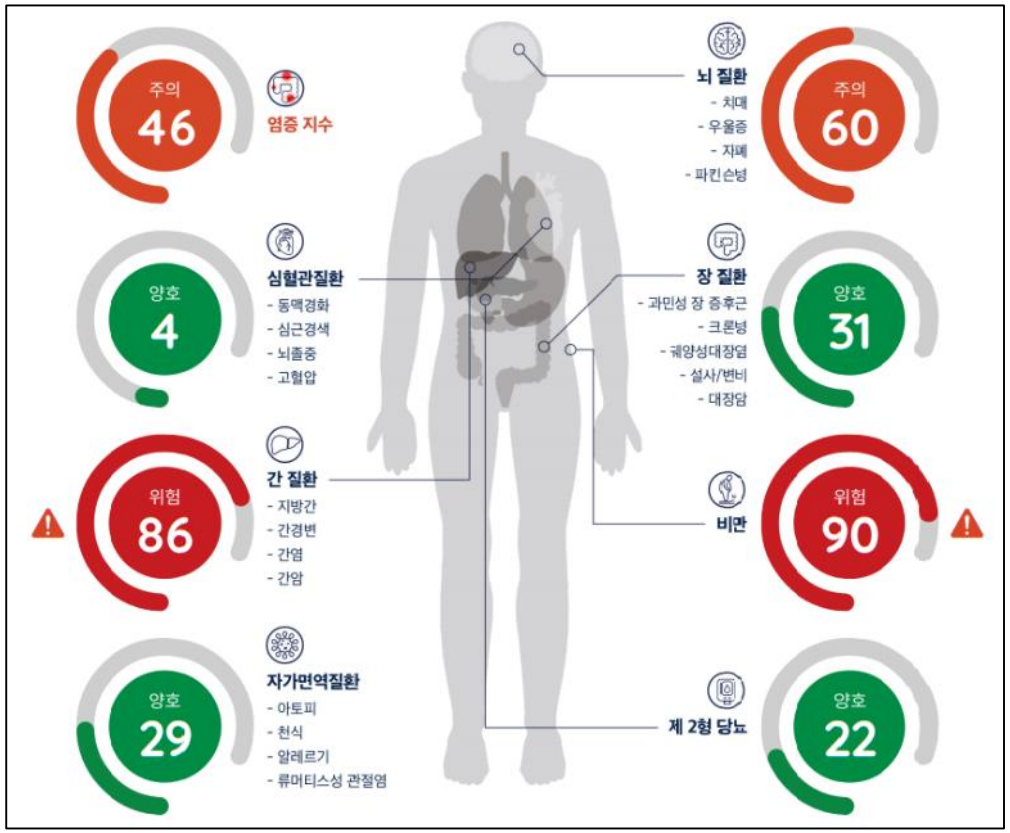
- 개인 맞춤형 식이, 건강기능식품 등 추천 등 가능

■ 전신/뇌 염증에 관여하여 다양한 질병과 연관: 비만, 당뇨, 염증성장질환, 자가면역, 뇌질환 (치매, 파킨슨, 자폐), 암 등

– 질병 예방, 신약 개발 등에 응용



Oh et al. (2022) J Microbiol.

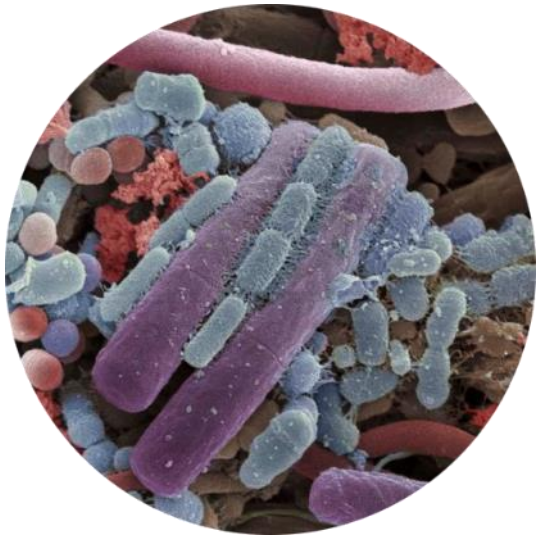


Source : CJ Bioscience, 것인사이드

마이크로바이옴 연구 방법

마이크로바이옴 연구 방법

■ Microorganisms

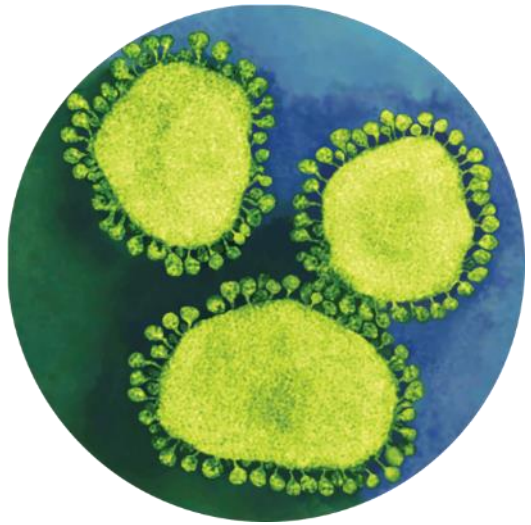


Bacteria

16S rRNA gene

Fungi

ITS



Viruses

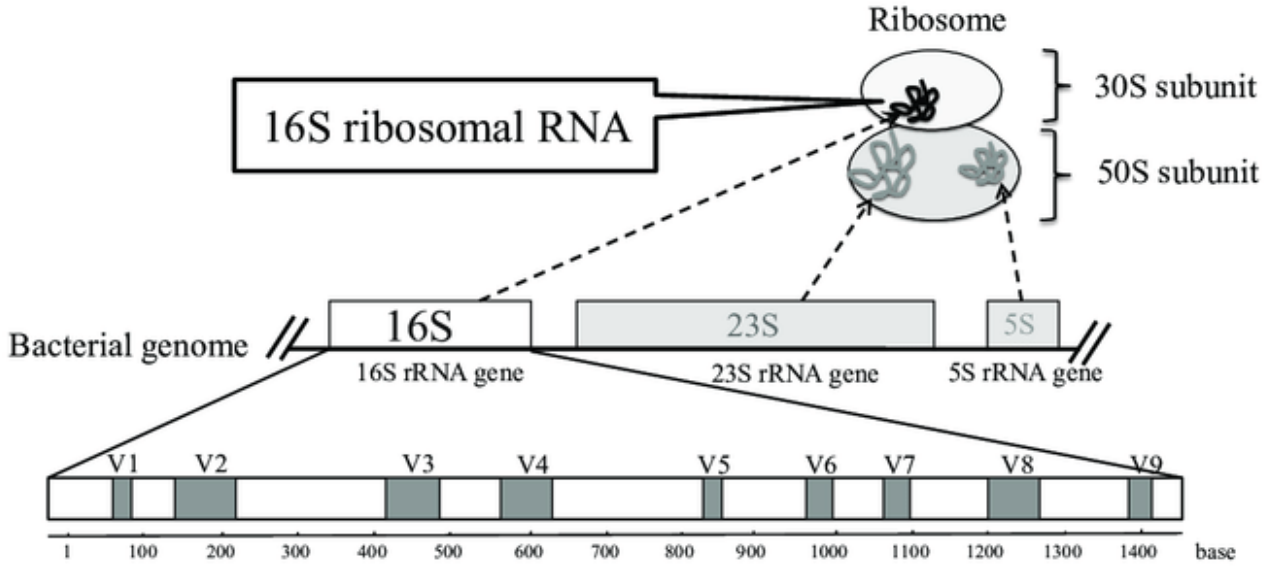
Only shotgun

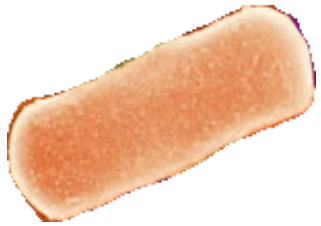
Protists

18S rRNA gene

마이크로바이옴 연구 방법

■ 세균의 경우 종마다 다른 서열을 가진 16S 유전자를 DNA 바코드로 사용





AGCTGATGACAGATAG
AGCTAGATAGATCGAT
AGCTGATGACAGATAG
CCCTGATAGATCGATTT
……

=

마이크로바이옴 연구 방법

■ 한 샘플 (분변, 피부 등)에 섞여 있는 수 조 개의 세균 종을 DNA 바코드로 분석 가능

Microbial Genome database

Human Microbiome Database
(Control + Disease group)

구분	비용	해상도	생태계 분석	단점
PCR	낮음	표적 분류군	**불가능**	단순한 유해/유익균 비율로 해석
유전자 (16S) Sequencing	적정	속/종	가능	균주 단계의 분석은 어려움
유전체 (Shotgun) Sequencing	높음	아종/균주	가능	높은 비용

BIO + IT = Bioinformatics

생명정보학 (융합형 문제해결)

미생물학 | 면역학 | 신경생물학 | ●●●

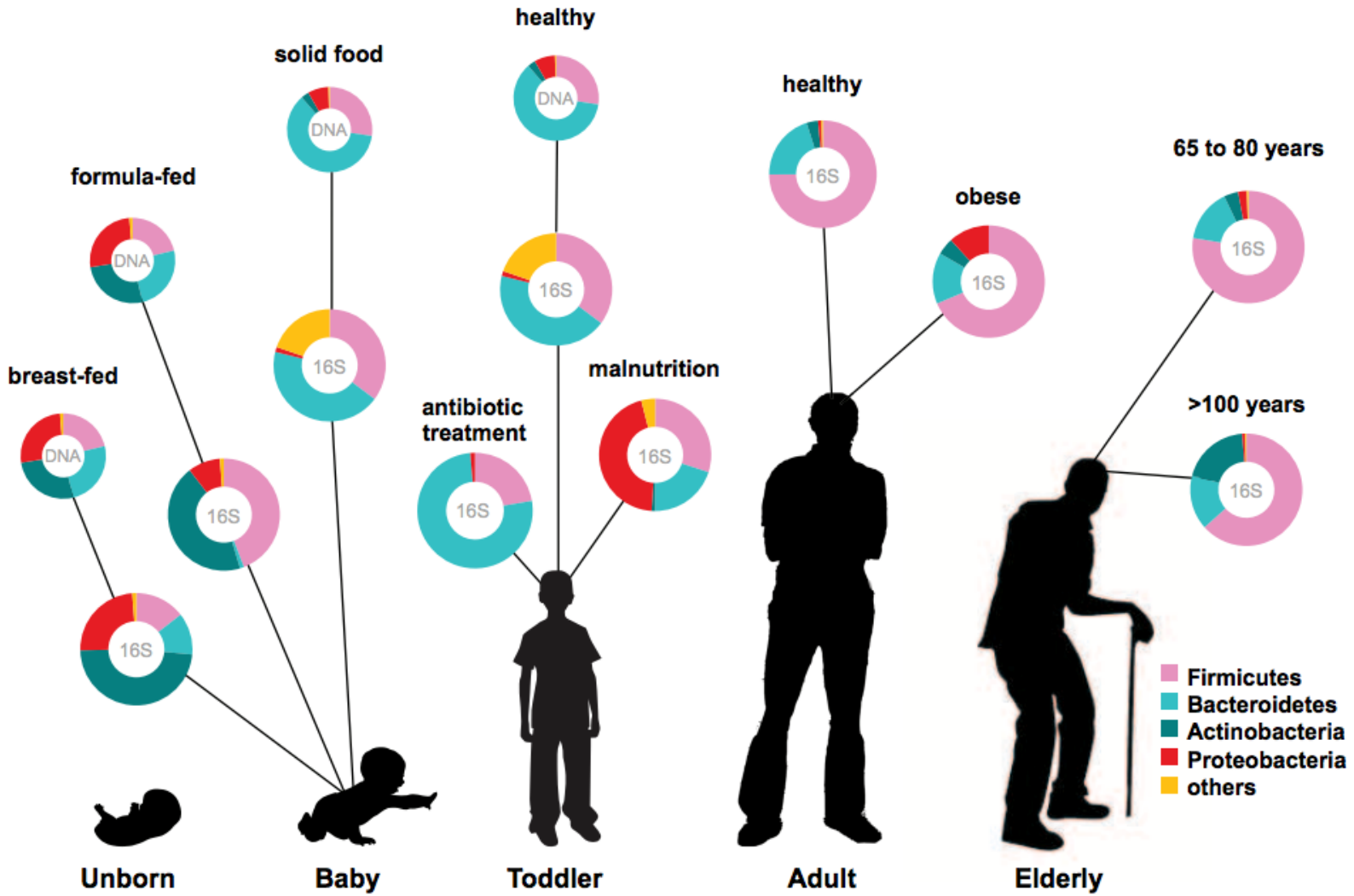
인공지능 | 클라우드 컴퓨팅 | 데이터 사이언스 | ●●●

생애주기 초기의 마이크로바이옴

신생아, 영유아

나이에 따라 변하는 마이크로바이옴

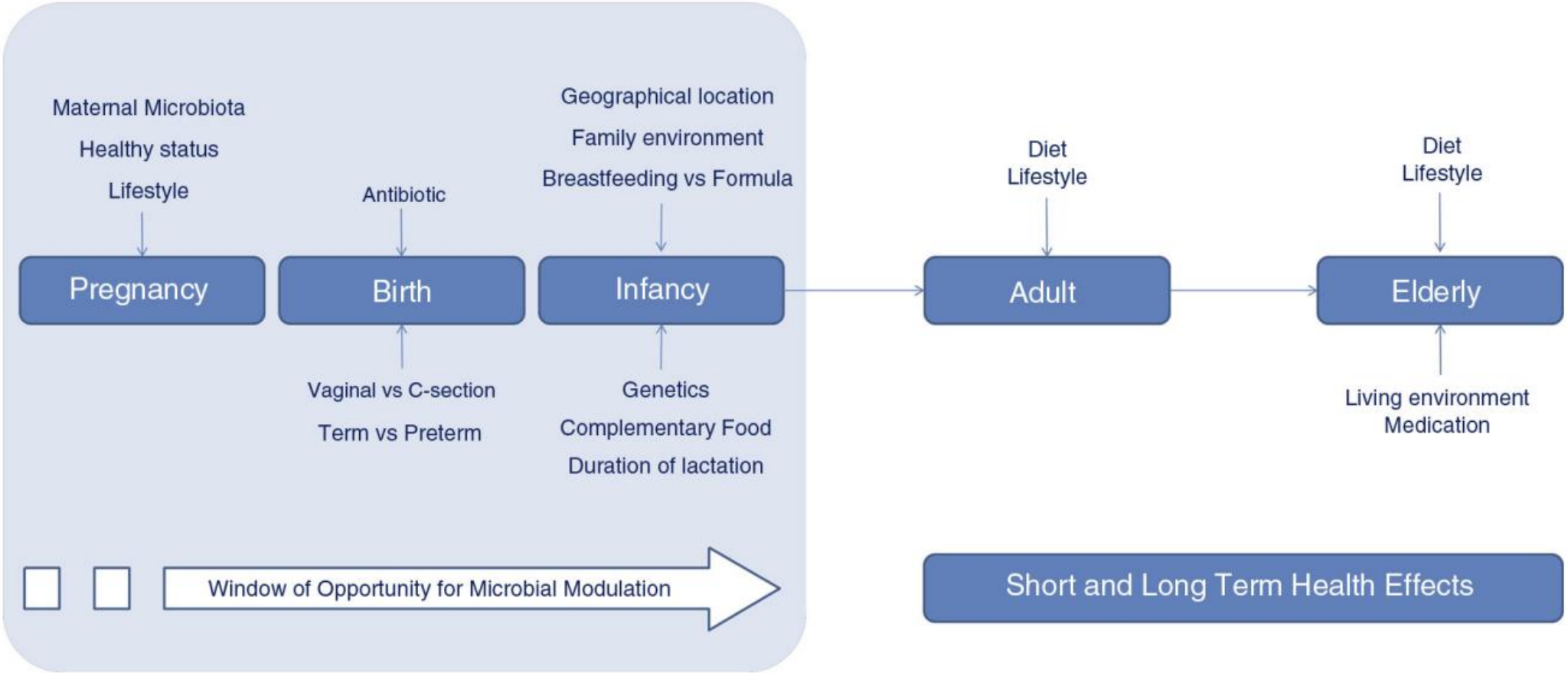
■ 일생동안 변하지 않는 유전자와 달리, 마이크로바이옴은 계속 변화함



Ottman et al. (2012) Front. Cell. Inf. Microbio.

생애주기와 마이크로바이옴

■ 출생 초기 출산, 수유, 돌봄과정 (보호자, 주위환경 등)을 통해 미생물을 전달받음
■ 미생물 다양성 (diversity)은 2~3년에 걸쳐 점차 증가
■ 식이는 마이크로바이옴 형태에 많은 영향을 미침

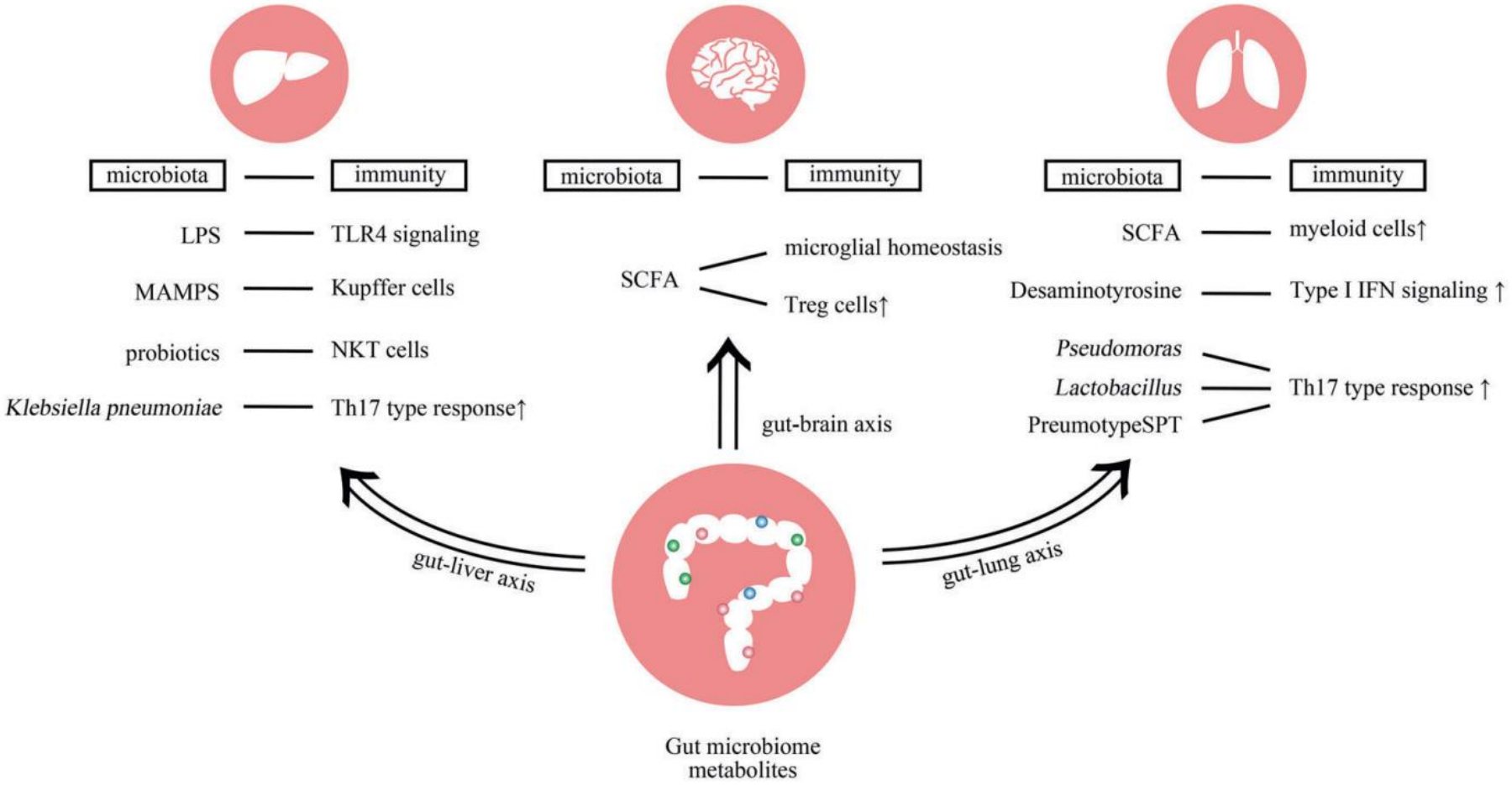


Rodriguez et al. (2015) Microb Exol Health Dis.

생애주기 초기의 마이크로바이옴

■ 신생아, 영유아의 장에 정착하는 미생물들은 1.면역 2.대사과정에 있어 중요한 역할

■ 영유아 시기의 마이크로바이옴 다양성과 다양한 미생물에의 노출이 면역에 중요함 (Rodirguez et al. (2015) Mocrob Ecol Health Dis.)



Zheng et al. (2020) Cell Res.

신생아의 마이크로바이옴 접촉

■ 사람은 어느 시기에 처음 미생물에 노출되는가?

- 태아는 Sterile이라고 생각해왔음
- 탯줄을 통해 모체의 미생물이 이동할 수 있는가는 여전히 논쟁중 (Rodriguez et al. (2015) Microb Exol Health Dis.)
  : 마우스 실험에서는 탯줄을 통해 미생물이 이동함을 확인

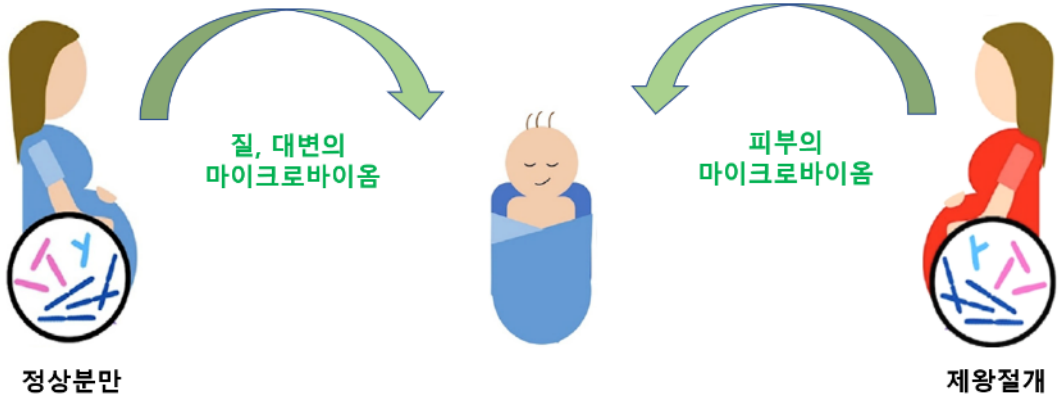
■ 출산 시 미생물과 접촉 시작

① 자연분만: 산모의 산도 및 분변을 통해 미생물 접촉
- 질내 마이크로바이옴은 다양성이 낮으며, 주로 Lactobacilli로 구성 (Aagaard et al. (2012) PLoS One)
- 신생아는 Lactobacilus, Bifidobacterium, Enterobacteriaceae, Bacteroides fragilis 등의 미생물을 전달받음

② 제왕절개: 피부, 병원내 환경의 미생물과 접촉
- 자연분만과 비교해서 마이크로바이옴의 다양성이 낮음

■ 피부 접촉을 통한 미생물에의 노출

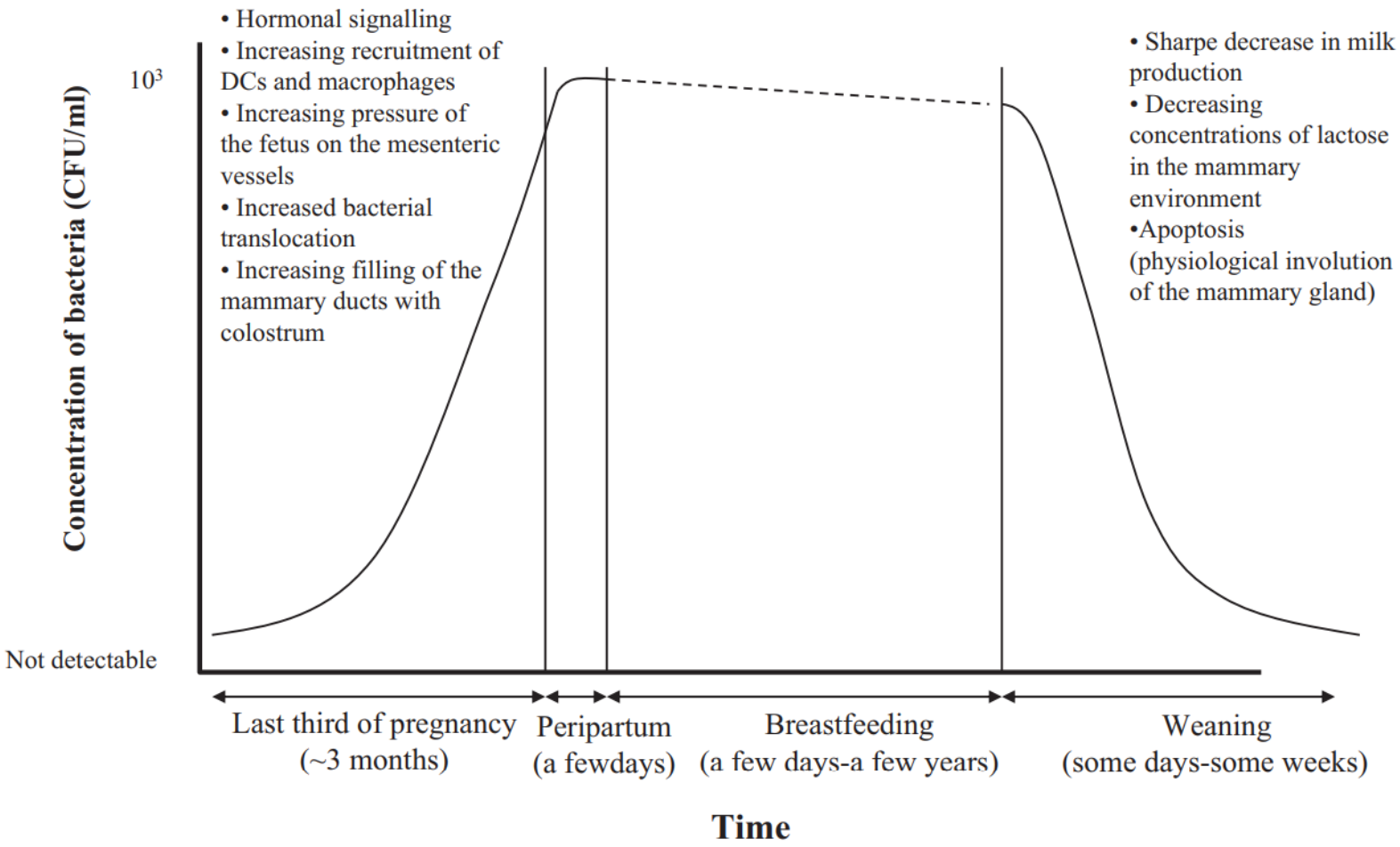
- 사람의 점막에 많은 Staphylococcus는 초기에 전달되는 미생물 중 하나임 (Costello et al. (2009) Science)



산모의 마이크로바이옴 변화

■ 유선내 마이크로바이옴 변화

- 출산이 다가올수록 박테리아 증가
- 수유기간 중 높은 박테리아 농도 유지



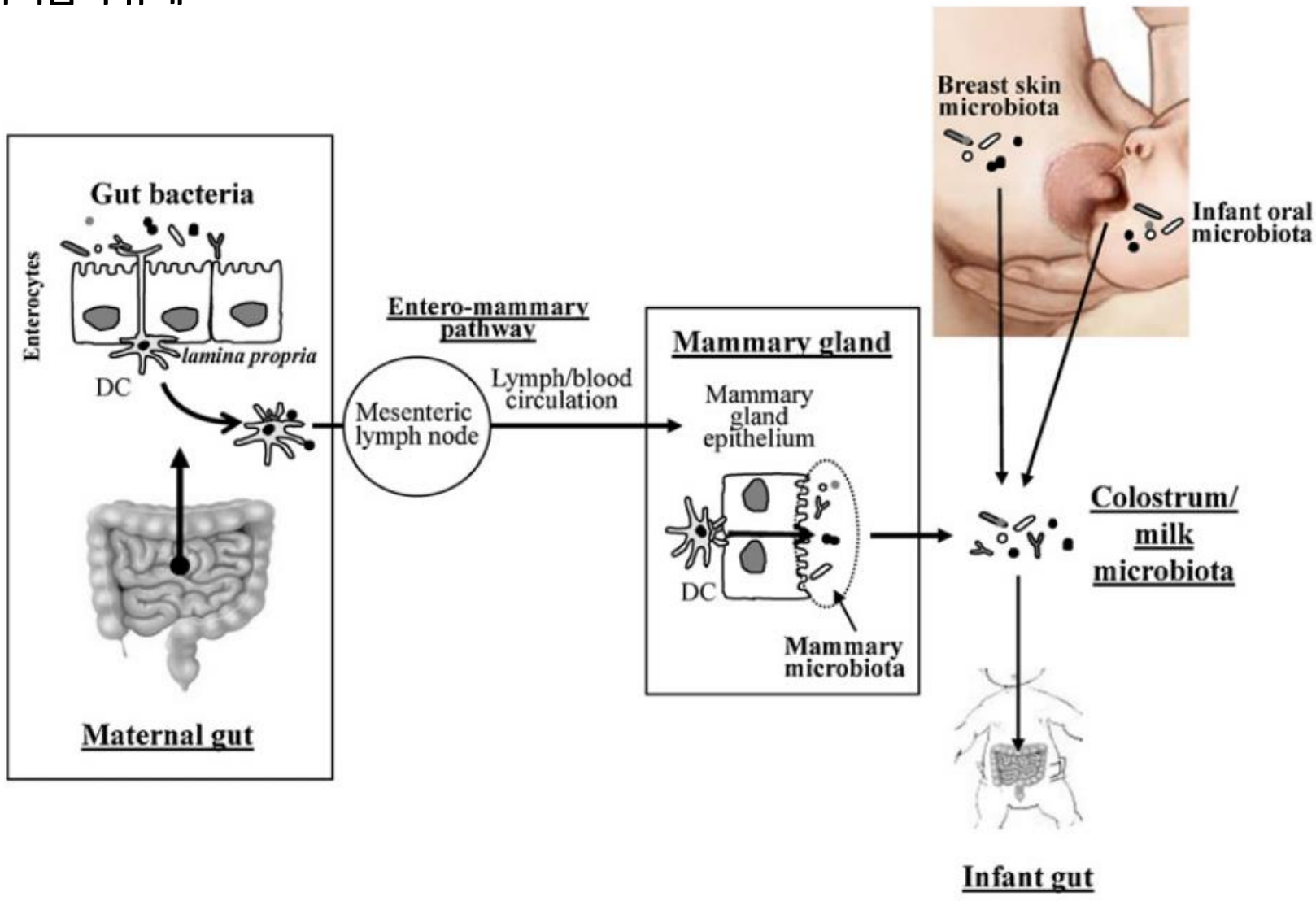
Fernandez et al. (2013) Pharmacol Res.

[모유내 미생물]

Method	Main species/genera[a]	References
Bacterial isolation	*L. acidophilus, L. fermentum, S. epidermidis, Str. mitis, Str. salivarius*	[18]
	L. plantarum, S. epidermidis, Streptococcus spp.	[19]
	E. faecium, L. fermentum, L. gasseri	[4]
	E. faecalis, L. crispatus, L. rhamnosus, Lc. lactis, Leuc. mesenteroides, R. mucilaginosa, S. aureus, S. capitis, S. epidermidis, S. hominis, Str. mitis, Str. oris, Str. parasanguis, Str. salivarius	[5,6]
	L. salivarius	[10]
	Corynebacterium spp., *Enterococcus* spp., *Lactobacillus* spp., *Peptostreptococcus* spp., *Staphylococcus* spp., *Streptococcus* spp.	[63]
	L. reuteri	[120]
	S. epidermidis	[7,8]
	B. adolescentis, B. bifidum, B. breve	[11]
	B. breve, B. longum, K. rhizophila, L. casei, L. fermentum, L. gasseri, L. gastricus, L. plantarum, L. reuteri, L. salivarius, L. vaginalis, P. pentosaceus, R. mucilaginosa, S. aureus, S. epidermidis, S. hominis, Str. lactarius, Str. mitis, Str. parasanguis, Str. salivarius	[20,24]
	E. durans, E. faecalis, E. faecium, E. hirae, E. mundtii, L. animalis, L. brevis, L. fermentum, L. gasseri, L. helveticus, L. oris, L. plantarum, P. pentosaceous, Str. australis, Str. gallolyticus, Str. vestibularis	[22]
	B. longum	[23]
DNA detection	*E. faecalis, E. faecium, L. fermentum, L. gasseri, L. rhamnosus, Lc. lactis, Leuc. citreum, Leuc. fallax, Prop. acnes, S. epidermidis, S. hominis, Str. mitis, Str. parasanguis, Str. salivarius, W. cibaria, W. confusa*	[27,28]
	B. longum, Clostridium spp., *Lactobacillus* spp., *Staphylococcus* spp., *Streptococcus* spp.	[65]
	B. adolescentis B. animalis, B. bifidum, B. breve, B. catenolatum, B. longum	[29]
	Bifidobacterium spp., *Clostridium* spp., *Enterococcus* spp., *Lactobacillus* spp., *Staphylococcus* spp., *Streptococcus* spp.	[121]
	B. adolescentis, B. bifidum, B. breve, B. longum	[11]
	Bradyrhizobiaceae, Corynebacterium spp., *Propionibacterium* spp., *Pseudomonas* spp., *Ralstonia* spp., *Serratia* spp., *Sphingomonas* spp., *Staphylococcus* spp., *Streptococcus* spp.	[25]

산모의 마이크로바이옴 변화

■ 모유 마이크로바이옴의 유래

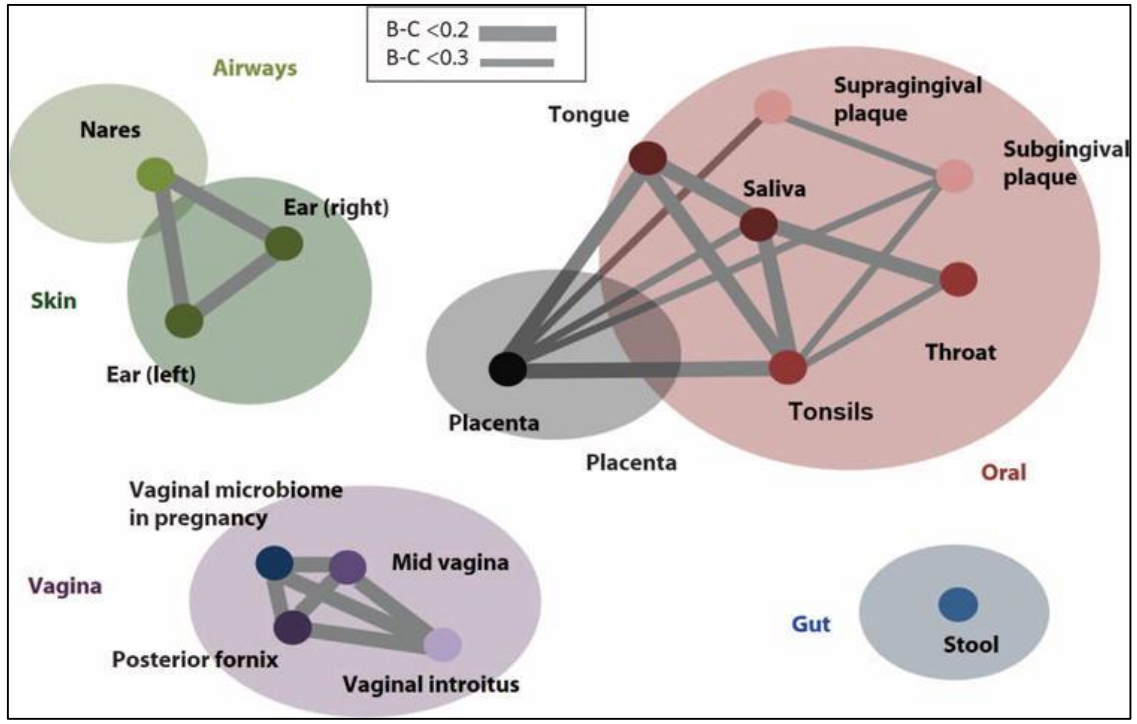


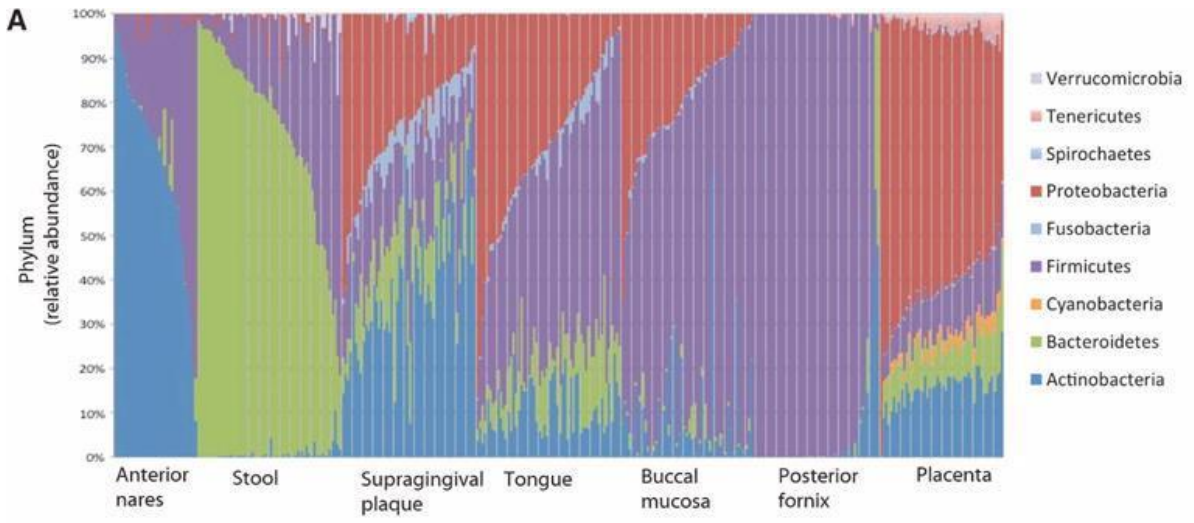
Fernandez et al. (2013) Pharmacol Res.

영유아의 신체 부위별 마이크로바이옴

■ 태반의 마이크로바이옴은 구강의 마이크로바이옴과 유사함

– 신생아 및 영유아 320명 대상 연구

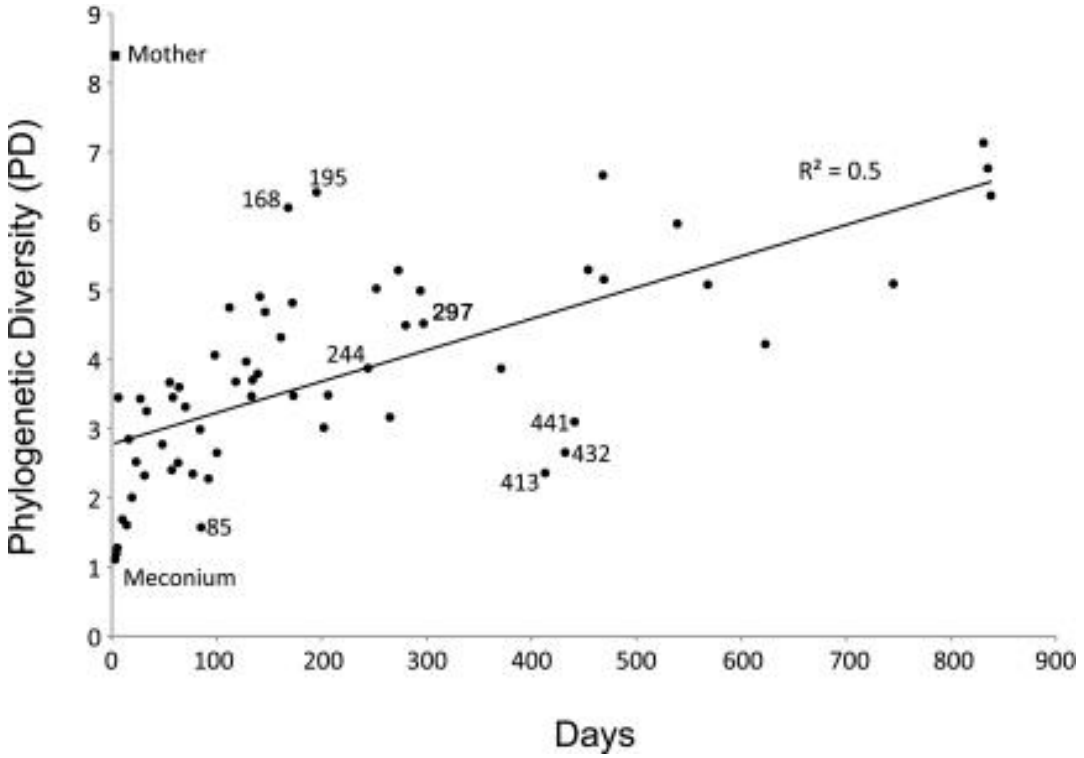




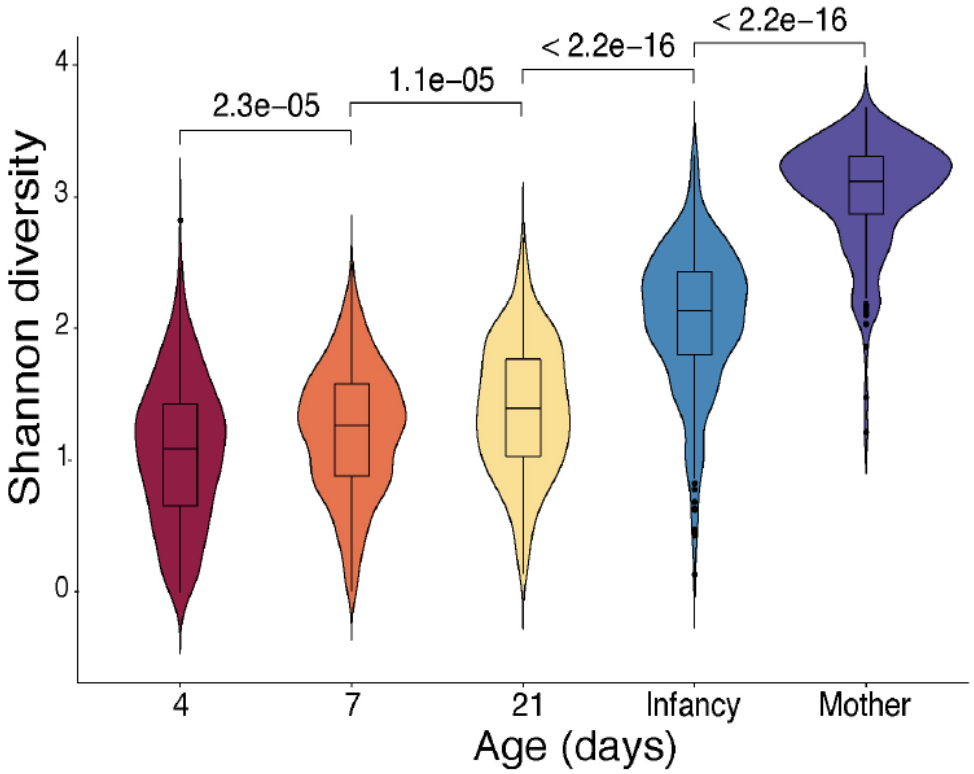
Aagaard et al. (2014) Sci Transl med.

영유아의 마이크로바이옴

■ 출생 이후 지속적으로 다양성이 증가함



Koenig et al. (2011) Proc Natl Acad Sci USA

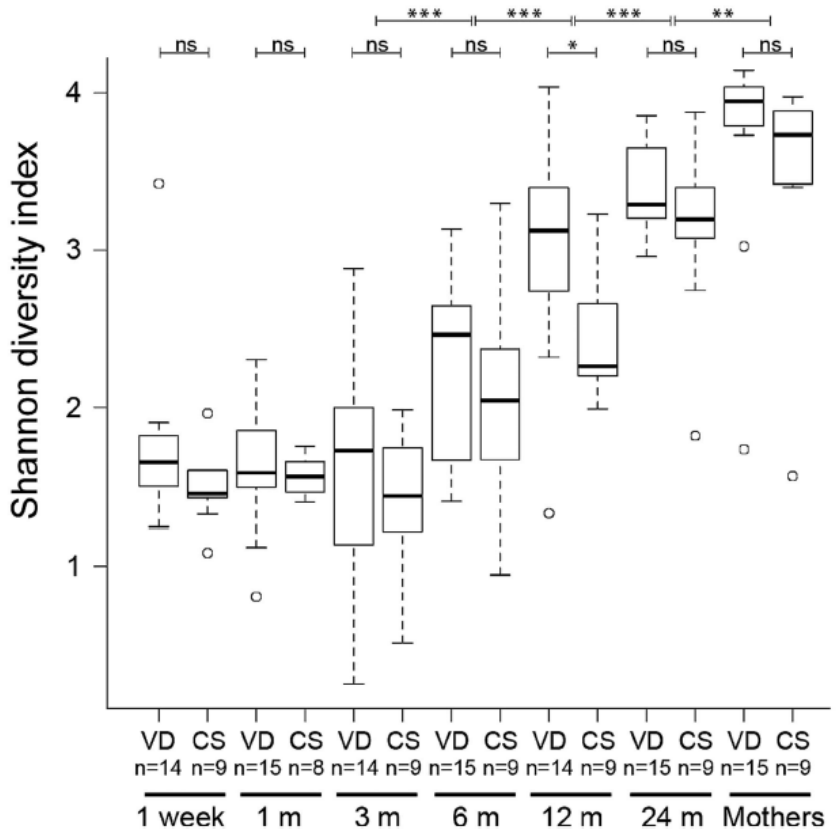


Shao et al. (2019) Nature

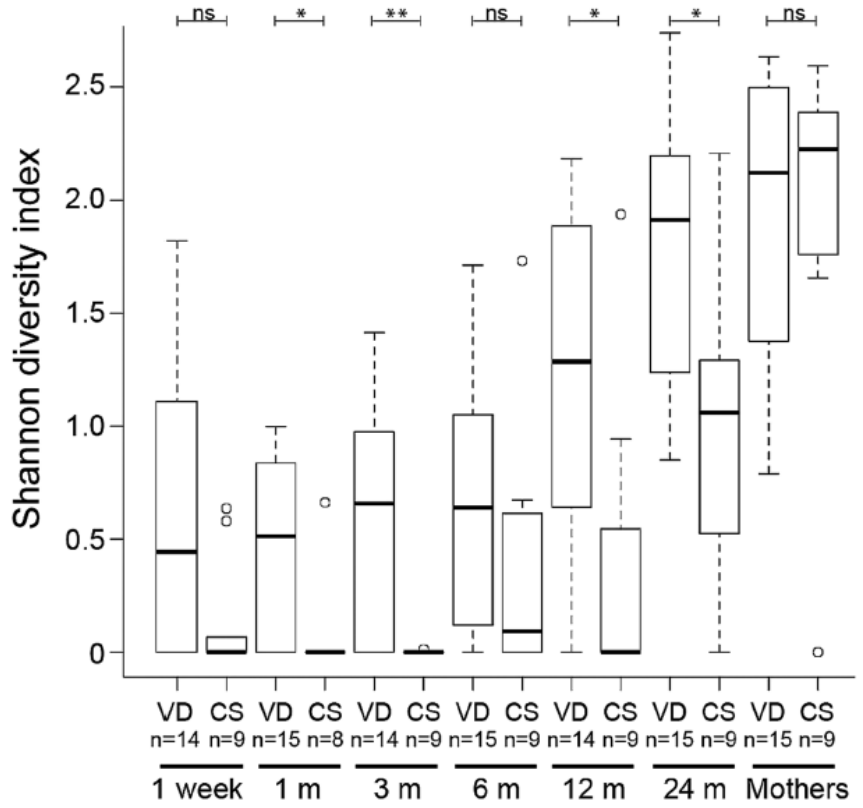
출산형태와 신생아의 마이크로바이옴

■ 출산 방식에 따라 신생아의 마이크로바이옴 다양성에 차이가 있음

자연분만



제왕절개

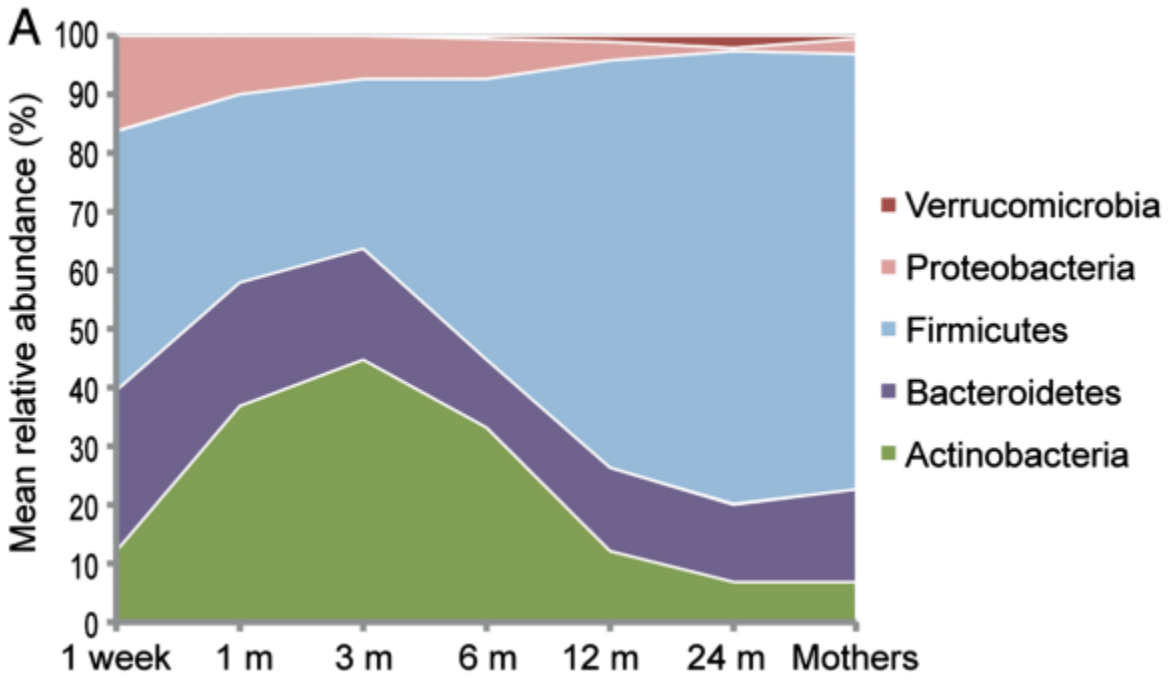


Koenig et al. (2011) Proc Natl Acad Sci USA

출산형태와 신생아의 마이크로바이옴

■ 신생아의 미생물 군집 변화: 출생후 1주 ~ 24개월

자연분만



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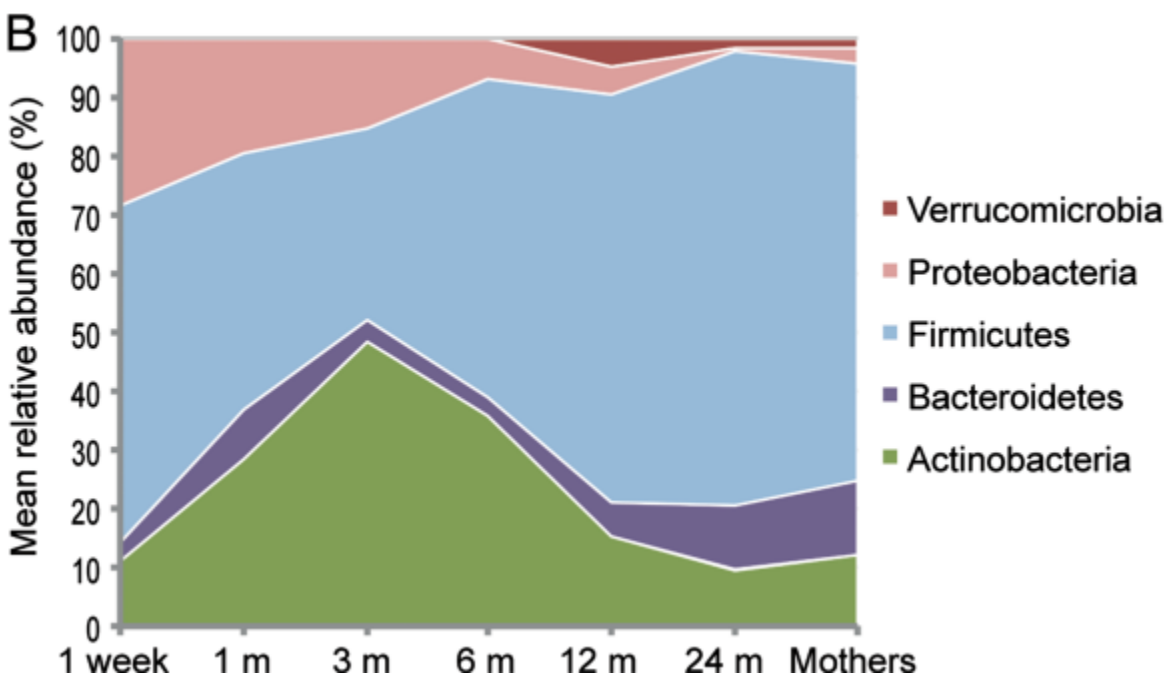
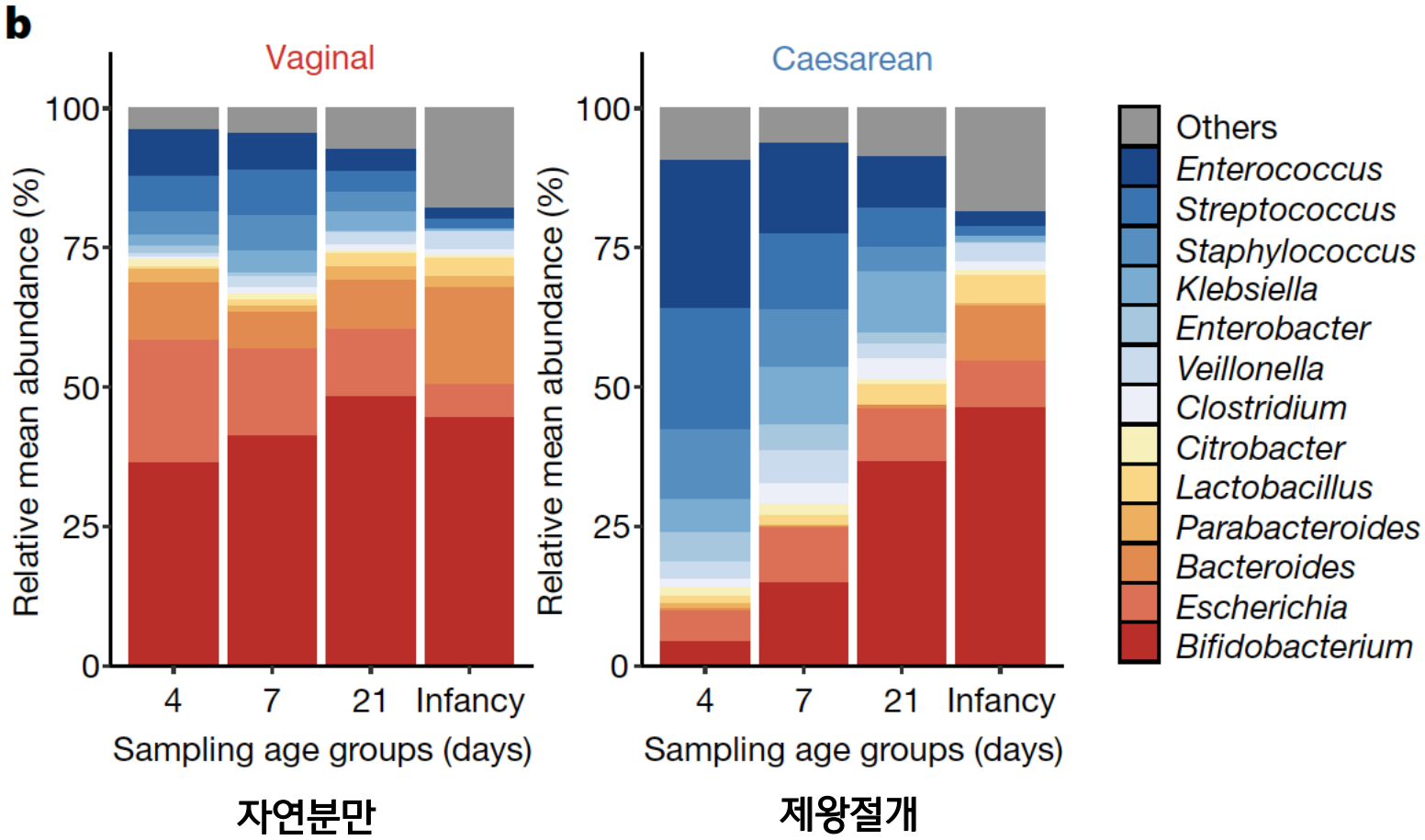


Jakobsson et al. (2013) Gut microbiota

출산형태와 신생아의 마이크로바이옴

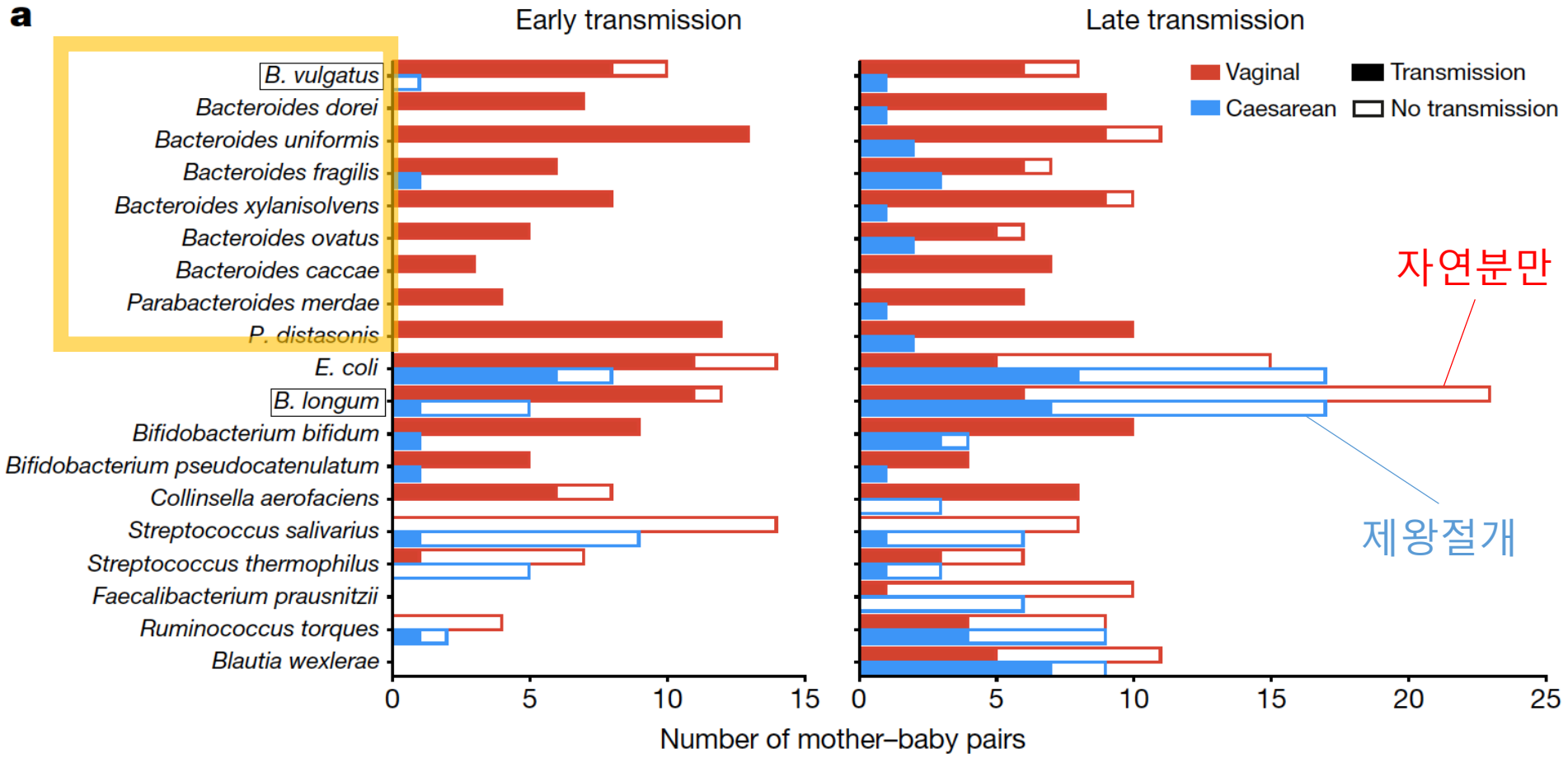
■ 유아기와 신생아의 마이크로바이옴 차이



Shao et al. (2019) Nature

출산형태와 신생아의 마이크로바이옴 : 산모-신생아 사이 전파

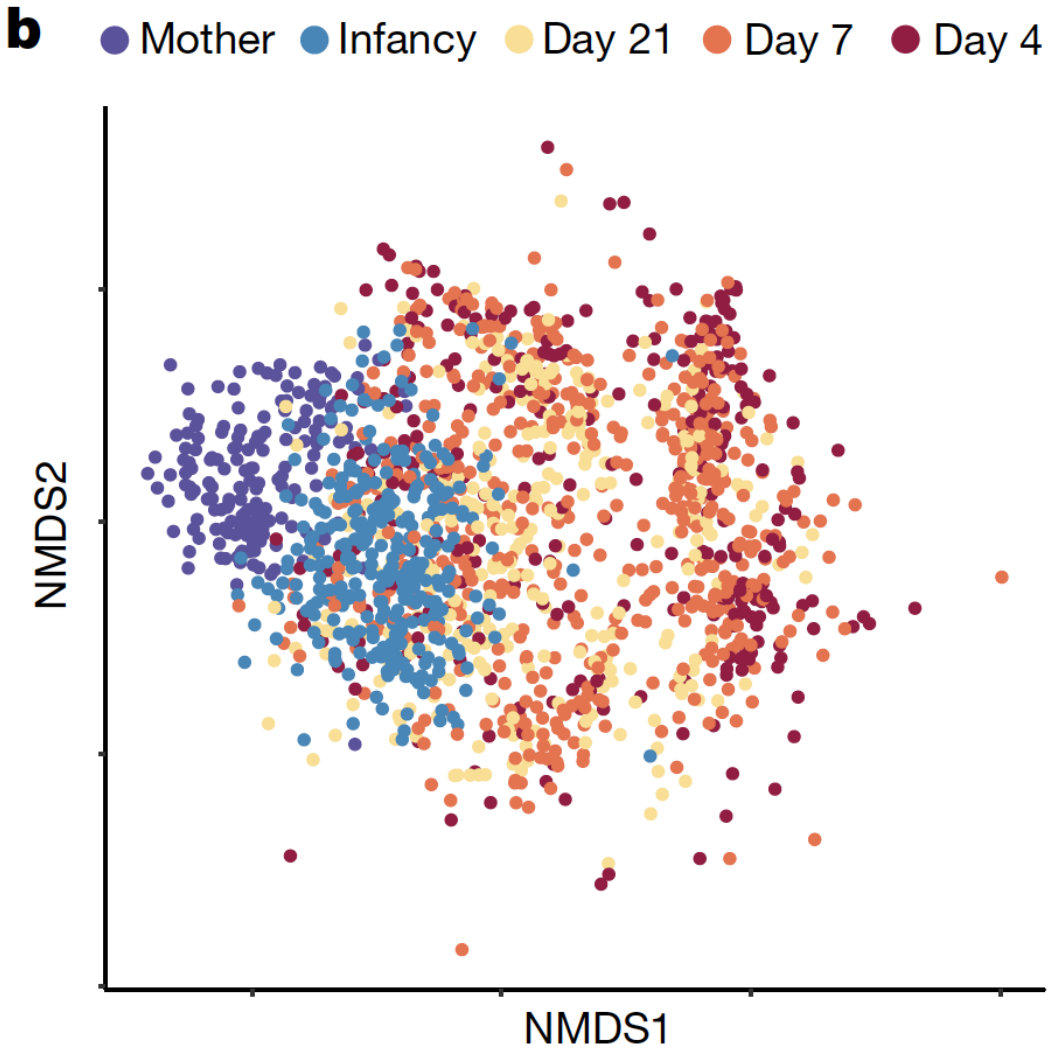
■ 제왕절개의 경우 생후 초기에 장내 세균 (특히 Bacteroides)의 전파가 없다가 나중에 전파가 됨



Shao et al. (2019) Nature

영유아의 마이크로바이옴 발달

■ 마이크로바이옴의 구성은 성인을 닮아 감

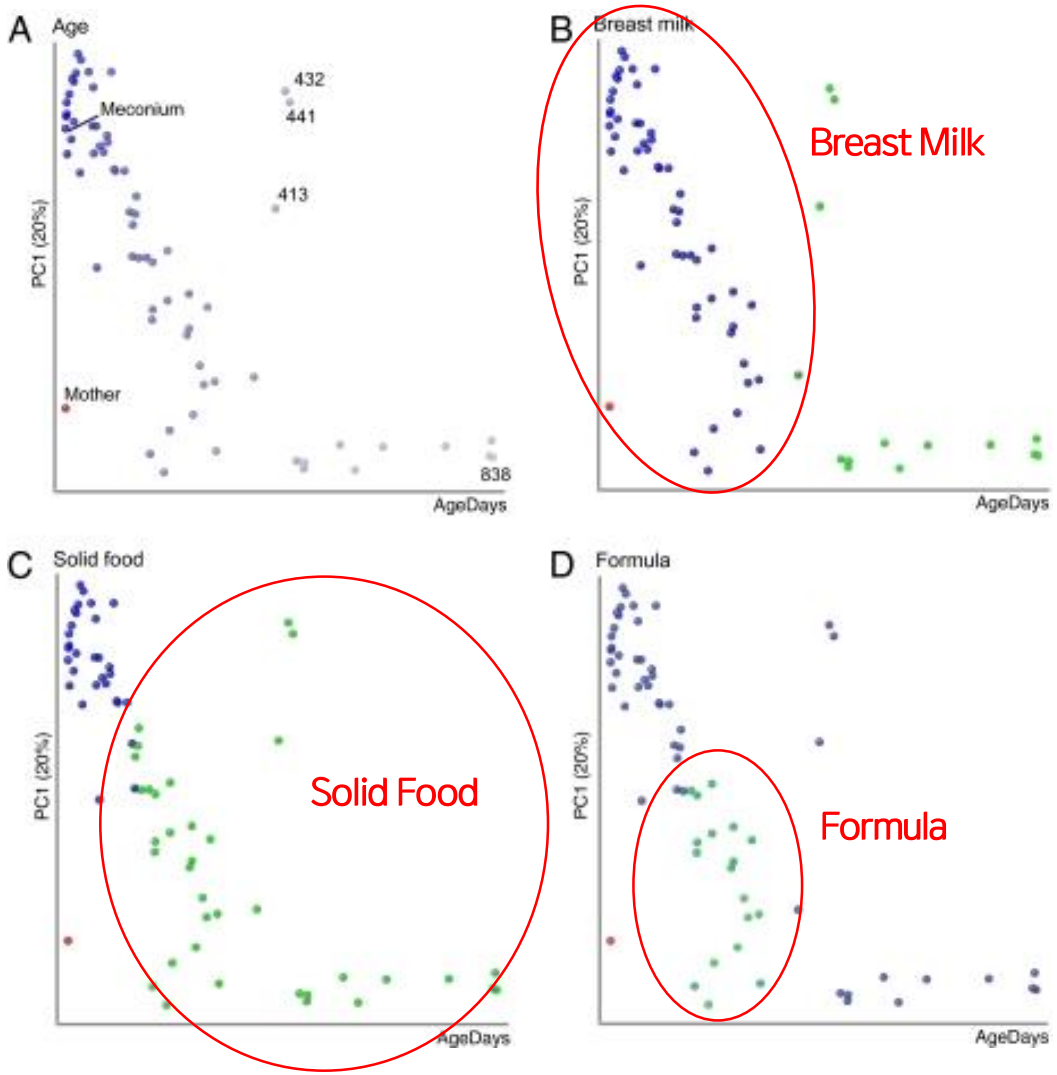


Shao et al. (2019) Nature

식이형태와 영유아의 마이크로바이옴

■ 개월수에 따른 마이크로바이옴 변화

– 첫 134일은 모유수유만, 이후 9개월까지 혼합수유, 4개월때부터 이유식 시작한 경우의 사례



Koenig et al. (2011) Proc Natl Acad Sci USA

출산 방식이 사람에 미치는 영향

■ 제왕절개와 면역 질환

- 덴마크 연구 (1973~2016년에 태어난 2.7백만 아이를 추적 조사)
- 최소한 40년까지는 다양한 면역 질환을 증가 시킴
  - 염증성 장질환 (크론병), 류마티스 관절염, 셀리악 병, 제1형 당뇨

Clinical Epidemiology — Dovepress

ORIGINAL RESEARCH

Caesarean Delivery and Risk of Chronic Inflammatory Diseases (Inflammatory Bowel Disease, Rheumatoid Arthritis, Coeliac Disease, and Diabetes Mellitus): A Population Based Registry Study of 2,699,479 Births in Denmark During 1973–2016

This article was published in the following Dove Press journal: *Clinical Epidemiology*

Vibeke Andersen[1–3], Sören Möller[4], Peter Bjødstrup Jensen[4], Frederik Trier Møller[5,6], Anders Green[4]

[1]Focused Research Unit for Molecular Diagnostic and Clinical Research (MOK), Hospital of Southern Jutland, Åbenrå DK-6200, Denmark; [2]Institute of Regional Research (IRS-Center Sønderjylland), University of Southern Denmark, Odense C DK-5000, Denmark; [3]Institute of Molecular Medicine, University of Southern Denmark, Odense C DK-5000, Denmark; [4]Open Patient data Explorative Network (OPEN), Department of Clinical Research, Odense University Hospital and University of Southern Denmark, Odense C DK-5000, Denmark; [5]Department of Epidemiology Research, Statens Serum Institute, Copenhagen DK-2300, Denmark; [6]Department of Infectious Disease Epidemiology and Prevention, Statens Serum Institute, Copenhagen DK-2300, Denmark

Background: Chronic inflammatory diseases in childhood and early adult life share aetiological factors operating from birth and onwards. In this study, we use data from the national Danish health registers to evaluate the risk of developing four common, immune-mediated hospital-diagnosed childhood chronic inflammatory diseases.

Methods: A national population-based registry study. Data from the Danish Medical Birth Registry and the Danish National Patient Registry from January 1973 to March 2016 were linked at a personal level to evaluate any potential associations between caesarean section and development of Inflammatory bowel diseases, rheumatoid arthritis, coeliac disease and diabetes mellitus among the offspring. A model adjusted for parental age at birth, decade of birth, gender of child, and parents' chronic inflammatory disease status was used.

Results: This register-based national cohort study of 2672708 children with information on delivery mode found an increased risk of diabetes, arthritis, coeliac disease, and inflammatory bowel disease for both girls and boys after caesarean section compared with vaginal delivery. The higher risk was present at least 40 years after delivery. In a subgroup analysis, both acute and elective caesarean section was associated with an increased risk of developing a chronic inflammatory disease.

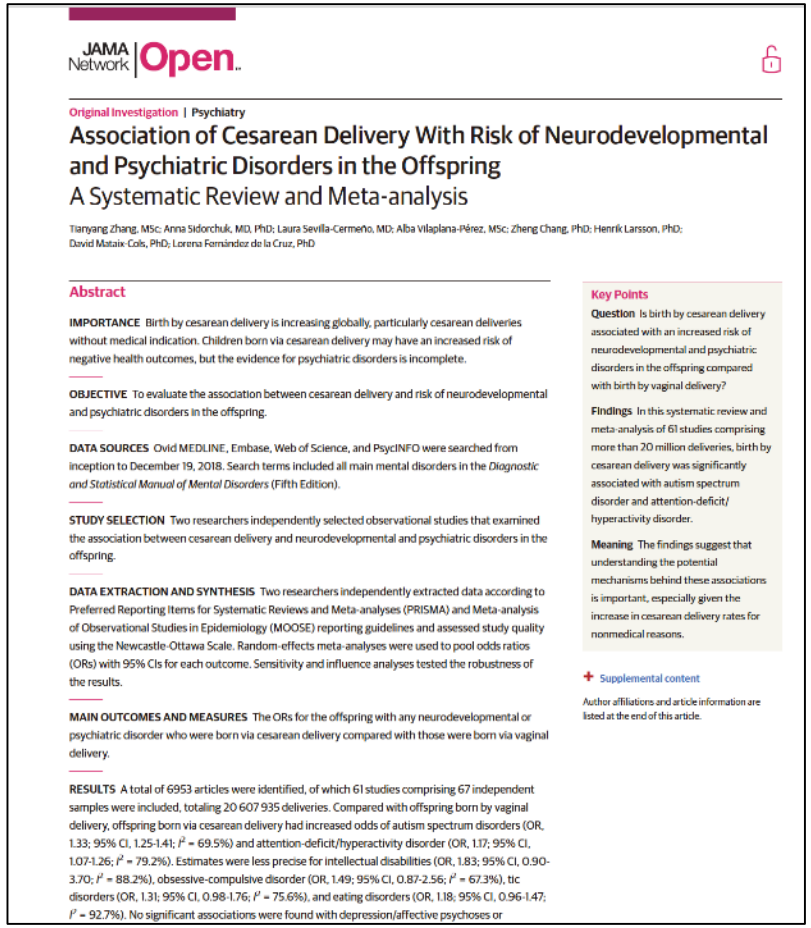
Conclusions: Being born by caesarean section leads to increased host susceptibility for chronic inflammatory diseases that last for decades. This finding should be further addressed in future studies with the aim to support the development of new strategies for prevention, treatment, and maybe even cure.

Keywords: caesarean delivery, population study, vaginal birth, chronic inflammatory disease, inflammatory bowel diseases, rheumatoid arthritis, coeliac disease

Andersen et al. (2020) Clinical Epidemiology

■ 제왕절개와 자폐/ADHD 연구

- 61개 연구의 메타분석
- 제왕절개 분만은 자폐 스펙트럼 장애와 ADHD와 역학적으로 연관
- 자폐 스펙트럼 장애 33% 증가, ADHD = 17% 증가



JAMA Network Open

Original Investigation | Psychiatry

Association of Cesarean Delivery With Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring
A Systematic Review and Meta-analysis

Tianyang Zhang, MSc; Anna Sidorchuk, MD, PhD; Laura Sevilla-Cermeño, MD; Alba Vilaplana-Pérez, MSc; Zheng Chang, PhD; Henrik Larsson, PhD; David Mataix-Cols, PhD; Lorena Fernández de la Cruz, PhD

Abstract

IMPORTANCE Birth by cesarean delivery is increasing globally, particularly cesarean deliveries without medical indication. Children born via cesarean delivery may have an increased risk of negative health outcomes, but the evidence for psychiatric disorders is incomplete.

OBJECTIVE To evaluate the association between cesarean delivery and risk of neurodevelopmental and psychiatric disorders in the offspring.

DATA SOURCES Ovid MEDLINE, Embase, Web of Science, and PsycINFO were searched from inception to December 19, 2018. Search terms included all main mental disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

STUDY SELECTION Two researchers independently selected observational studies that examined the association between cesarean delivery and neurodevelopmental and psychiatric disorders in the offspring.

DATA EXTRACTION AND SYNTHESIS Two researchers independently extracted data according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines and assessed study quality using the Newcastle-Ottawa Scale. Random-effects meta-analyses were used to pool odds ratios (ORs) with 95% CIs for each outcome. Sensitivity and influence analyses tested the robustness of the results.

MAIN OUTCOMES AND MEASURES The ORs for the offspring with any neurodevelopmental or psychiatric disorder who were born via cesarean delivery compared with those were born via vaginal delivery.

RESULTS A total of 6953 articles were identified, of which 61 studies comprising 67 independent samples were included, totaling 20 607 935 deliveries. Compared with offspring born by vaginal delivery, offspring born via cesarean delivery had increased odds of autism spectrum disorders (OR, 1.33; 95% CI, 1.25-1.41; I^2 = 69.5%) and attention-deficit/hyperactivity disorder (OR, 1.17; 95% CI, 1.07-1.26; I^2 = 79.2%). Estimates were less precise for intellectual disabilities (OR, 1.83; 95% CI, 0.90-3.70; I^2 = 88.2%), obsessive-compulsive disorder (OR, 1.49; 95% CI, 0.87-2.56; I^2 = 67.3%), tic disorders (OR, 1.31; 95% CI, 0.98-1.76; I^2 = 75.6%), and eating disorders (OR, 1.18; 95% CI, 0.96-1.47; I^2 = 92.7%). No significant associations were found with depression/affective psychoses or

Key Points

Question Is birth by cesarean delivery associated with an increased risk of neurodevelopmental and psychiatric disorders in the offspring compared with birth by vaginal delivery?

Findings In this systematic review and meta-analysis of 61 studies comprising more than 20 million deliveries, birth by cesarean delivery was significantly associated with autism spectrum disorder and attention-deficit/hyperactivity disorder.

Meaning The findings suggest that understanding the potential mechanisms behind these associations is important, especially given the increase in cesarean delivery rates for nonmedical reasons.

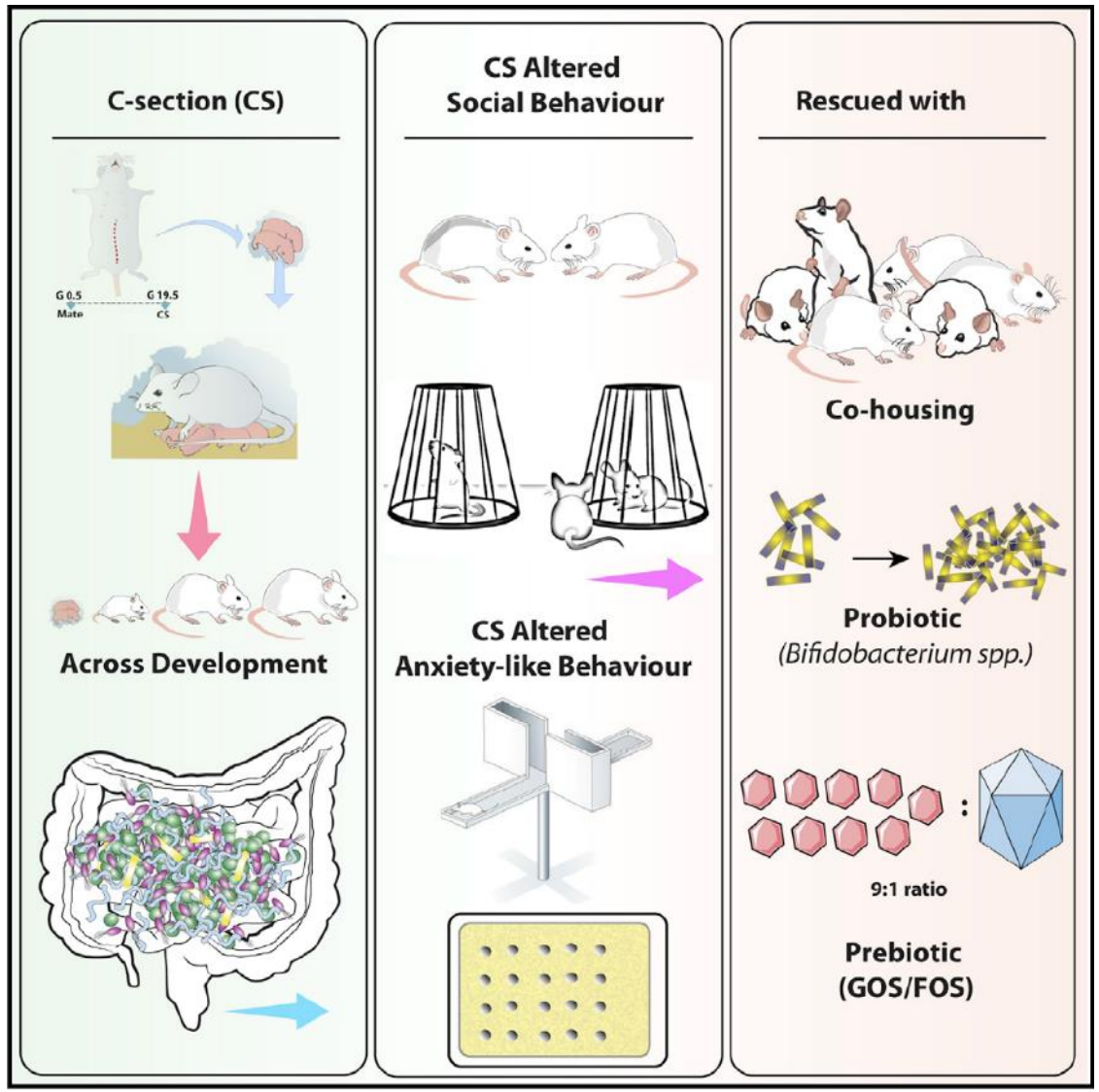
Supplemental content

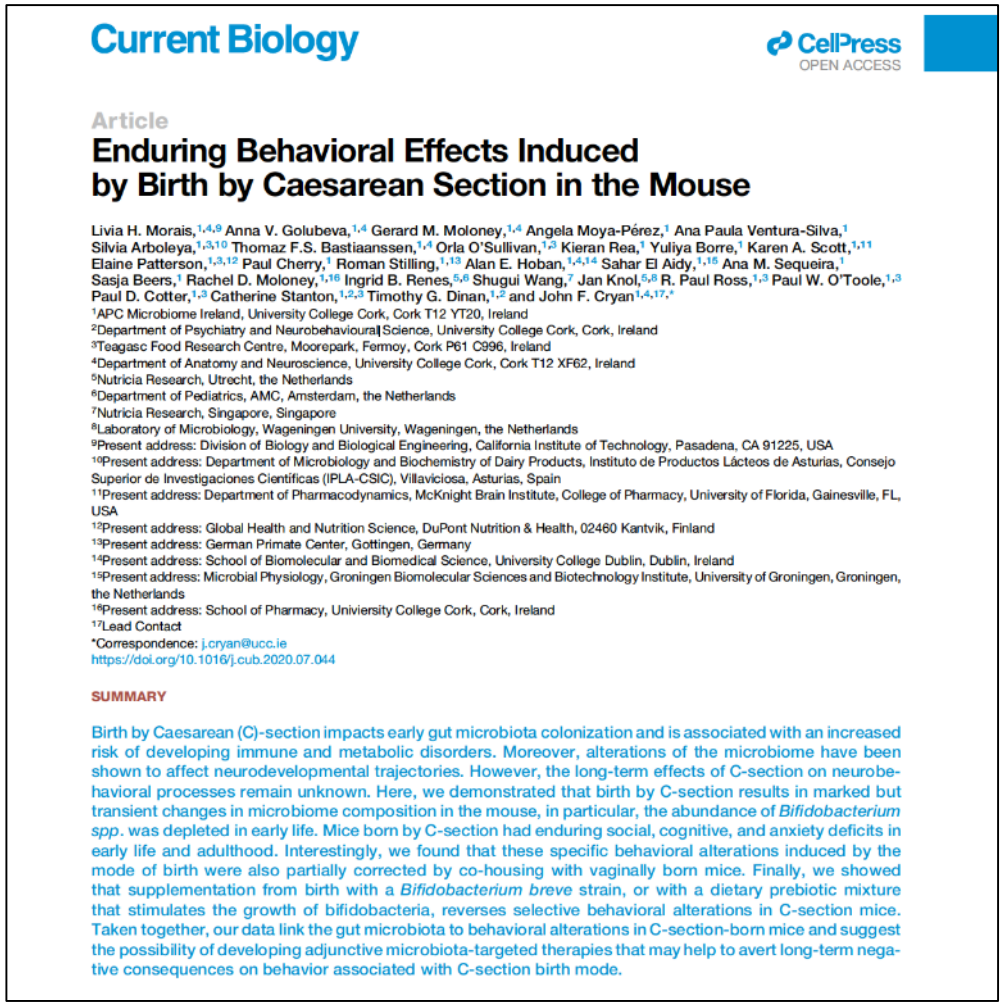
Author affiliations and article information are listed at the end of this article.

Zhang et al., (2020) JAMA Network Open

제왕절개가 행동에 미치는 영향 연구

■ 마우스 실험으로 제왕 절개가 생후 초기의 마이크로바이옴 변화를 통해 성체에 영향을 줌을 확인





Current Biology

CellPress
OPEN ACCESS

Article

Enduring Behavioral Effects Induced by Birth by Caesarean Section in the Mouse

Livia H. Morais,[1,4,9] Anna V. Golubeva,[1,4] Gerard M. Moloney,[1,4] Angela Moya-Pérez,[1] Ana Paula Ventura-Silva,[1] Silvia Arboleya,[1,3,10] Thomaz F.S. Bastiaanssen,[1,4] Orla O'Sullivan,[1,3] Kieran Rea,[1] Yuliya Borre,[1] Karen A. Scott,[1,11] Elaine Patterson,[1,3,12] Paul Cherry,[1] Roman Stilling,[1,13] Alan E. Hoban,[1,4,14] Sahar El Aidy,[1,15] Ana M. Sequeira,[1] Sasja Beers,[1] Rachel D. Moloney,[1,16] Ingrid B. Renes,[5,6] Shugui Wang,[7] Jan Knol,[5,8] R. Paul Ross,[1,3] Paul W. O'Toole,[1,3] Paul D. Cotter,[1,3] Catherine Stanton,[1,2,3] Timothy G. Dinan,[1,2] and John F. Cryan[1,4,17,*]

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[6]Department of Pediatrics, AMC, Amsterdam, the Netherlands
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[15]Present address: Microbial Physiology, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Groningen, the Netherlands
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https://doi.org/10.1016/j.cub.2020.07.044

SUMMARY

Birth by Caesarean (C)-section impacts early gut microbiota colonization and is associated with an increased risk of developing immune and metabolic disorders. Moreover, alterations of the microbiome have been shown to affect neurodevelopmental trajectories. However, the long-term effects of C-section on neurobehavioral processes remain unknown. Here, we demonstrated that birth by C-section results in marked but transient changes in microbiome composition in the mouse, in particular, the abundance of *Bifidobacterium spp*. was depleted in early life. Mice born by C-section had enduring social, cognitive, and anxiety deficits in early life and adulthood. Interestingly, we found that these specific behavioral alterations induced by the mode of birth were also partially corrected by co-housing with vaginally born mice. Finally, we showed that supplementation from birth with a *Bifidobacterium breve* strain, or with a dietary prebiotic mixture that stimulates the growth of bifidobacteria, reverses selective behavioral alterations in C-section mice. Taken together, our data link the gut microbiota to behavioral alterations in C-section-born mice and suggest the possibility of developing adjunctive microbiota-targeted therapies that may help to avert long-term negative consequences on behavior associated with C-section birth mode.

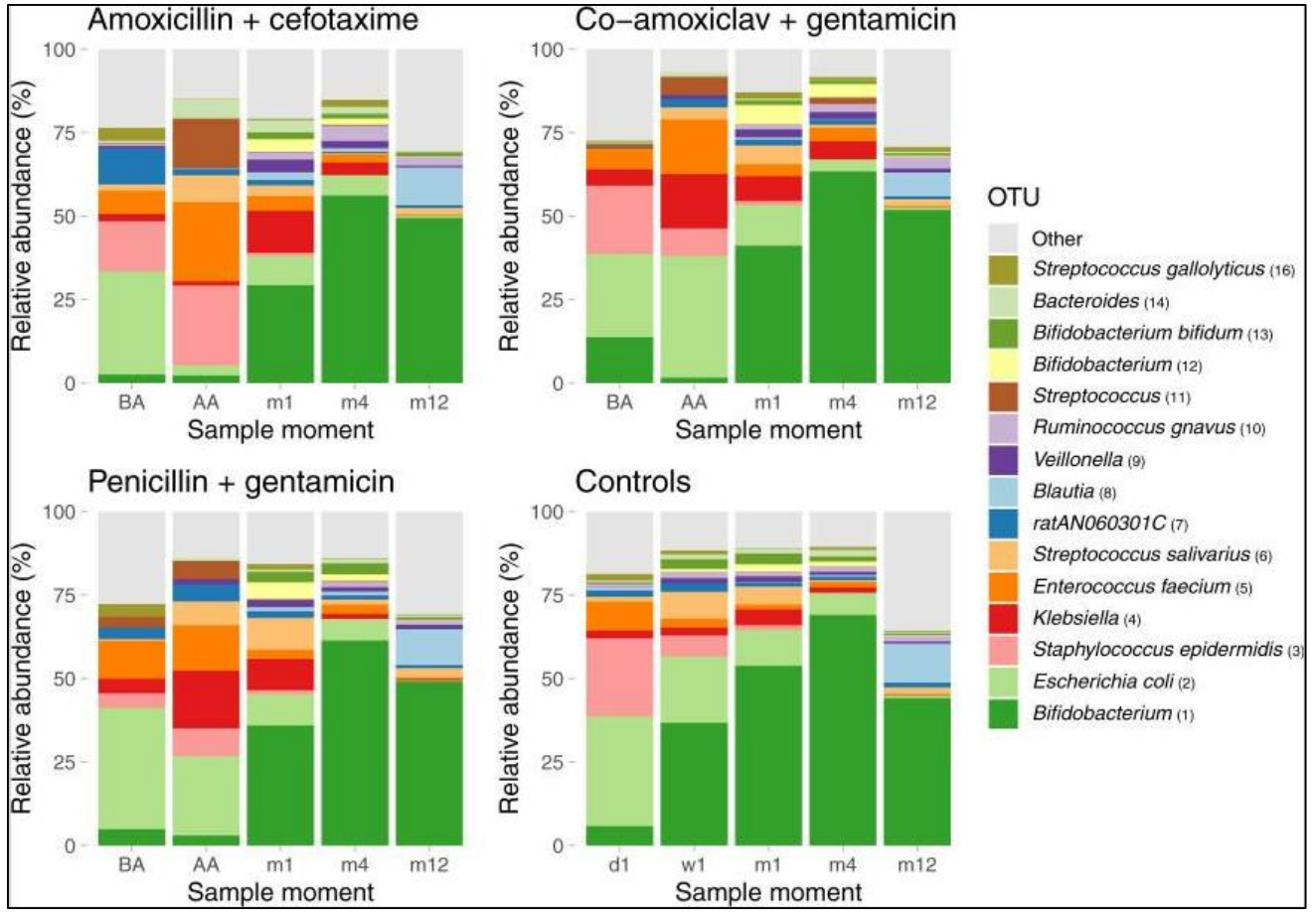
Morais et al., 2020, Cur. Biol.

신생아 시기 마이크로바이옴의 중요성

■ 신생아 시기 연구에 따르면 장내 마이크로바이옴의 발달에 문제가 있으면 이후 생애주기에서 질병에 취약해진다고 함

■ 항생제 처리가 장내 마이크로바이옴 발달에 주는 영향

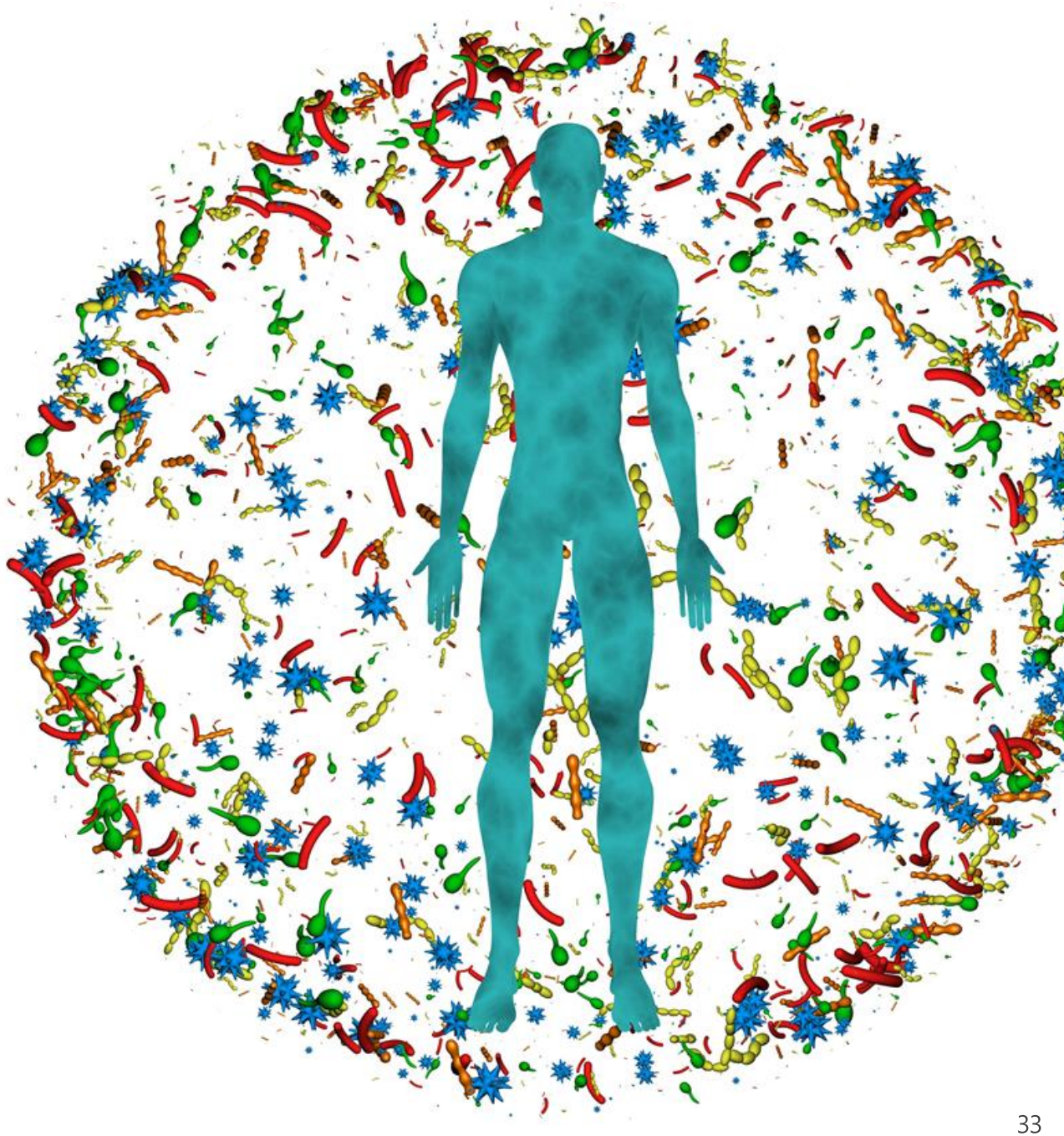
1. 신생아 1152명을 1년간 추적관찰한 결과, Preterm Birth나 신생아 시기 항생제 처방시 위장관장애 발생 사례 증가 (Salvatore et al. (2019) J Prediate)
2. 영유아 149명의 혈액내 염증 마커 조사결과, 생후 1주차에 항생제 처방을 받은 아이의 염증 마커 level이 다름 (Oosterloo et al. (2020) Front Immunol.)
3. 생후 첫 주에 항생제 처방(평균 48시간)을 받은 신생아 (재태기간 36주 이상) 147명을 1년간 추적관찰



Reyman et al. (2022) Nat Commun.

분변이식

FECAL MICROBIOTA TRANSPLANTATION



FMT (FECAL MICROBIOTA PLANTATION) 연구결과①

■ 유아기부터 만성적인 GI 문제 (설사/변비)를 가지고 있던 18명의 소아청소년 ASD 환자에게 FMT 실시

Kang *et al. Microbiome* (2017) 5:10
DOI 10.1186/s40168-016-0225-7

Microbiome

RESEARCH Open Access

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Dae-Wook Kang[1†], James B. Adams[2†], Ann C. Gregory[3,15†], Thomas Borody[4], Lauren Chittick[5,15], Alessio Fasano[6], Alexander Khoruts[7,8,9], Elizabeth Geis[2], Juan Maldonado[1], Sharon McDonough-Means[10], Elena L. Pollard[2], Simon Roux[5,15], Michael J. Sadowsky[8,11], Karen Schwarzberg Lipson[12], Matthew B. Sullivan[3,5,15,16*], J. Gregory Caporaso[12,13*] and Rosa Krajmalnik-Brown[1,14*]

Kang et al. (2017) Microbiome

FMT 연구결과①

■ 6개월 동안 6회의 FMT 실행

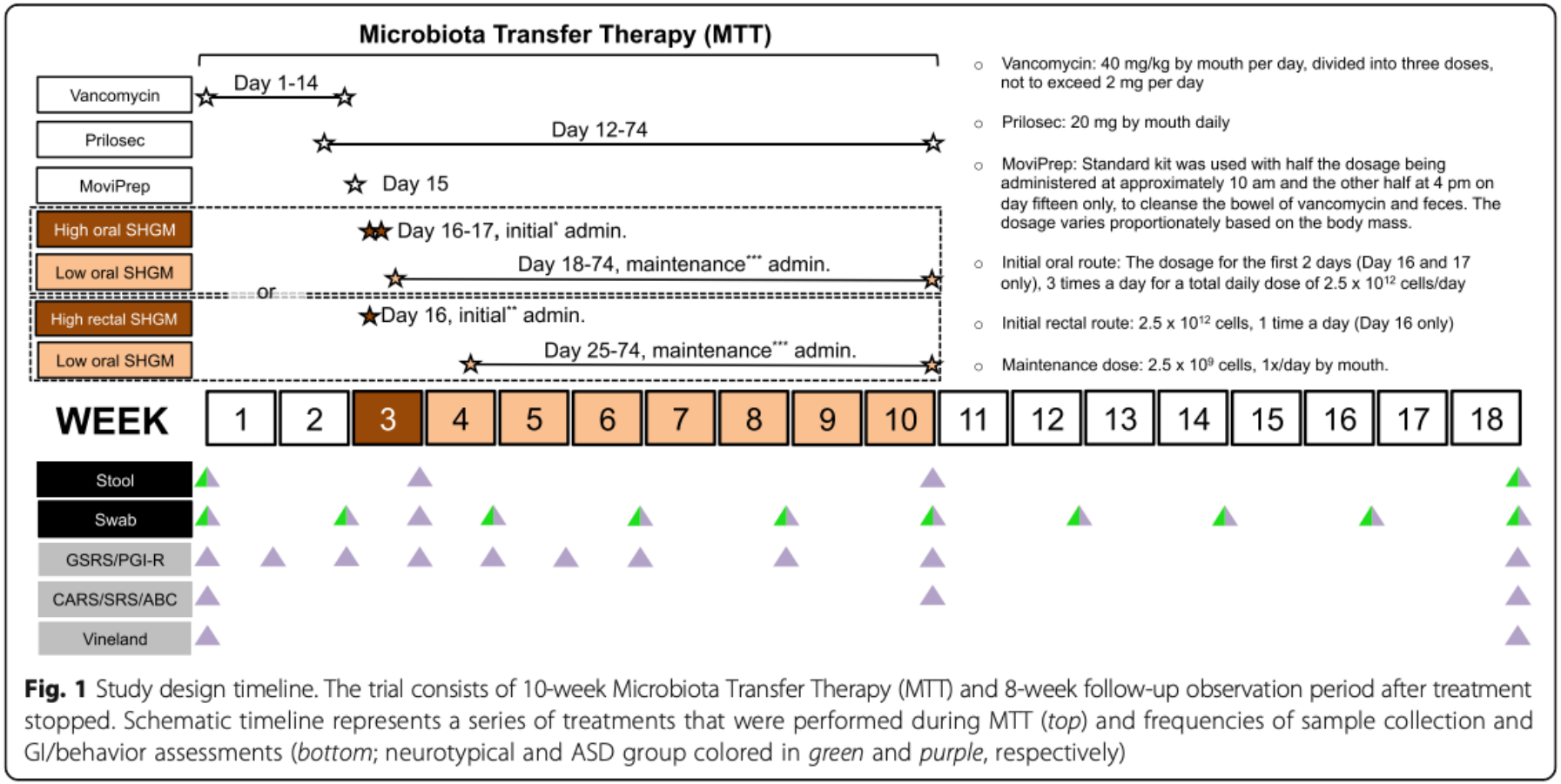
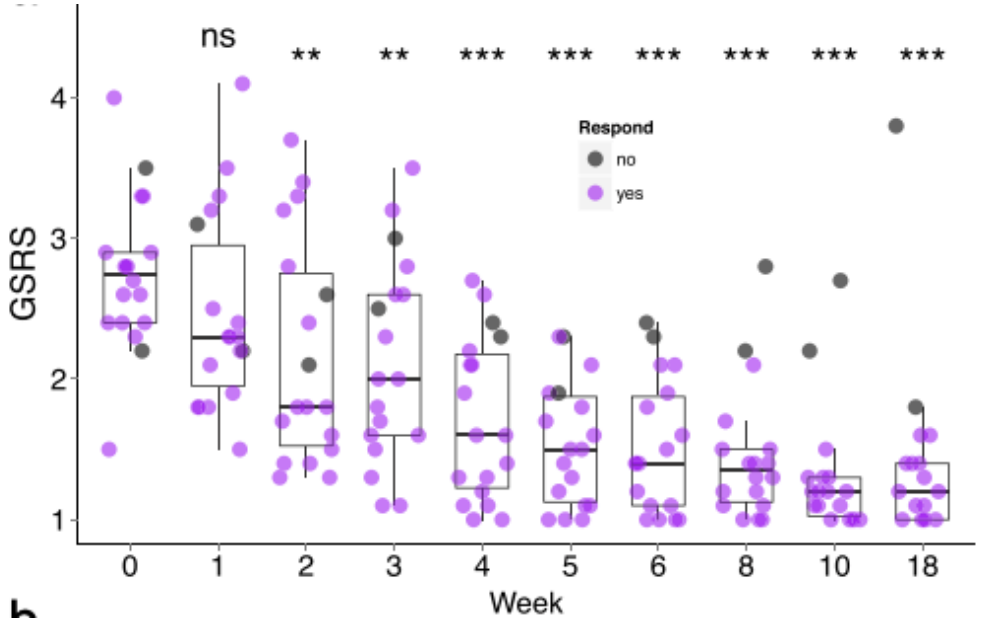


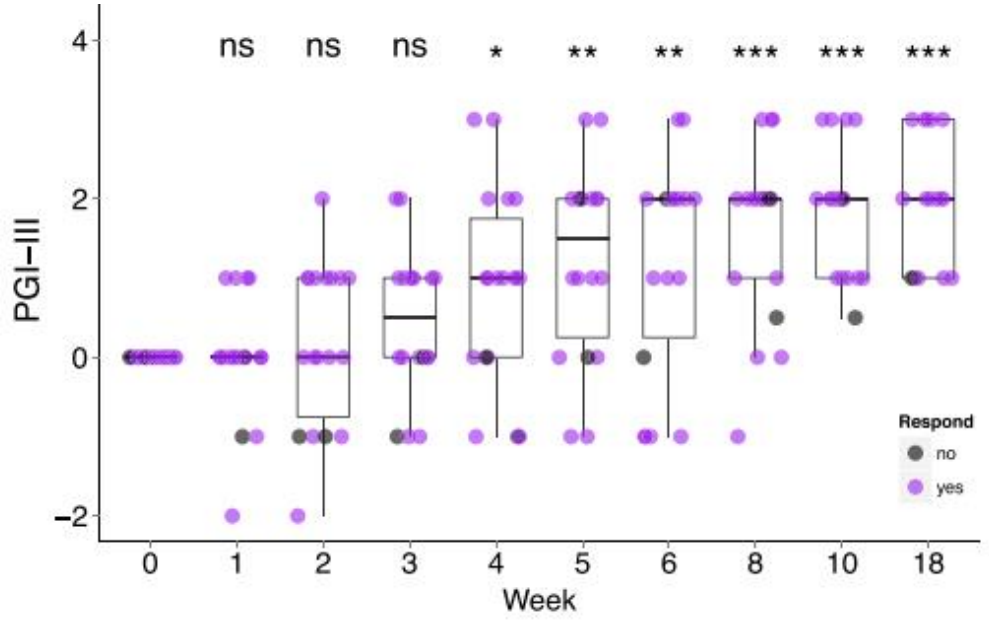
Fig. 1 Study design timeline. The trial consists of 10-week Microbiota Transfer Therapy (MTT) and 8-week follow-up observation period after treatment stopped. Schematic timeline represents a series of treatments that were performed during MTT (*top*) and frequencies of sample collection and GI/behavior assessments (*bottom*; neurotypical and ASD group colored in *green* and *purple*, respectively)

Kang et al. (2017) Microbiome

FMT 연구결과①

■ 대변 미생물 이식 직후





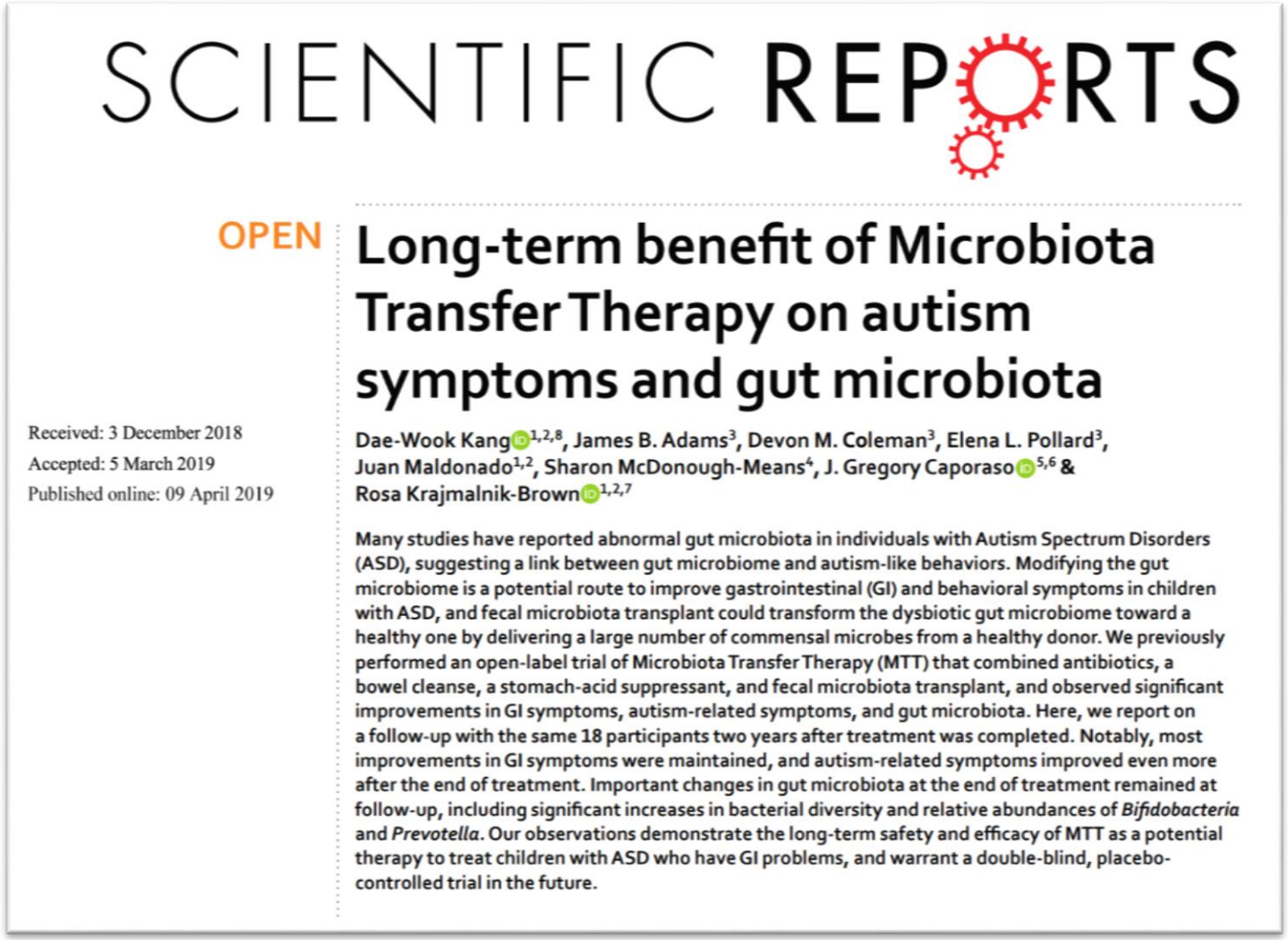
대부분의 참여자가 GI 문제 완화
(Responder:Non-responder = 16:2)

대부분의 참여자가 인지 기능 향상

Kang et al. (2017) Microbiome

FMT 연구결과②

■ 이전 연구의 18명을 추가 치료 없이 2년간 추적 관찰한 연구



SCIENTIFIC REPORTS

OPEN

Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota

Received: 3 December 2018
Accepted: 5 March 2019
Published online: 09 April 2019

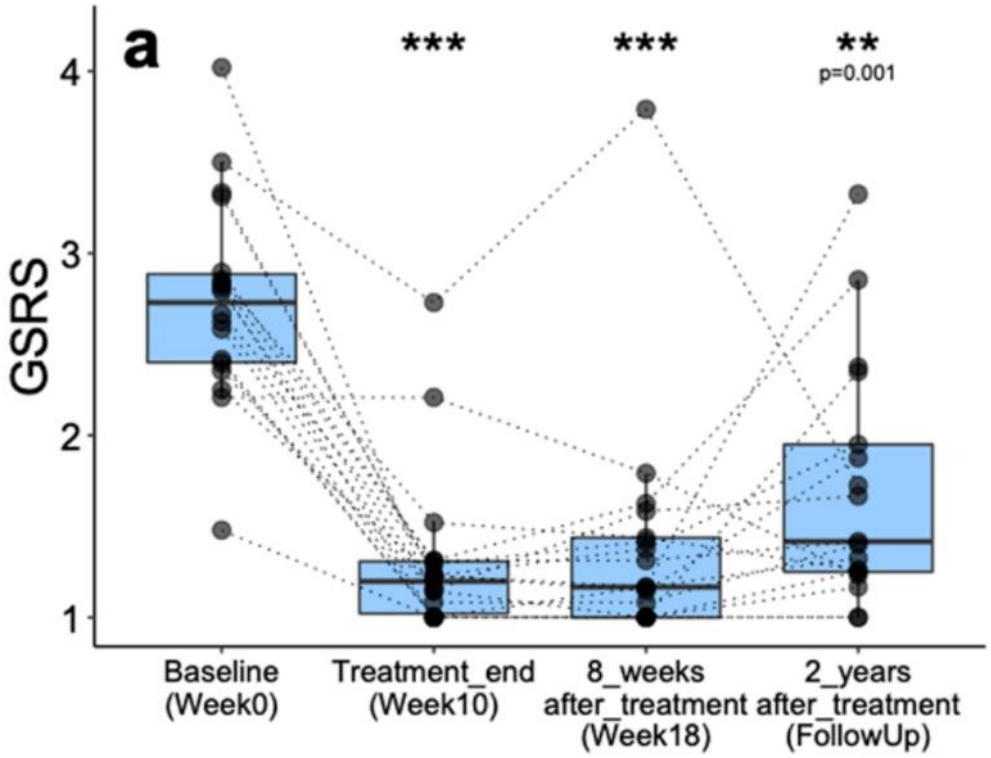
Dae-Wook Kang[1,2,8], James B. Adams[3], Devon M. Coleman[3], Elena L. Pollard[3], Juan Maldonado[1,2], Sharon McDonough-Means[4], J. Gregory Caporaso[5,6] & Rosa Krajmalnik-Brown[1,2,7]

Many studies have reported abnormal gut microbiota in individuals with Autism Spectrum Disorders (ASD), suggesting a link between gut microbiome and autism-like behaviors. Modifying the gut microbiome is a potential route to improve gastrointestinal (GI) and behavioral symptoms in children with ASD, and fecal microbiota transplant could transform the dysbiotic gut microbiome toward a healthy one by delivering a large number of commensal microbes from a healthy donor. We previously performed an open-label trial of Microbiota Transfer Therapy (MTT) that combined antibiotics, a bowel cleanse, a stomach-acid suppressant, and fecal microbiota transplant, and observed significant improvements in GI symptoms, autism-related symptoms, and gut microbiota. Here, we report on a follow-up with the same 18 participants two years after treatment was completed. Notably, most improvements in GI symptoms were maintained, and autism-related symptoms improved even more after the end of treatment. Important changes in gut microbiota at the end of treatment remained at follow-up, including significant increases in bacterial diversity and relative abundances of *Bifidobacteria* and *Prevotella*. Our observations demonstrate the long-term safety and efficacy of MTT as a potential therapy to treat children with ASD who have GI problems, and warrant a double-blind, placebo-controlled trial in the future.

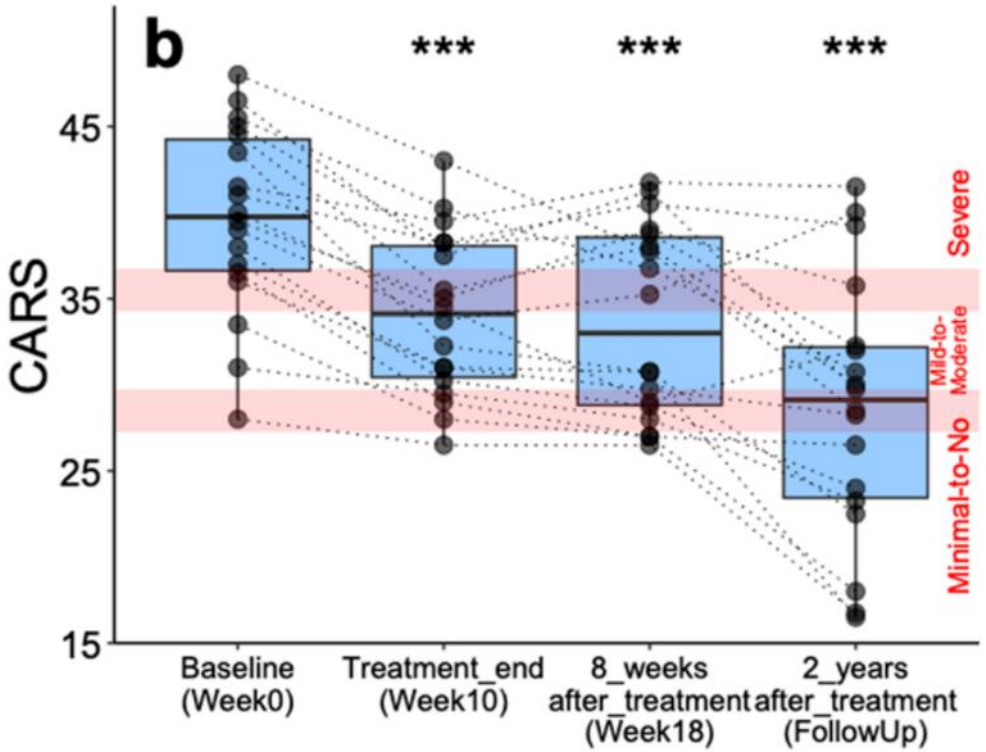
Kang et al. (2019) Scientific Reports

FMT 연구결과②

■ 대변 미생물 이식 치료 2년 후



Gastrointestinal Symptom Rating Scale (GSRS)가 baseline 대비 58% 감소

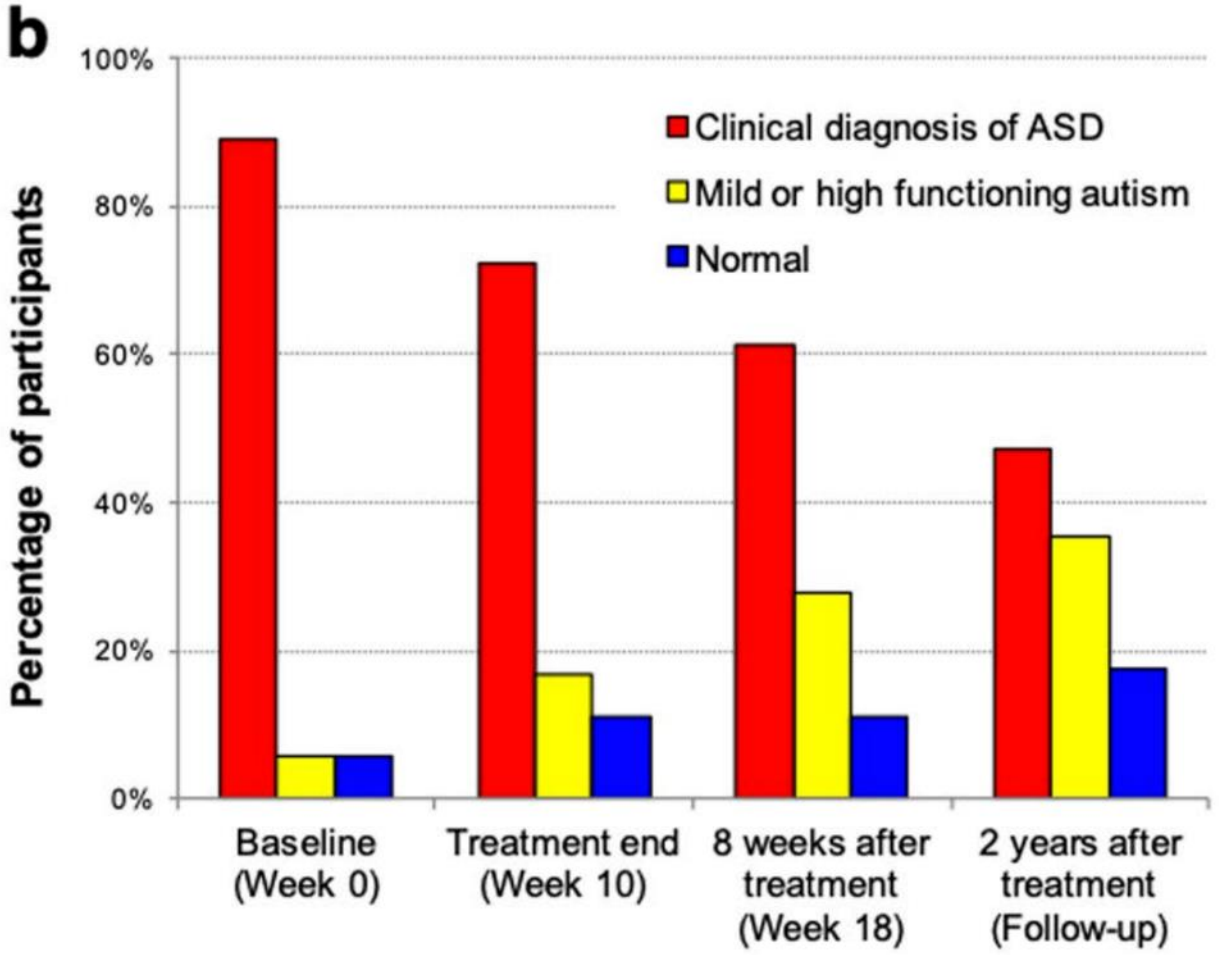


전문의가 평가하는 Childhood Autism Rating Scale (CARS)이 baseline 대비 47% 감소

Kang et al. (2019) Scientific Reports

FMT 연구결과②

■ 대변 미생물 이식 치료 2년 후 ASD 진단 90%가 50%로 감소



Kang et al. (2019) Scientific Reports

동물 및 인간 임상 FMT 실험으로 치료 가능성이 증명된 연구

CJ 바이오사이언스

분야	질병	동물실험으로 치료 가능성 증명	인간 대상의 임상시험으로 치료효과가 보인 경우
대사질환	비만	Ridaura et al. (2013) *Science*	
	당뇨	Suez et al. (2014) *Nature*	Vrieze et al. (2012) *Gastroenterology* (RR : x, 포도당 감소율 26.2에서 45.3로 상승 (μmol/kg/min, 중앙값 기준))
암질환	면역항암제 병용요법	Gopalakrishnan et al. (2018) *Science* (Anti-PD-1/흑색종) Matson et al. (2018) *Science* (Anti-PD-1/흑색종) Routy et al. (2018) *Science* NSCLC/신장암	Wang et al. (2018) *Nature medicine* (RR : 100%, 2명)
	대장암	Wong et al. (2017) *Gastroenterology* Bullman et al. (2017) *Science*	
소화기질환	급성췌장염	Zhu et al. (2019) *Journal of Gastroenterology*	
	과민성 대장 증후군	Touw et al. (2017) *Physiological Reports* De et al. (2017) *Sci Trans Med*	Johnsen et al. *(2018) Lancet Gastroenterology & Hepatology* (RR: 65%)
	염증성 장 질환		Meighani et al. (2017) *Digestive Diseases and Sciences* (RR: 75%)
	만성 변비	Cao et al. (2017) *Scientific Reports*	Ding et al. (2018) *Gastroenterology Report* (RR : 50%)
감염질환	클로스트리디움 디피실 감염증	Battaglioli et al. (2018) *Sci Trans Med*	Zipursky et al. (2014) *Canadian Journal of Gastroenterology and Hepatology* (RR : 97%)
	다제내성균 감염증		Wei et al. (2015) *BMC Infectious Diseases* (RR : 100%)
심혈관질환	고혈압	Li et al. (2017) *Microbiome*	
뇌질환	알츠하이머	Kim et al. (2019) Gastroenterology	
	자폐 스펙트럼 장애		Kang et al. (2019) *Scientific Reports* (RR : 83%) Kang et al. (2017) *Microbiome* (RR : 89%)
	파킨슨병	Sampson et al. (2016) *Cell*	
	조현병	Zeng et al. (2019) *Science Advances*	

Thank You