Human microbiome and health benefits of exposure to microbial diversity the environment

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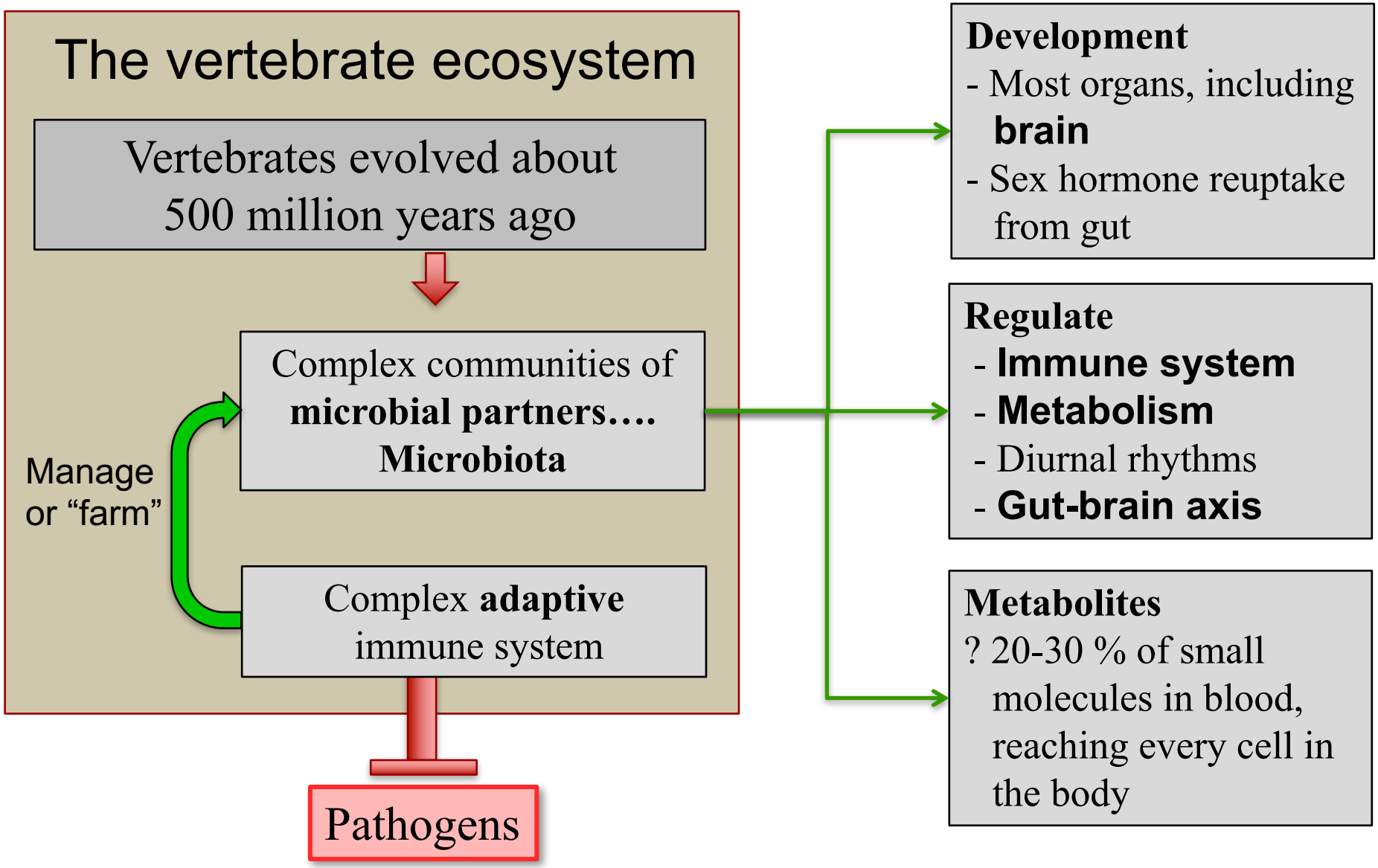
UCL



Shu et al. (1999) Lower Cambrian vertebrates from south China. *Nature* **402**:42-6.
Pancer & Cooper (2006) The evolution of adaptive immunity. *Annu Rev Immunol* **24**:497-518
McFall-Ngai (2007) Adaptive immunity: care for the community. *Nature* **445**:153
Fuhrman *et al* (2014) *J Clin Endocrinol Metab* **99**:4632 Thaiss *et al* (2014) *Cell* **159:** 514

Organisms with which humans co-evolved : the “Old Friends”

Microbiota
from mother and family and environment

Natural environment.
Spores, organisms (and their genes)

DATA

Immune system **at birth**
- hardware
- software
- needs **DATA**

DATA

- Epigenetic
- Development
- Repertoire

Attack

Repertoire: biodiversity drives a wide range of “memory” cells that can rapidly recognise pathogens

Immunoregulation

- **Do not attack “forbidden targets”**
  (self, allergens, gut contents)
- Increase **repertoire of tolerated microbiota**
- **Turn off redundant inflammation**
  (cardiovascular & metabolic disease, depression)

System failures in high-income urban settings

All have distorted microbiota

Metabolic dysregulation

- Obesity

Chronic unnecessary inflammation

- Depression
- Cancer (colon and breast)

Forbidden targets

- Autoimmunity
- Asthma, other allergies
- Inflammatory bowel disease

Risk increased by antibiotics

Trasande *et al* (2013) *Int J Obes (Lond)* **37**:16
Shao *et al* (2017) *Front Endocrinol* **8**:170
Cassidy-Bushrow *et al* (2017) *Int J Obes (Lond)*

Slykerman *et al* (2017) *Acta Paediatr* **106**:87
Neufeld *et al* (2017) *J Psychiatr Pract* **23**:25

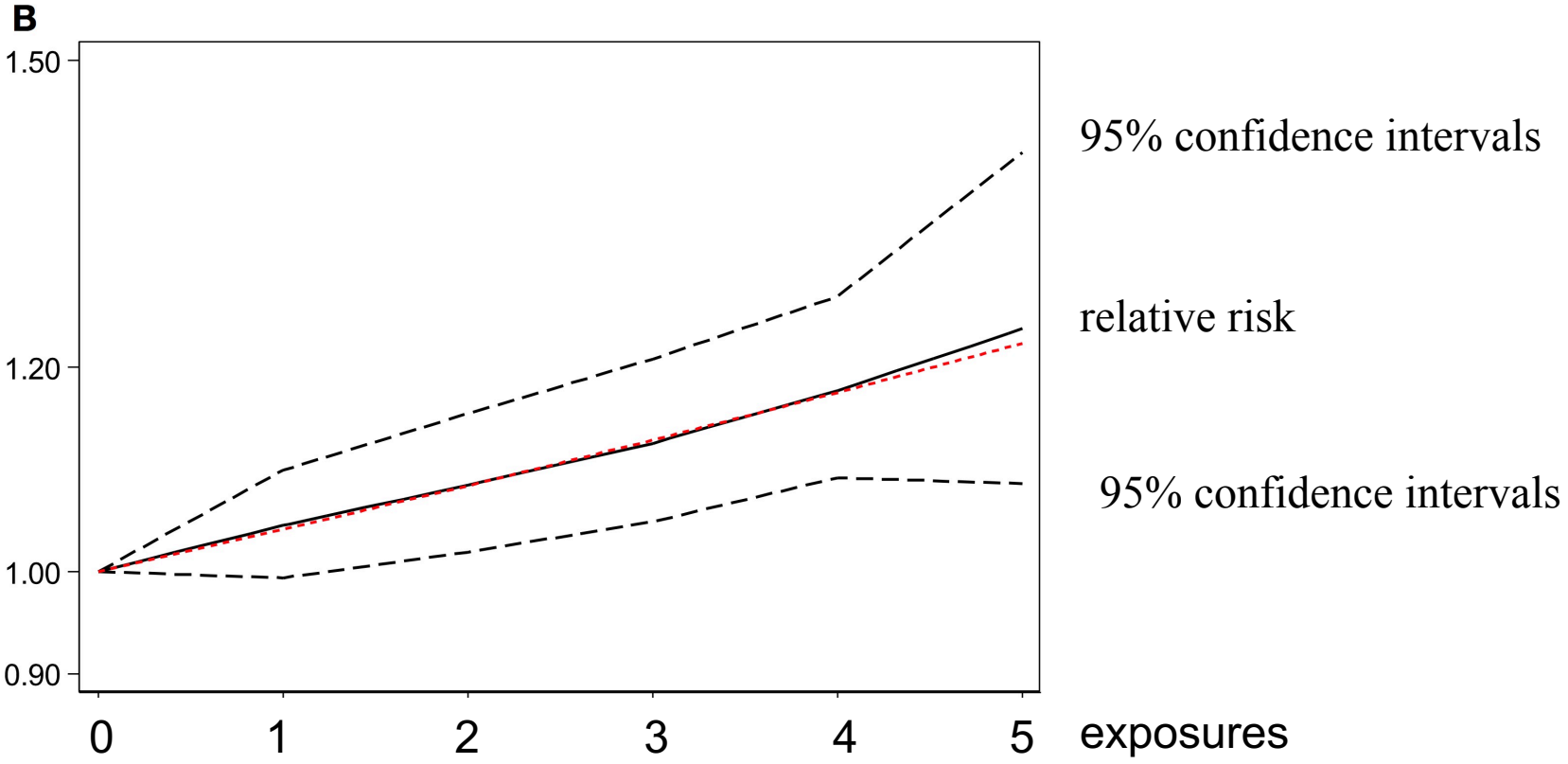
Cao *et al* (2017) Apr 4 *Gut*
Velicer *et al* (2004) *JAMA* **291**:827

Rosser & Mauri (2016) *J Autoimmun* **74**:85
Clausen *et al* (2016) *PLoS One* **11**:e0161654

Korpela *et al* (2016) *Nat Commun* **7**:10410
Metsala *et al* (2013) *Epidemiology* **24**:303

Shaw *et al* (2010) *Am J Gastroenterol* **105**:2687
Hviid *et al* (2011) *Gut* **60**:49

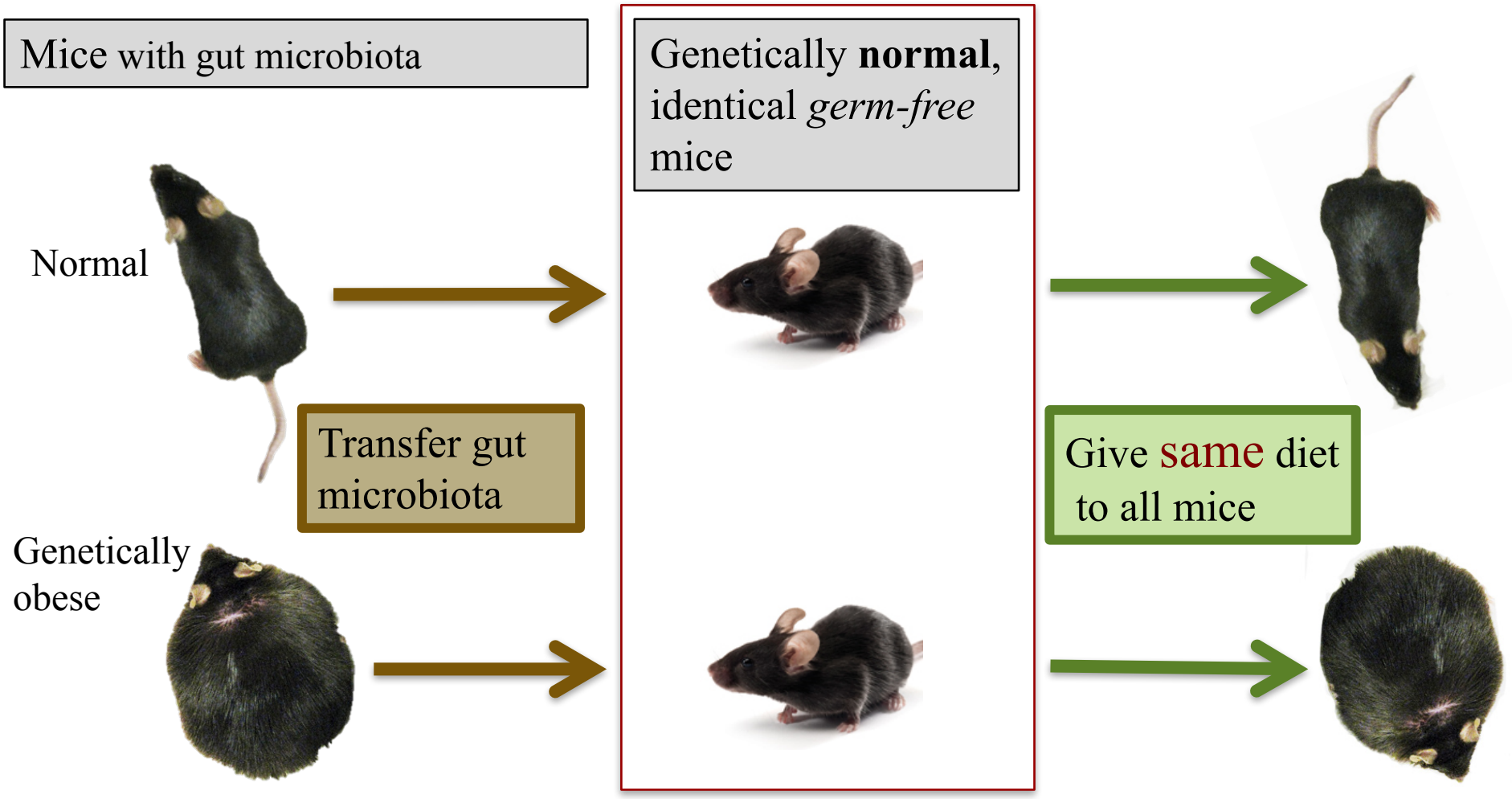
Perinatal (pregnancy or early life) antibiotic exposure and **obesity**



Dose–response meta-analysis of the association between antibiotic exposure in early life and childhood obesity

Shao *et al* (2017) *Front Endocrinol* **8**:170

The gut microbiota (the symbiotic bacteria that live in the gut) can influence **weight gain**



Turnbaugh et al (2006) *Nature* **444**:1027-31. Ridaura et al. (2013) *Science* **341**:1241214.

The gut microbiota (the symbiotic bacteria that live in the gut) can influence weight gain

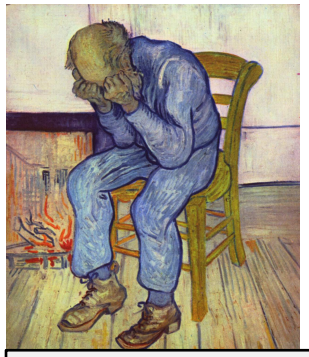
Transfer gut microbiota

Indentical germ-free mice

Give same diet to all mice

Turnbaugh et al (2006) *Nature* **444**:1027-31. Ridaura et al. (2013) *Science* **341**:1241214.

Gut microbiota from depressed humans induces "**depression**" in the rat and mouse



microbiota from *depressed* human

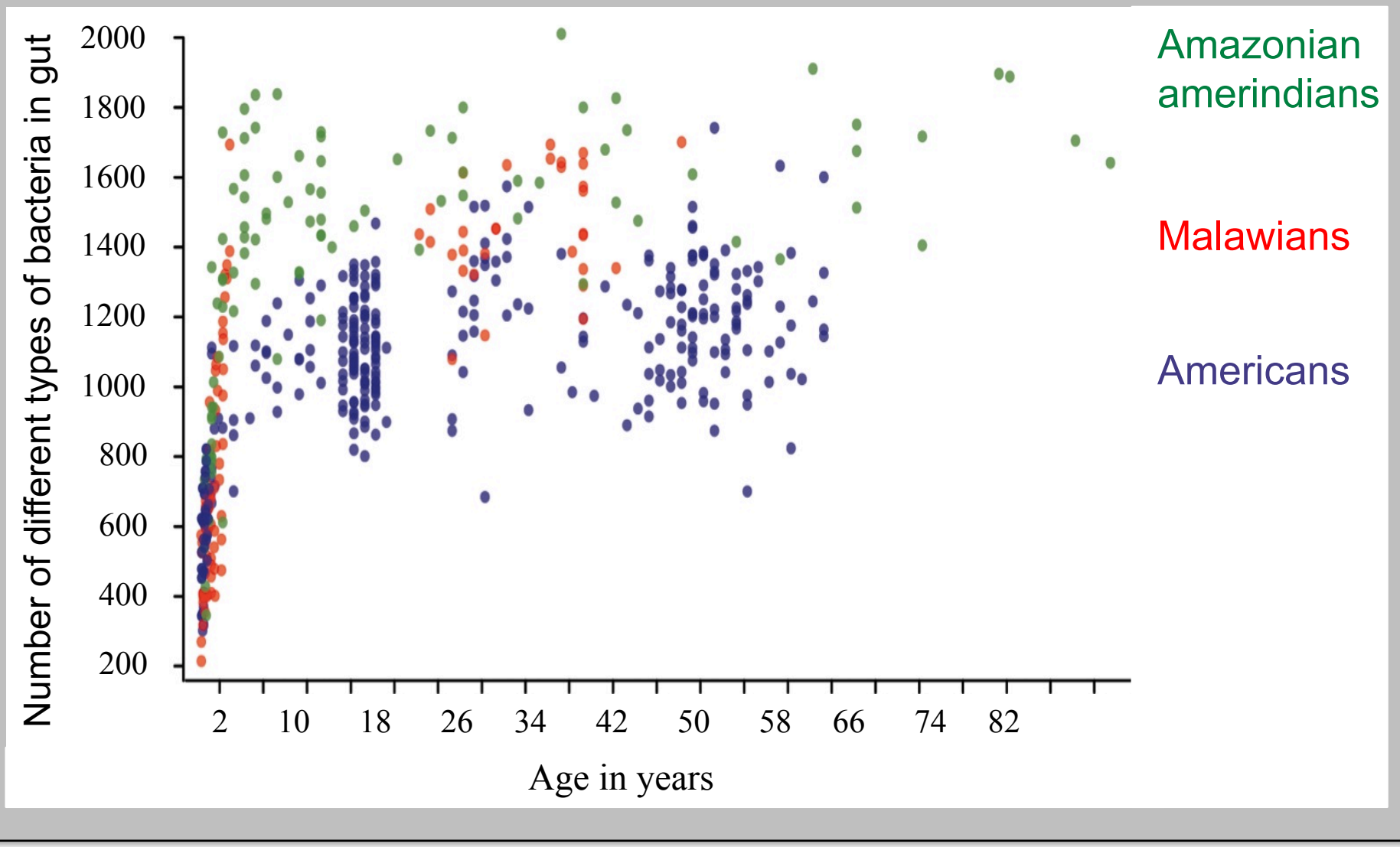
Antibiotics to deplete **rat**[1] microbiota or use germ-free **mice**[2]

microbiota from *happy* human

[1] Kelly *et al* (2016) *J Psychiatr Res* **82**:109

[2] Zheng *et al* (2016) *Mol Psychiatry* **21**:786

Gut microbiota in people from high- versus low-income countries



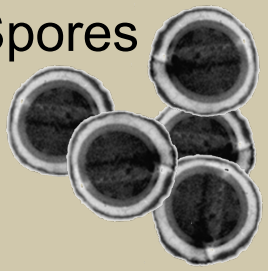
Yatsunenko *et al* (2012) *Nature* **486**:222

60% of bacterial genera in the microbiota make **spores** (= 30% of the total intestinal bacteria)

~20gm/day

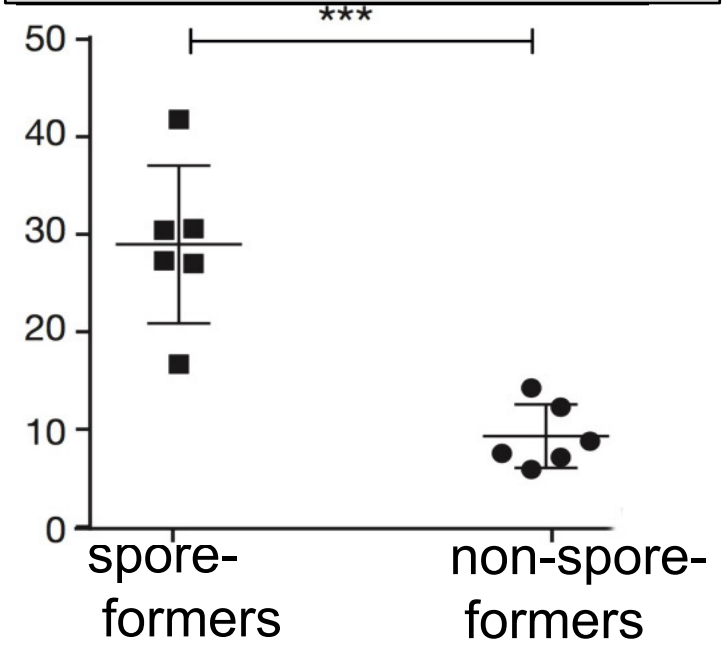
Bile acids

Spores



Germination in small bowel

% of species changed more than twofold after 1 year



Higher species turnover & shifts in relative abundance in the spore-forming bacterial species

Ngure *et al* (2013) *Am J Trop Med Hyg* **89**:709
Troyer (1984) *Behav Ecol Sociobiol* **14**:189
Hong *et al* (2009) *Res Microbiol* **160**:375

Hong *et al* (2009) *Res Microbiol* **160**:134
Rook *et al* (2014) *Clin Exp Immunol* **177**:1-12
Browne *et al* (2016) *Nature* **533**:543

Environmental microbes and allergies

Epidemiology

Riedler *et al* (2001*) Lancet* **358**:1129
Aichbhaumik *et al* (2008*) CEA **38***:1787
Sozanska *et al* (2013) *JACI* **133**:1347
Song *et al* (2013*) Elife* **2**:e00458
Lynch *et al* (2014) *JACI* **134**:593

- Farms
- Cowsheds
- Dogs *in the home*
- Rural versus urban
- Microbe-rich house dust

plants
soil
animals
outside air

Identification of candidate organisms

Ege *et al* (2012) *Allergy* **67**:1565
Hanski *et al* (2012) *PNAS* **109**:8334
Karvonen *et al* (2014*) Allergy*
Lynch *et al* (2014) *JACI*

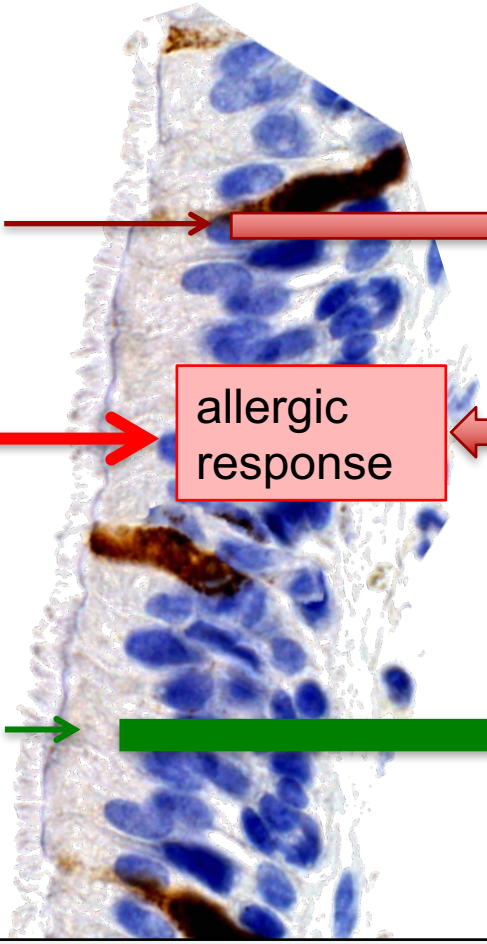
Test in animal models

Debarry *et al* (2007*) JACI.* **119**:1514
Vogel *et al* (2008) *JACI* **122**:307
Conrad *et al* (2009) *JEM* **206**:2869
Hagner *et al* (2013) *Allergy* **68**:322

Mechanisms

Treg (regulatory T lymphocytes),
earlier maturation of Th1, IL-10, DCreg

Effects in the airways of the microbiota we breathe



Microbiota of the air
(up to 10^{10} in 24hrs)

Allergen

Various inflammatory signals

allergic response

attract and activate cells of immune system

(-)

Bacterial components Including LPS

Regulatory mechanisms Including A20

Exposure to dust in a traditional farming environment causes:-
Decreased expression of markers of inflammation
& increased expression of A20 …**in blood cells**

Stein *et al* (2016) *N Engl J Med* **375**:411

Schuijs *et al* (2015) *Science* **349**:1106

Zhou *et al* (2016) *Nat Genet* **48**:67

Environmental microbial biodiversity & chronic inflammatory disorders in Russia, Finland & Estonia

4-fold higher prevalence of childhood atopy
6-fold higher prevalence of Type 1 diabetes
- in Finnish Karelia than in Russian Karelia

House dust dominated by gram-negative bacteria

High *Bacteroides* in *infant* **gut microbiota**

House dust dominated by gram-positive bacteria

7-fold more clones of ***animal***-associated species

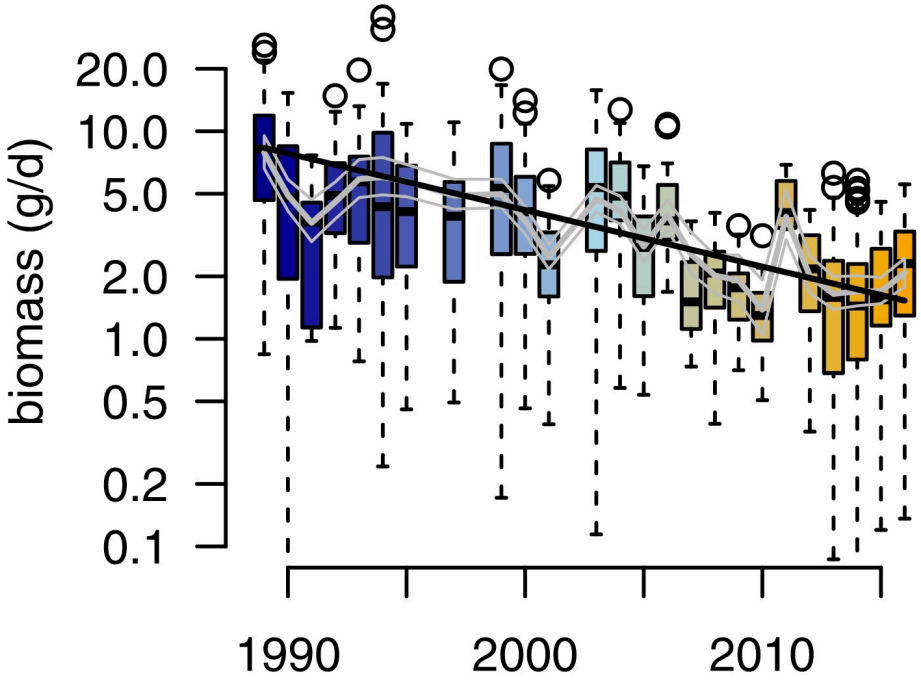
Low *Bacteroides* in *infant* **gut microbiota**

Fails to block mouse model of Type 1 diabetes
Fails to drive immunoregulation

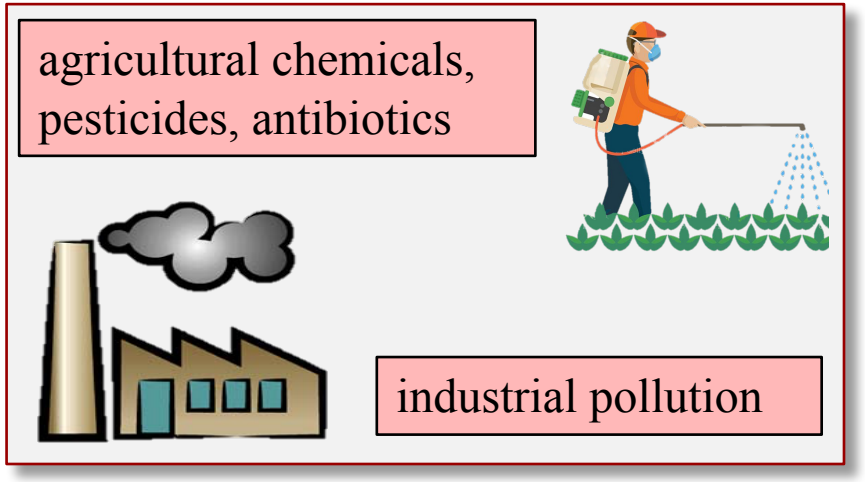
Blocks mouse model of Type 1 diabetes
Drives immunoregulation

Pakarinen *et al* (2008) *Environ Microbiol* **10**:3317 Kondrashova *et al* (2005) *Ann Med* **37**:67
Vatanen *et al* (2016) *Cell* **165**:842

Loss of ~80% of flying insect biomass in 27 years



Not attributable to changes in climate or vegetation

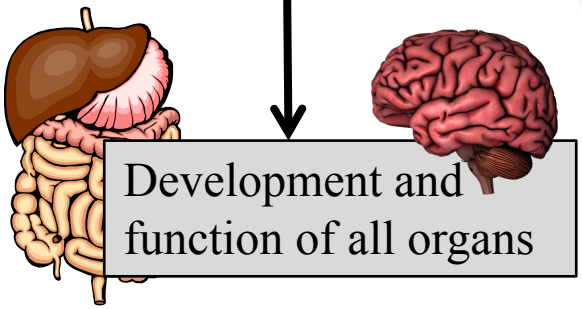


Hallmann *et al* (2017) *PLoS ONE* **12 (10)**:e0185809

Healthy human microbiota
- High biodiversity

organisms, spores, genes

Microbiota of natural environment
- High biodiversity



Development and function of all organs

Data to immune & metabolic systems

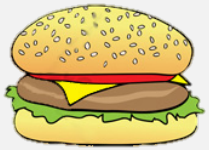
Health of ecosystems, & yields of plants, crops

Well regulated - immune system.
- metabolism
Chronic inflammatory disorders rare

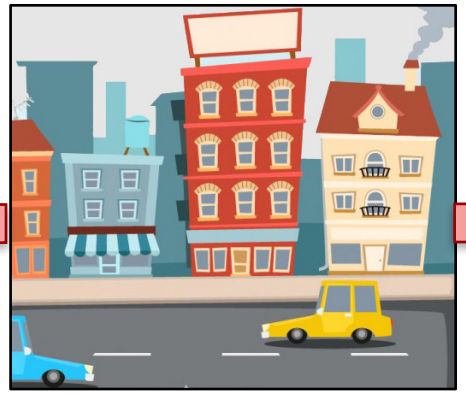
Sustainable agriculture

Good crop health & yields

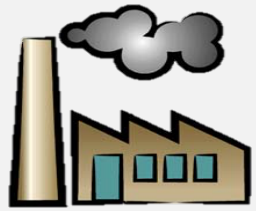
antibiotics, bad diet



lack of contact with natural environment



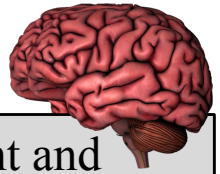
agricultural chemicals



industrial pollution

Distorted human microbiota
- Lower biodiversity

Microbiota of natural environment
- Lower biodiversity



Development and function of all organs

Less data to immune & metabolic systems

↓ Health of ecosystems, & yields of plants, crops

Failure to regulate the immune & metabolic systems:- autoimmunity, allergies, inflammatory bowel disease, some cancers, psychiatric disorders, diabetes, obesity, cardiovascular disease

Non-sustainable agriculture
Reduced crop health & yields

Reduced input to human immune system and to human microbiota