We are not alone:
a meeting with your gut microbiome

Omry Koren, PhD
Faculty of Medicine
Bar Ilan University

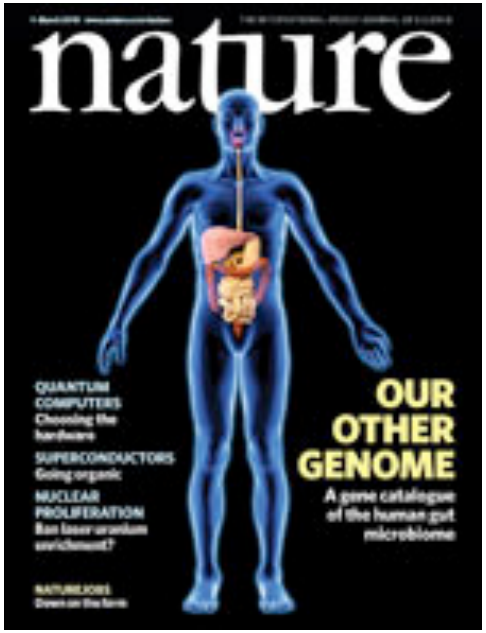
Bacterial Taxonomy

Kingdom	Bacteria			**ממלכה**
Phylum	Firmicutes	Proteobacteria	Bacteroidetes	**מערכה**
Class	Bacilli	Gamma Proteobacteria	Bacteroidetes	**מחלקה**
Order	Lactobacillales	Enterobacteriales	Bacteroidales	**סדרה**
Family	Lactobacillaceae	Enterobacteriaceae	Bacteroidaceae	**משפחה**
Genus	*Lactobacillus*	*Escherichia*	*Bacteroides*	**סוג**
Species	*L. rhamnosus*	*E. coli*	*B. fragilis*	**מין**

Bad guys?

Who’s good and who’s bad?

The Human Microbiome



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

A Glimpse of the Next 100 Years in Medicine

Isaac S. Kohane, M.D., Ph.D., Jeffrey M. Drazen, M.D., and Edward W. Campion, M.D.

N Engl J Med 2012; 367:2538-2539 | December 27, 2012 | DOI: 10.1056/NEJMe1213371

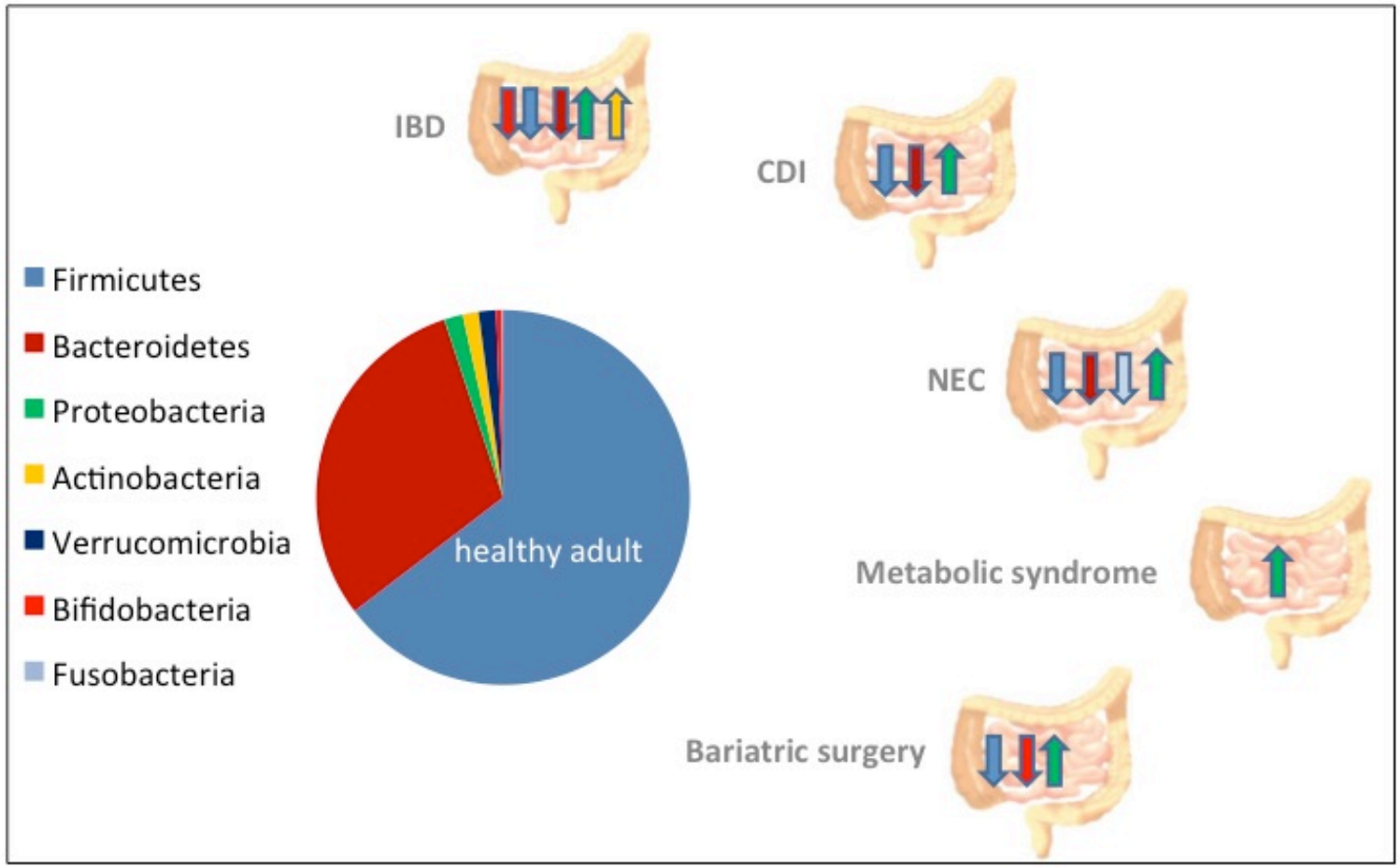
Over the past year, the *Journal* has commemorated 200 years of publication and the astonishing progress made since 1812 in the science and practice of medicine. Thanks to digital technology, our anniversary celebration has had a wide reach, with more than 1 million visits to the NEJM200.NEJM.org site; many viewers of our documentary video, *Getting Better*; and large numbers of viewers of our simulcast symposium, Dialogues in Medicine. As the *Journal*'s 200th year comes to a close, we want to think about the changes and challenges that medicine faces in the decades ahead. Although it is foolish to attempt specific predictions about the future, it would be unwise not to think about the emerging trends, new opportunities, and the principles that should guide the medicine of the future.

In the decades ahead, the pace of biomedical discovery will accelerate. The state of an individual person will be characterized with increasing precision from the molecular level to the genomic level to the organ level and by interactions with medications, nutrients, the microbiome, therapeutic devices, and the environment. This precision medicine[1] will become possible because of huge data

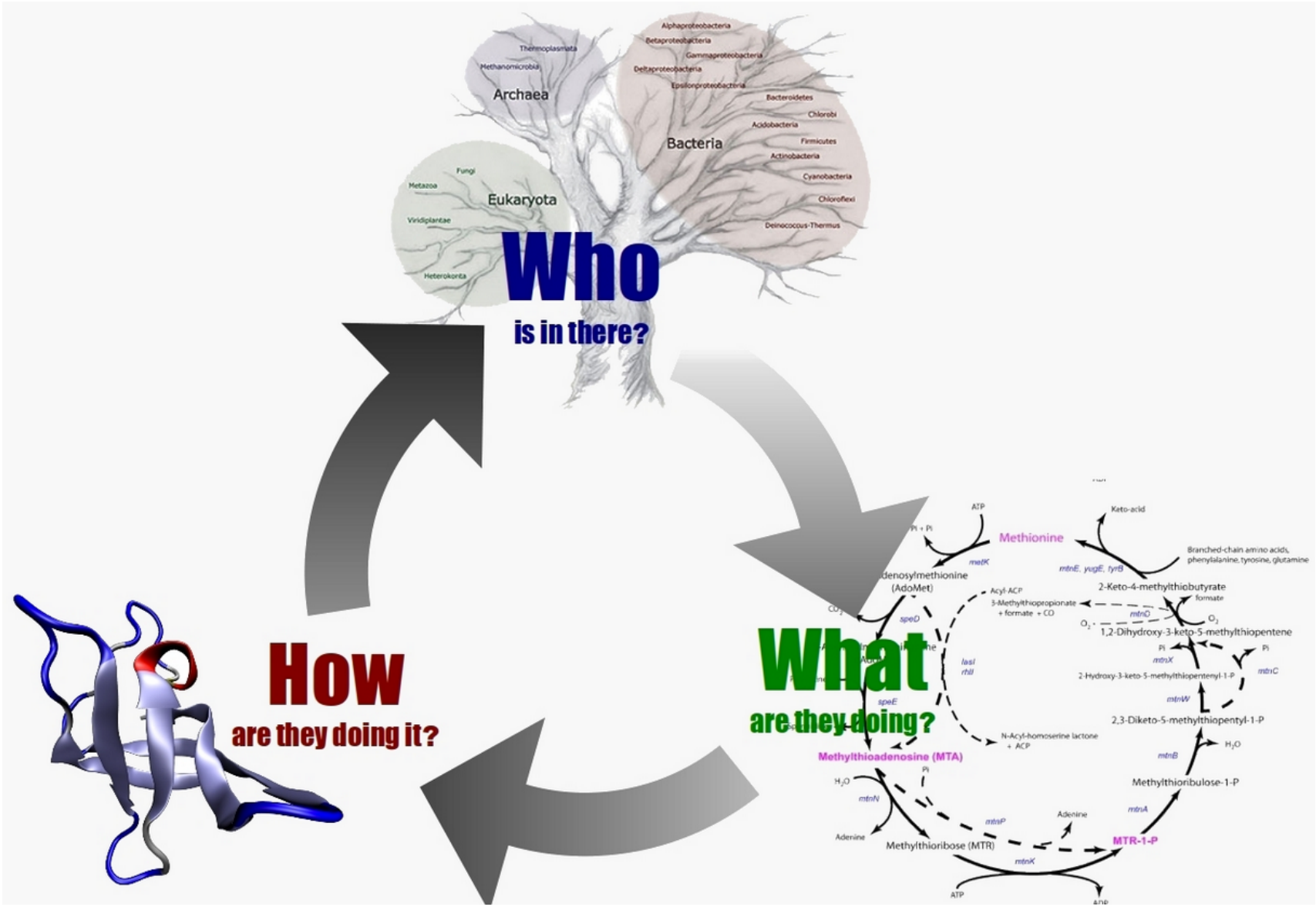
Little Friends

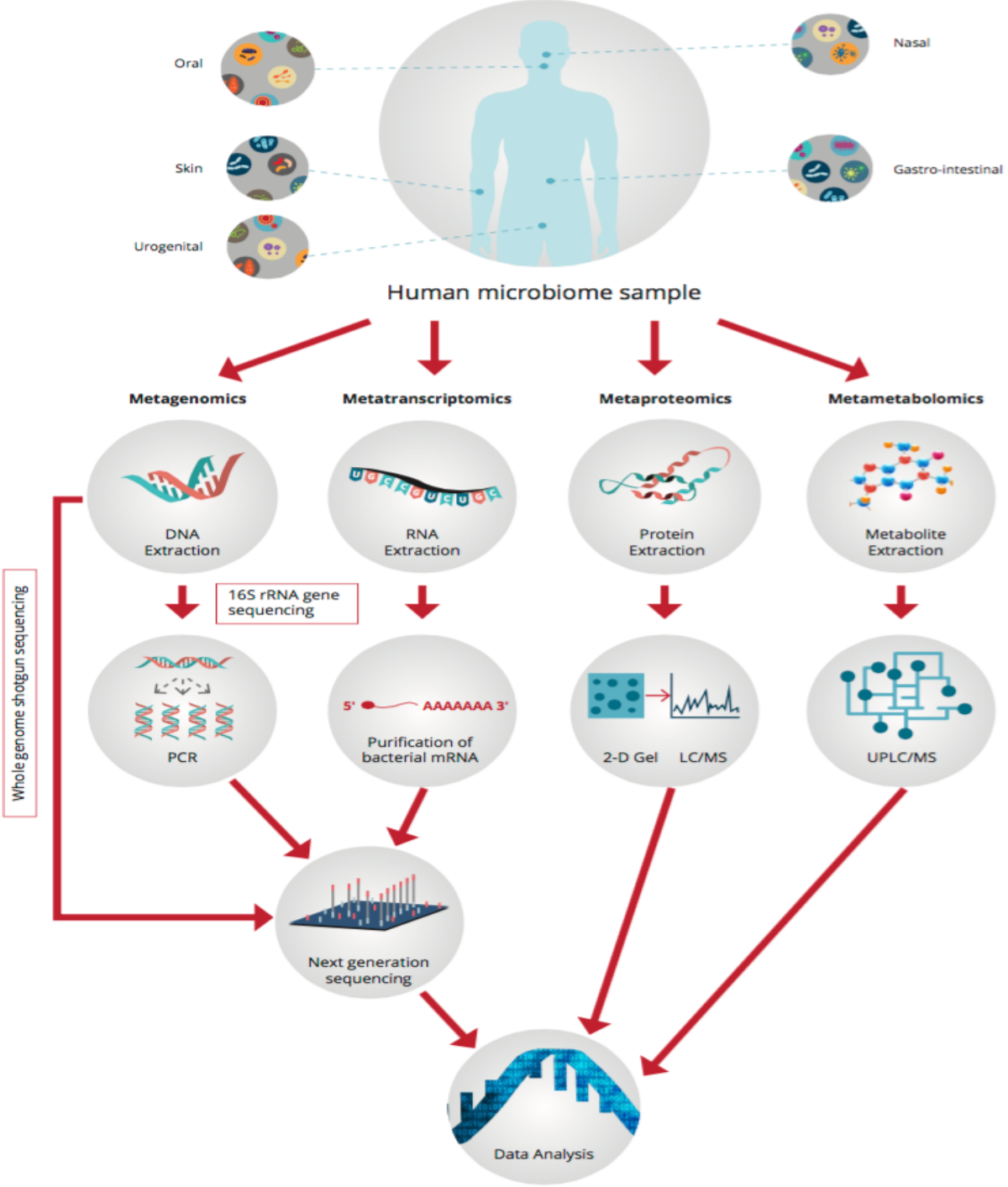
- More microbial cells than human cells on the human body
- Majority in large intestine
- Provide enhanced nutrition and protection against pathogens

Dysbiosis - Shifts in the Microbiome



Neuman and Koren, In press


Who
is in there?
Archaea
Bacteria
Eukaryota
Alphaproteobacteria
Betaproteobacteria
Gammaproteobacteria
Deltaproteobacteria
Epsilonproteobacteria
Bacteroidetes
Chlorobi
Acidobacteria
Firmicutes
Actinobacteria
Cyanobacteria
Chloroflexi
Deinococcus-Thermus
Thermoplasmata
Methanomicrobia
Fungi
Metazoa
Viridiplantae
Heterokonta
What
are they doing?
Methionine
Keto-acid
Branched-chain amino acids, phenylalanine, tyrosine, glutamine
2-Keto-4-methylthiobutyrate
1,2-Dihydroxy-3-keto-5-methylthiopentene
2-Hydroxy-3-keto-5-methylthiopentenyl-1-P
2,3-Diketo-5-methylthiopentyl-1-P
Methylthioribulose-1-P
MTR-1-P
Methylthioribose (MTR)
Methylthioadenosine (MTA)
Adenine
ATP
ADP
How
are they doing it?


Oral
Skin
Urogenital
Nasal
Gastro-intestinal
Human microbiome sample
Metagenomics
Metatranscriptomics
Metaproteomics
Metametabolomics
DNA Extraction
RNA Extraction
Protein Extraction
Metabolite Extraction
16S rRNA gene sequencing
Whole genome shotgun sequencing
PCR
5' AAAAAAA 3'
Purification of bacterial mRNA
2-D Gel
LC/MS
UPLC/MS
Next generation sequencing
Data Analysis

In press

THE HUMAN MICROBIOME PROJECT

CONTAINS **10** TIMES **MORE** MICROBIAL CELLS THAN HUMAN CELLS.

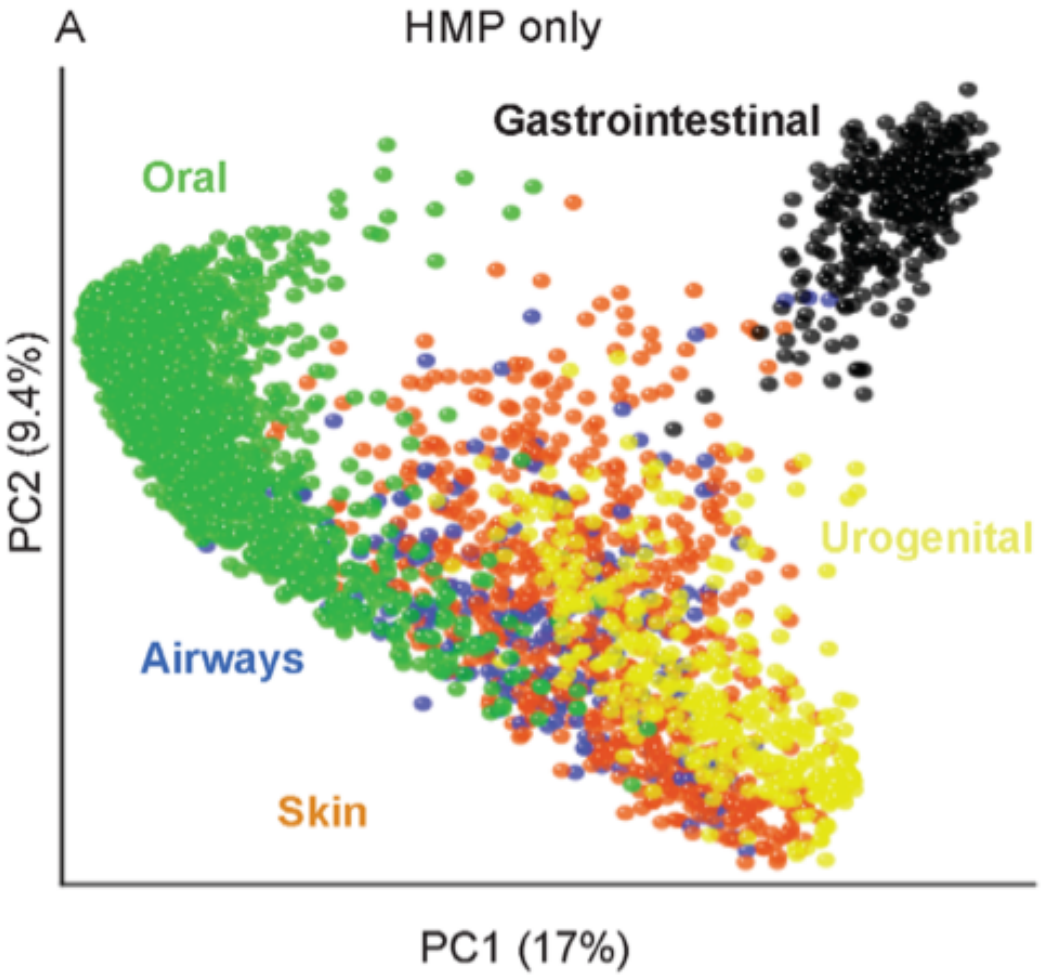
MICROORGANISMS, THEIR GENOMES & ENVIRONMENTAL INTER ACTIONS

250 HEALTHY PEOPLE

SPOTS SAMPLED:

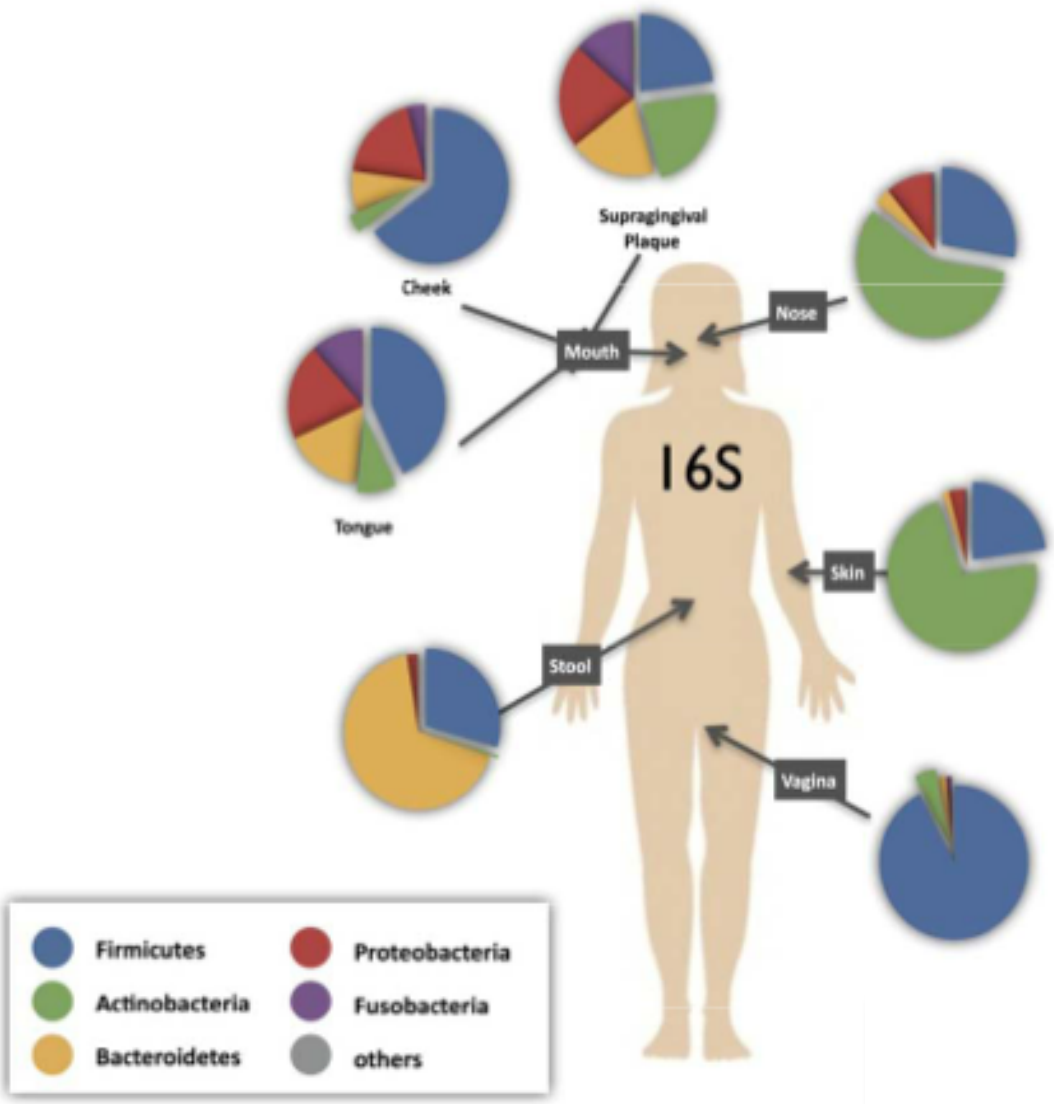
PRI

Each body site has a unique microbiota



Koren et al, 2013, PLoS Comp Biol

A healthy adult microbiota at the phylum level



HMP, 2012, Nature

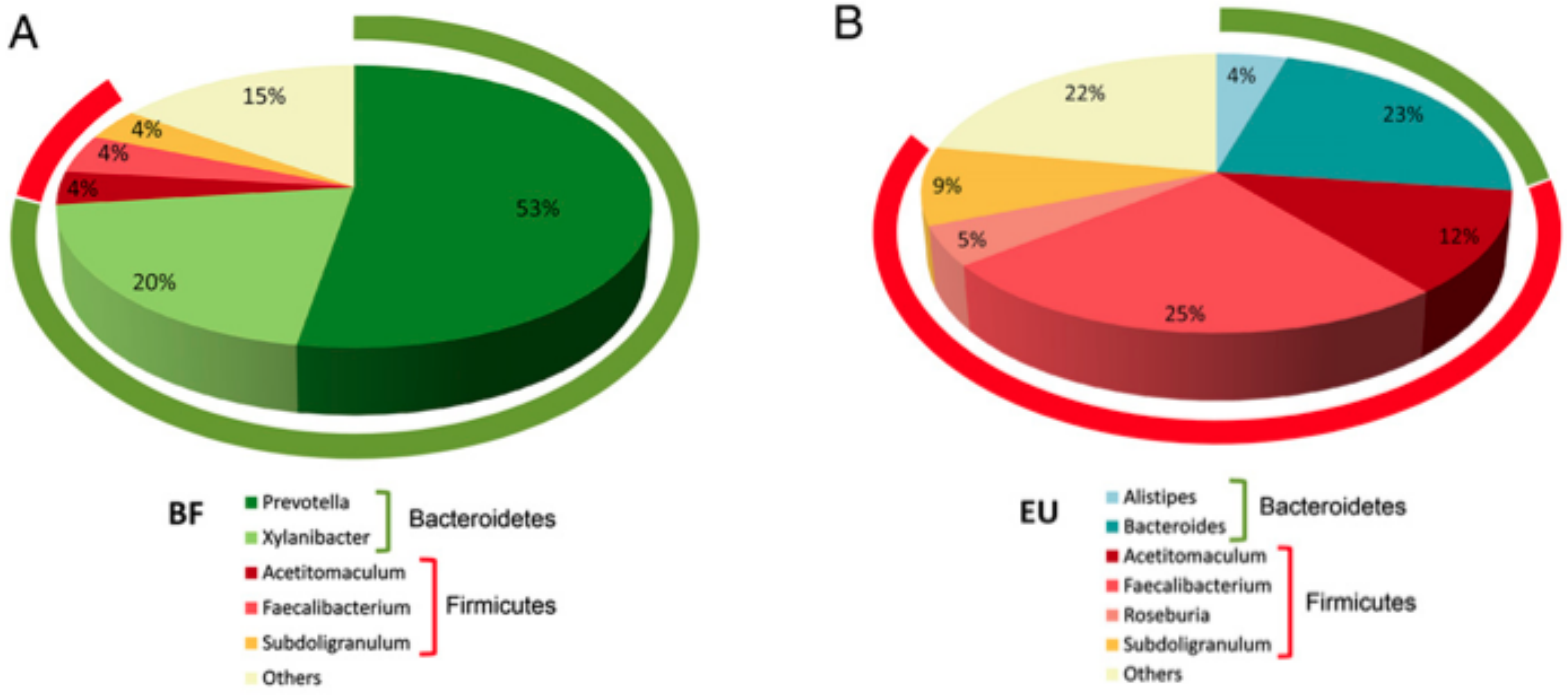
Do we all have the same bacteria

Burkina Faso

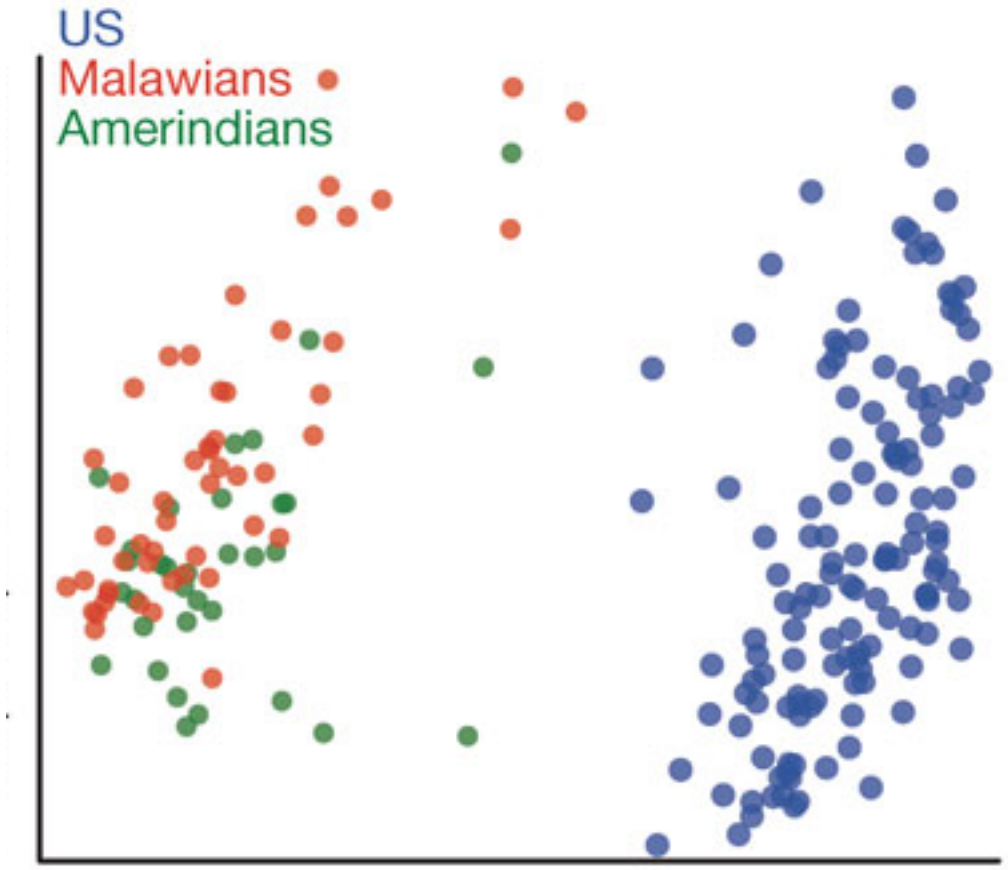
Florence, Italy

De Filippo, 2010

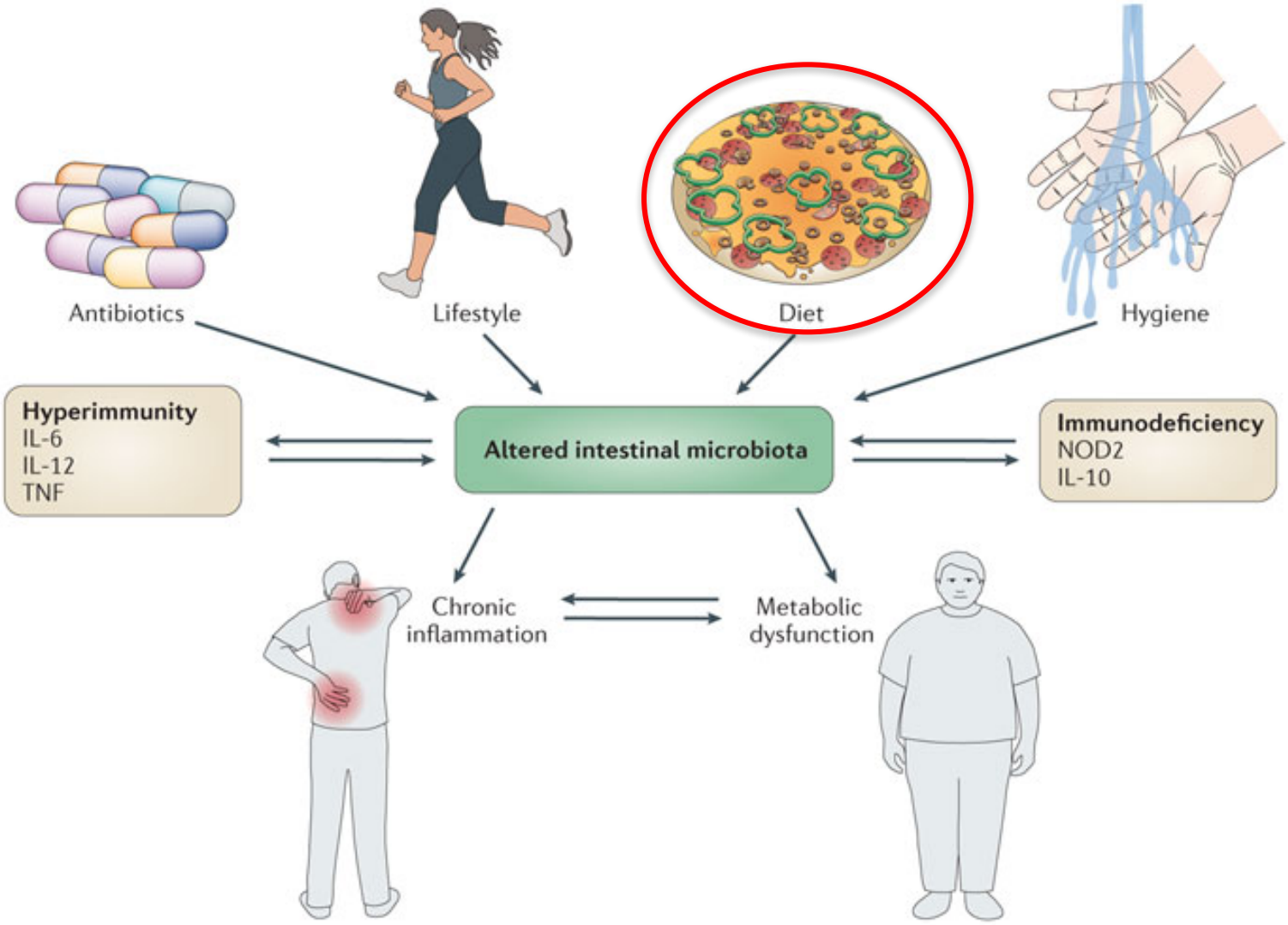
Do we all have the same bacteria



De Filippo, 2010

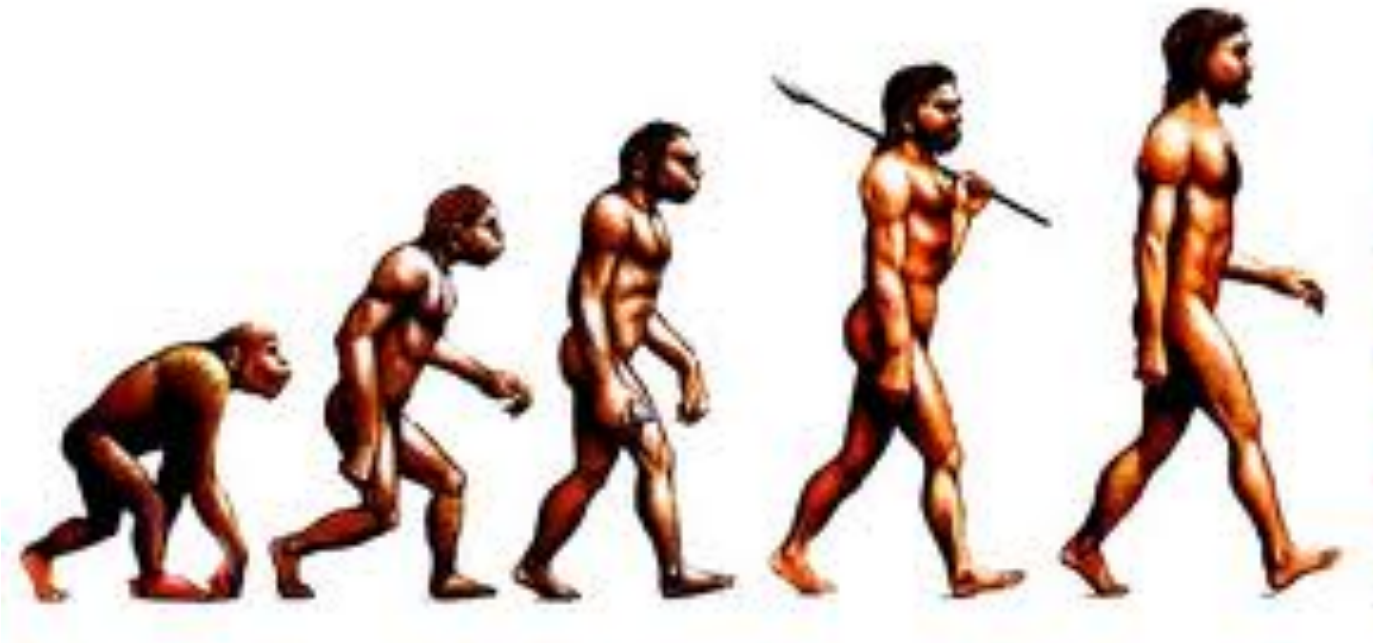


Yatsunenko, 2012

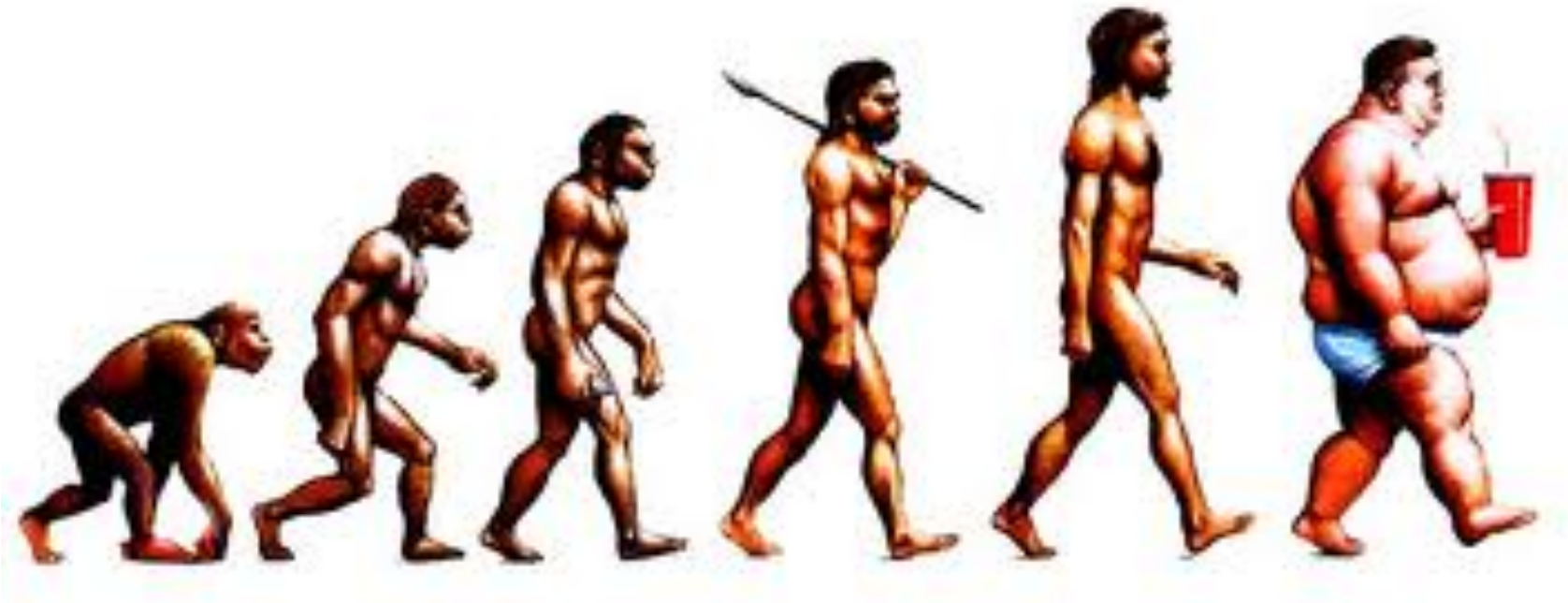

Antibiotics
Lifestyle
Diet
Hygiene
Hyperimmunity
IL-6
IL-12
TNF
Altered intestinal microbiota
Immunodeficiency
NOD2
IL-10
Chronic inflammation
Metabolic dysfunction

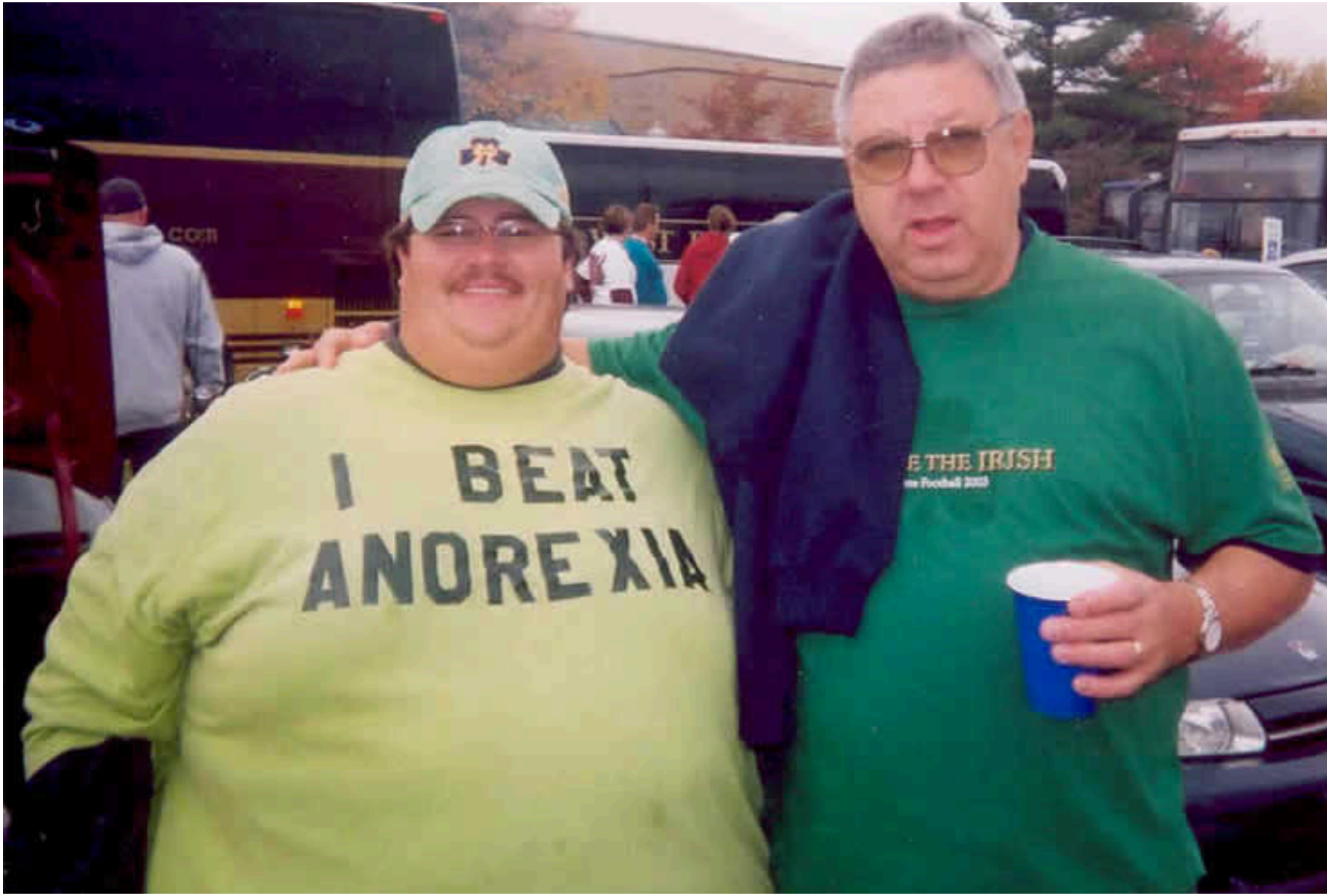
Sommer, 2013

Our diet is changing



Our diet is changing

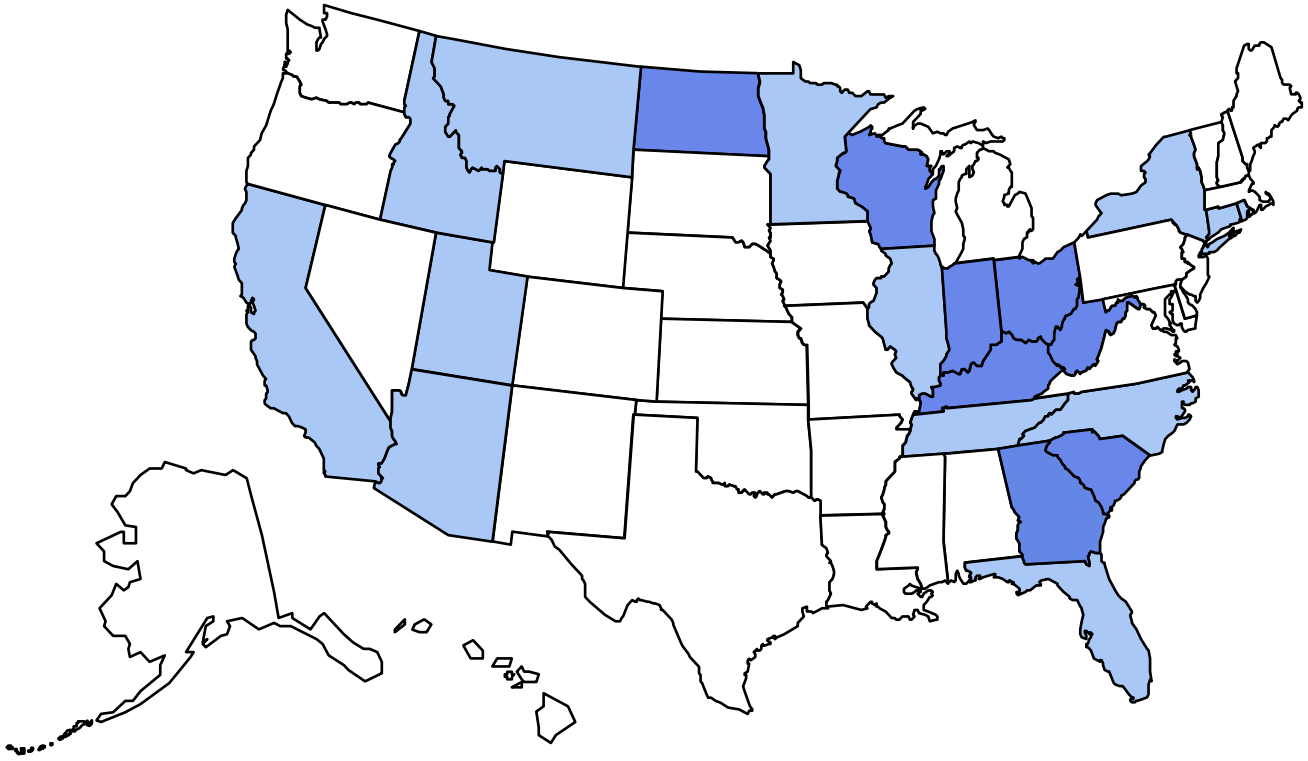



I BEAT
ANOREXIA
E THE IRISH

OBESITY IN THE US

BRSFF, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

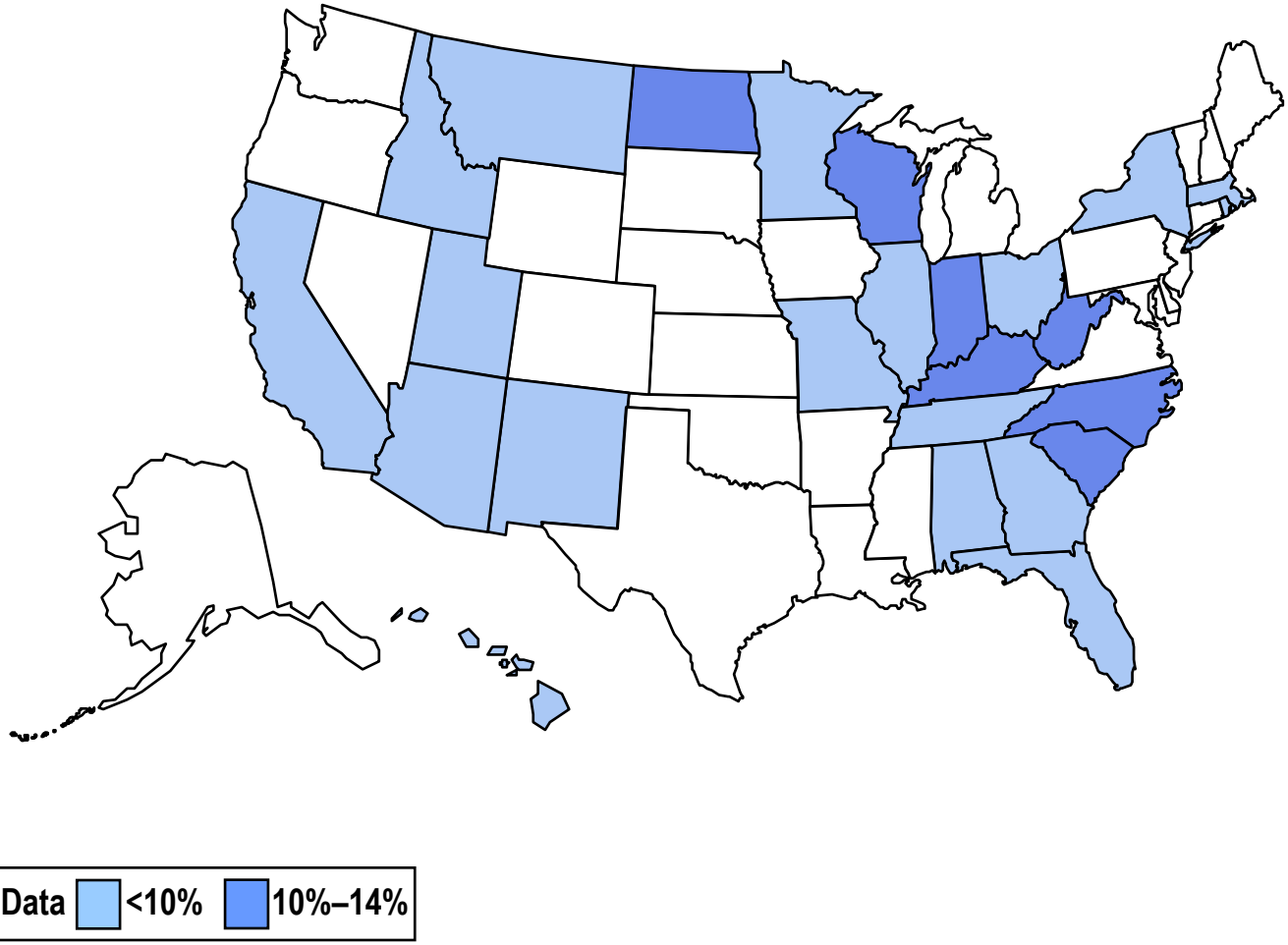


No Data | <10% | 10%–14%

OBESITY IN THE US

BRSFF, 1986

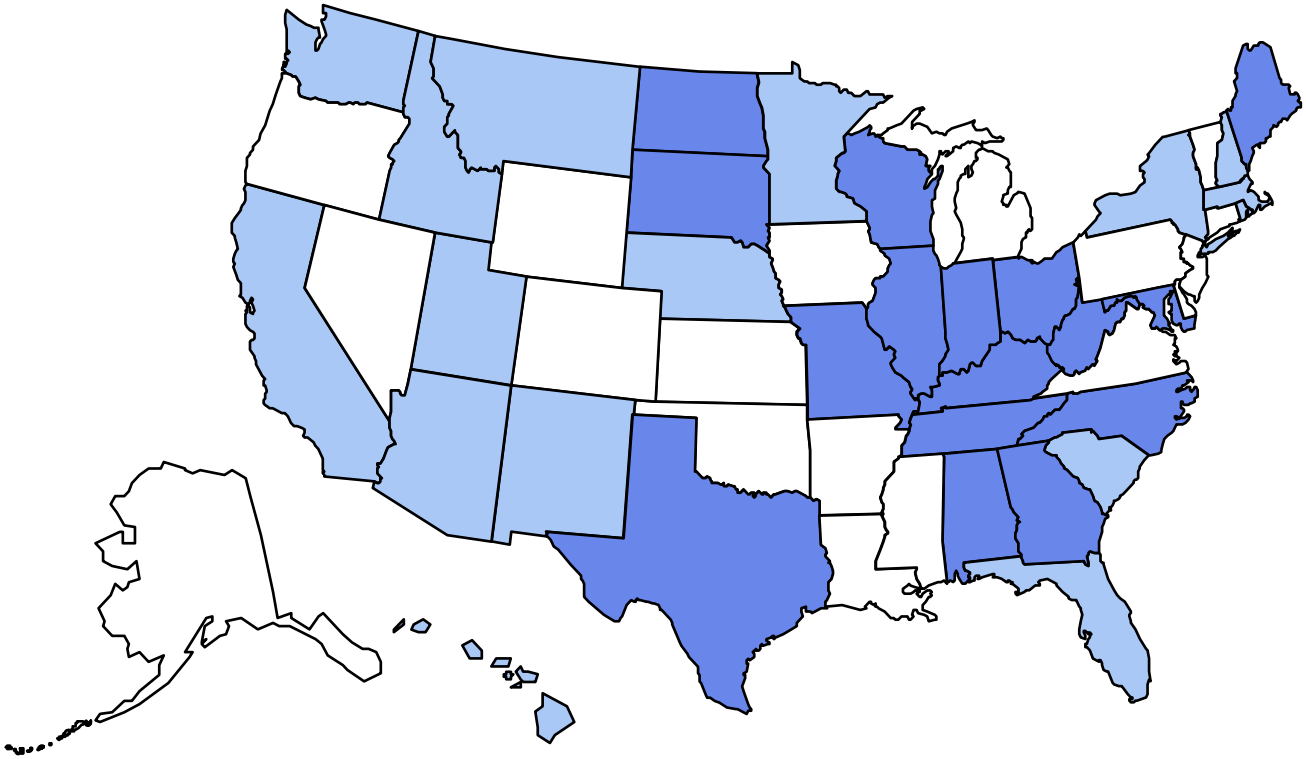
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



OBESITY IN THE US

BRSFF, 1987

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

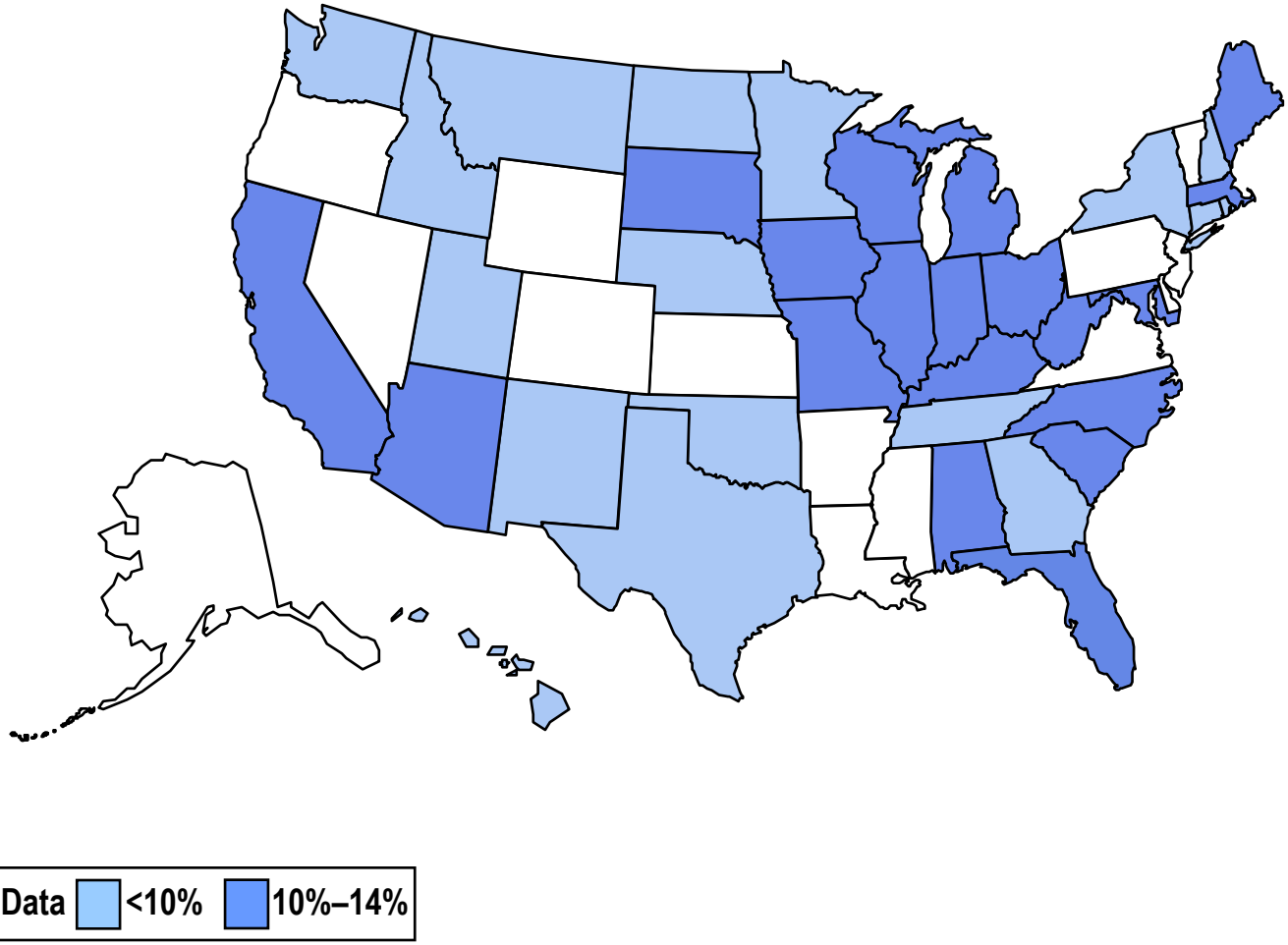


No Data | <10% | 10%–14%

OBESITY IN THE US

BRSFF, 1988

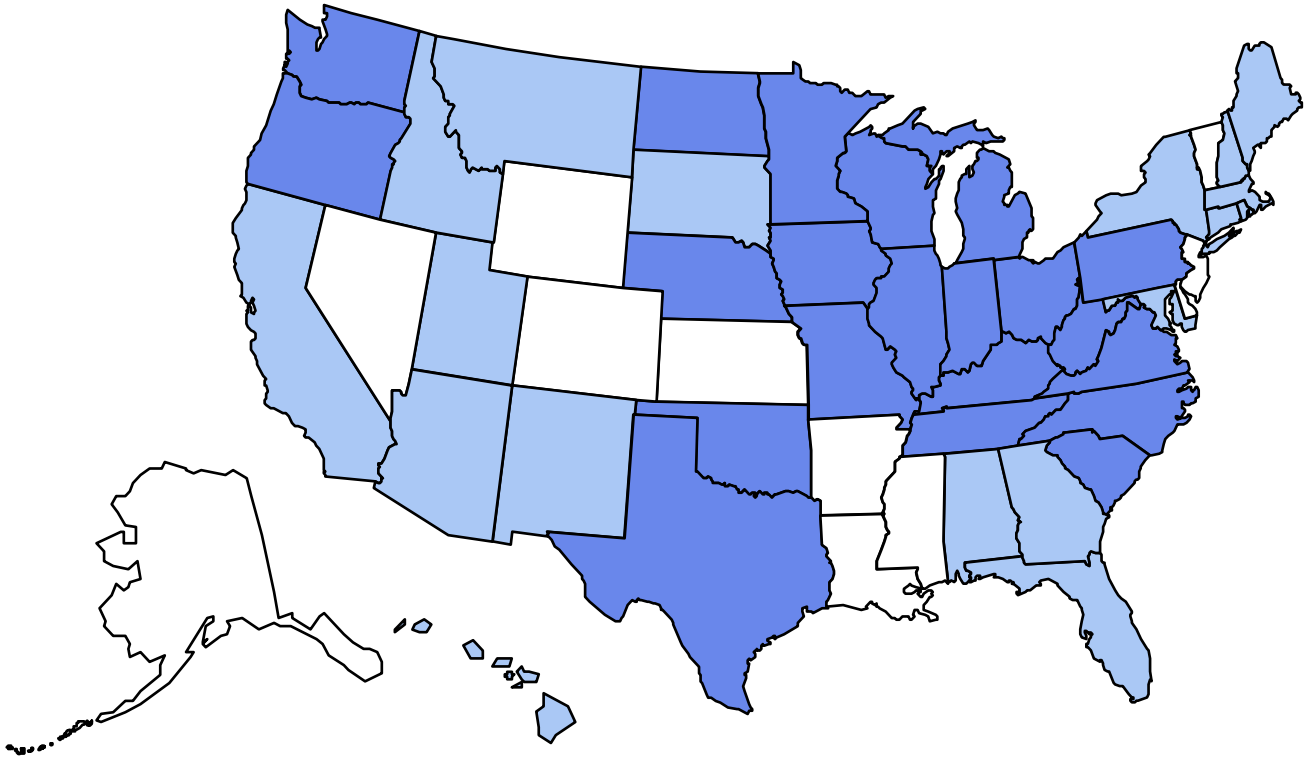
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



OBESITY IN THE US

BRSFF, 1989

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

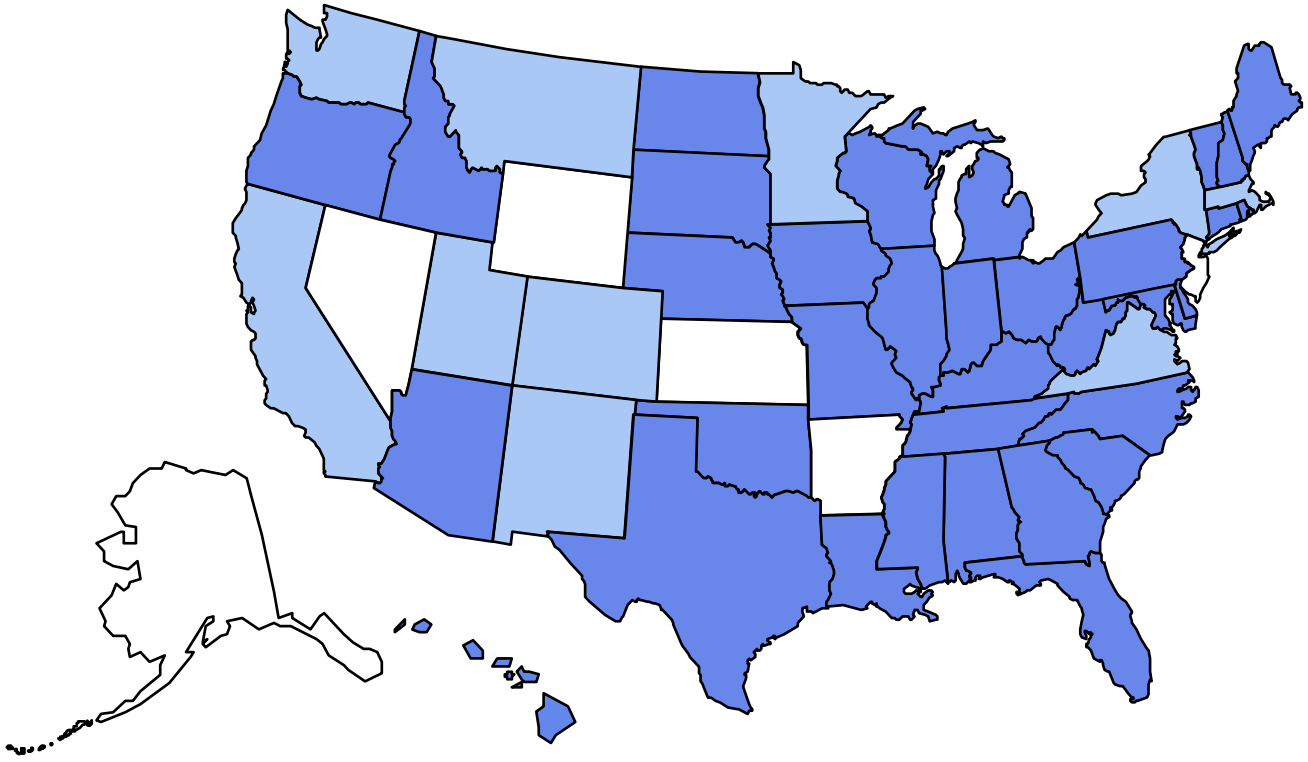


No Data | <10% | 10%–14%

OBESITY IN THE US

BRSFF, 1990

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

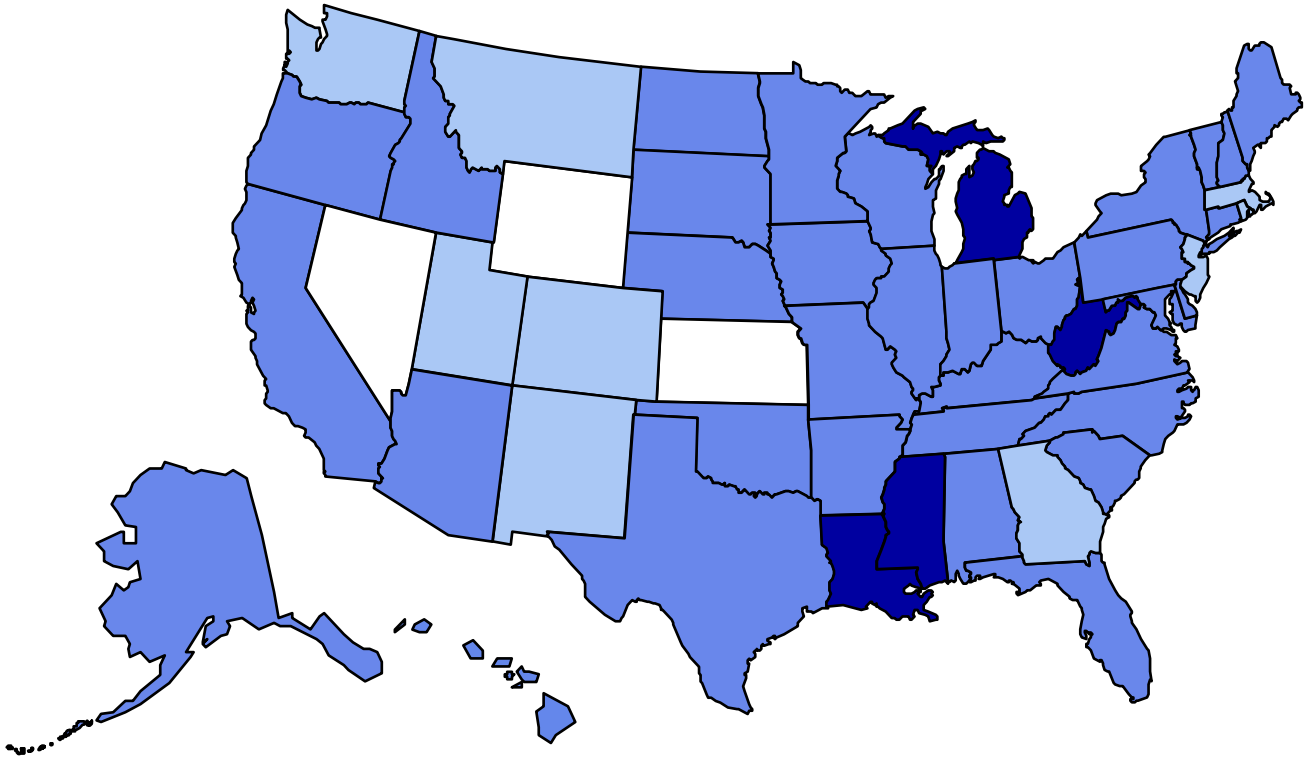


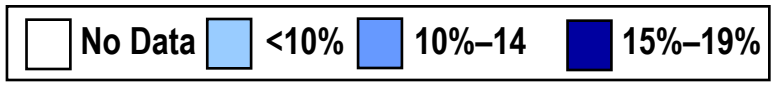
No Data | <10% | 10%–14%

OBESITY IN THE US

BRSFF, 1991

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

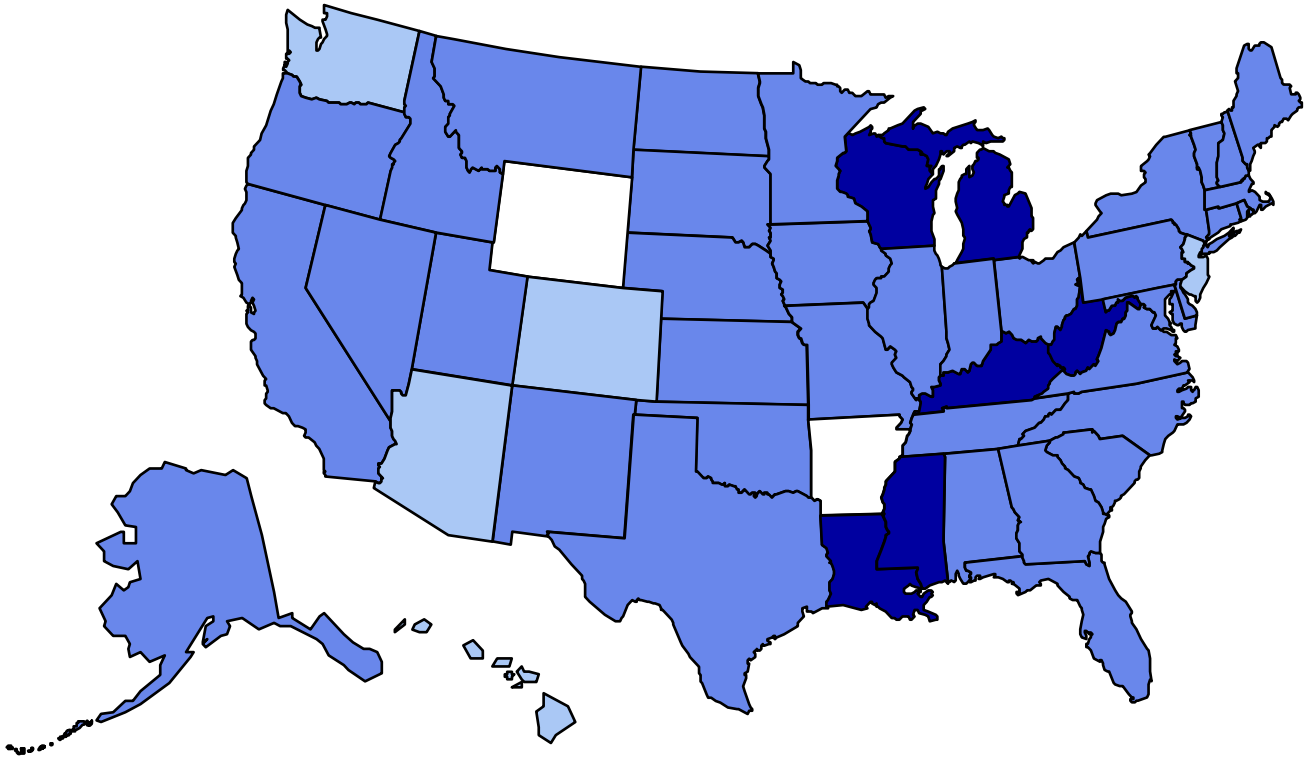


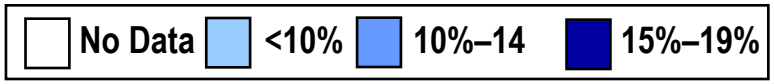


OBESITY IN THE US

BRSFF, 1992

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

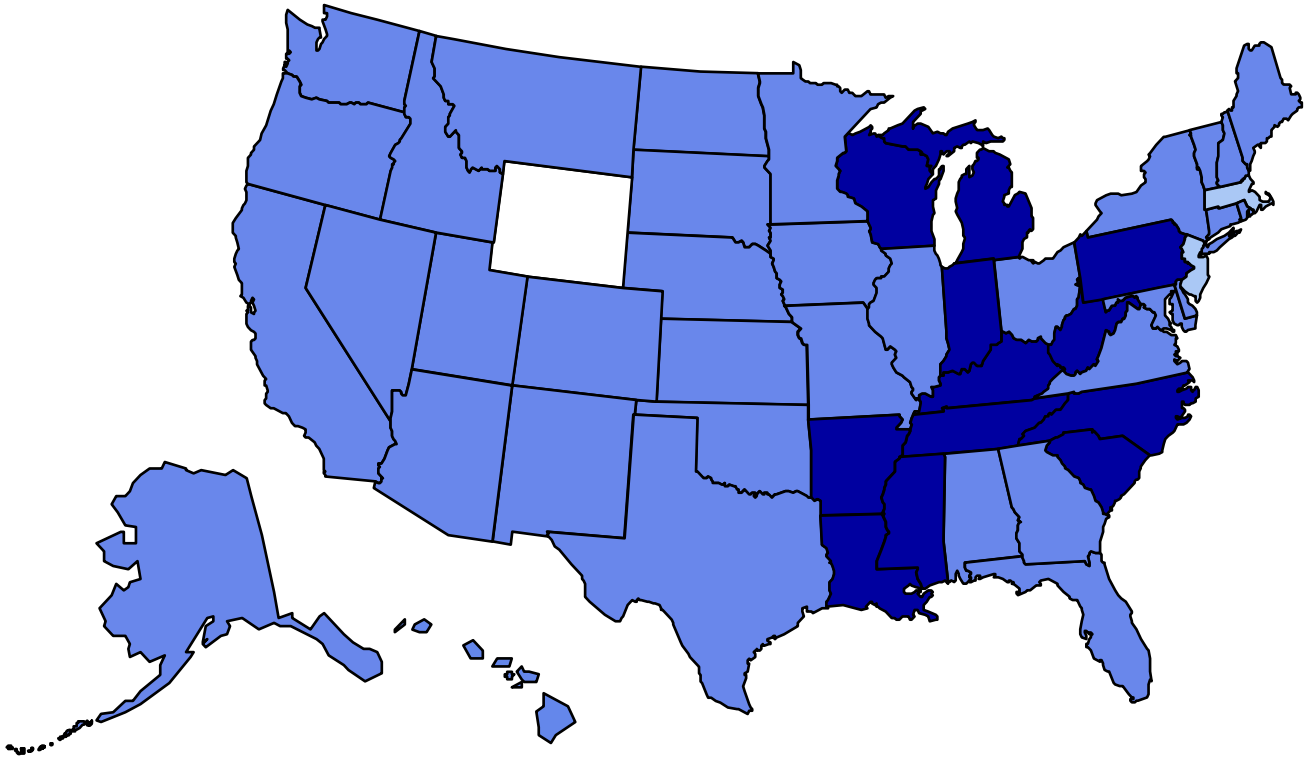


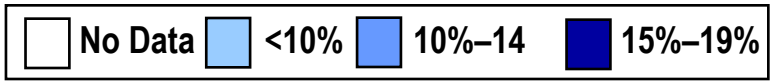


OBESITY IN THE US

BRSFF, 1993

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

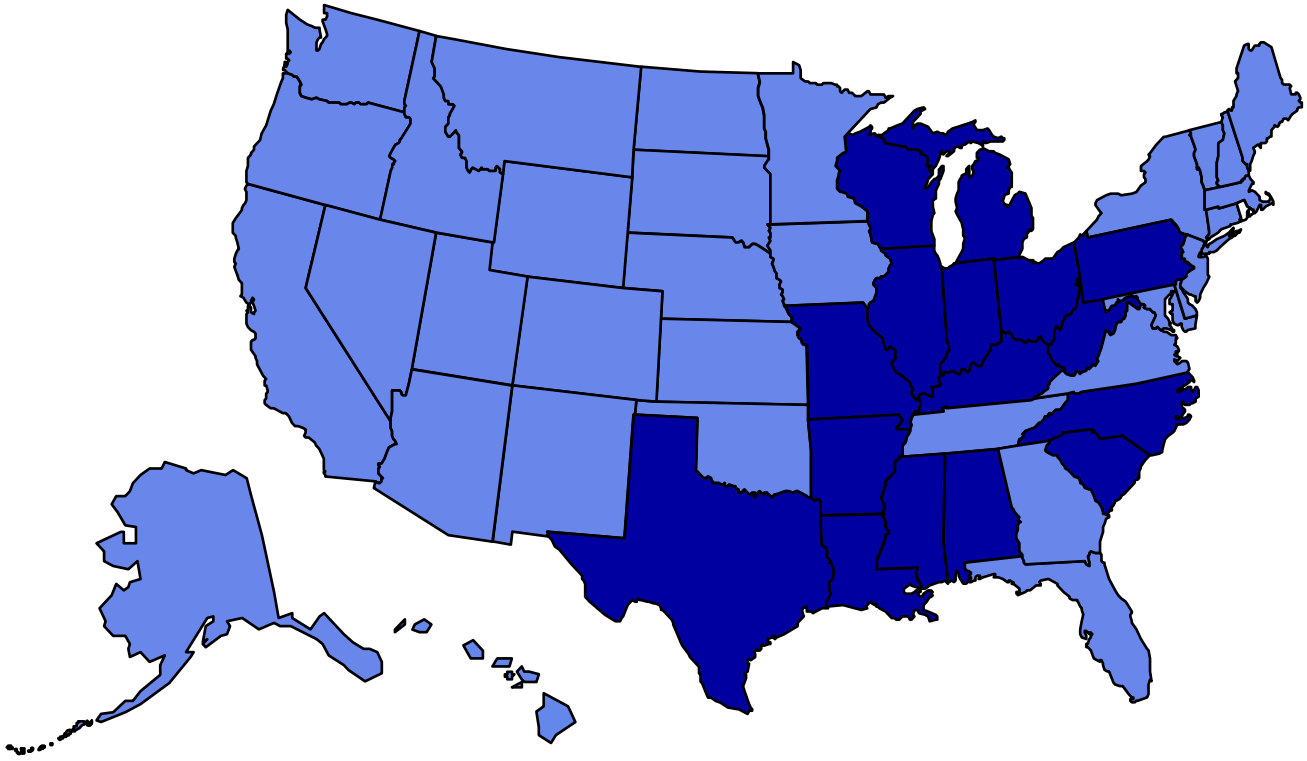


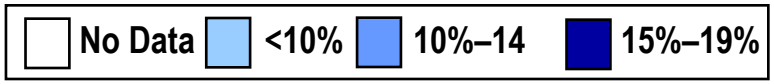


OBESITY IN THE US

BRSFF, 1994

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

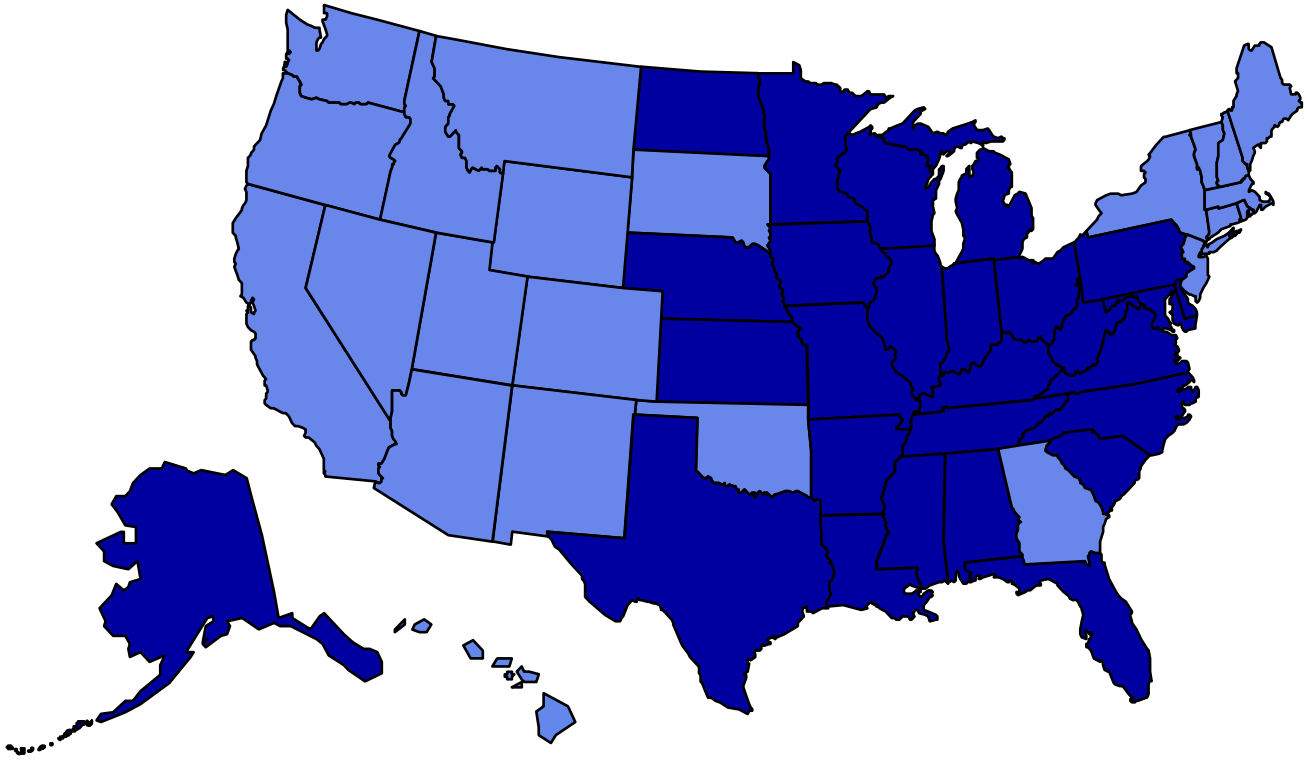


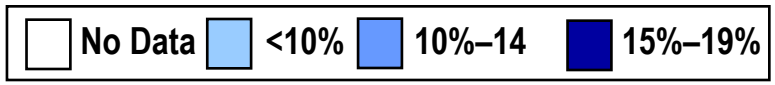


OBESITY IN THE US

BRSFF, 1995

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

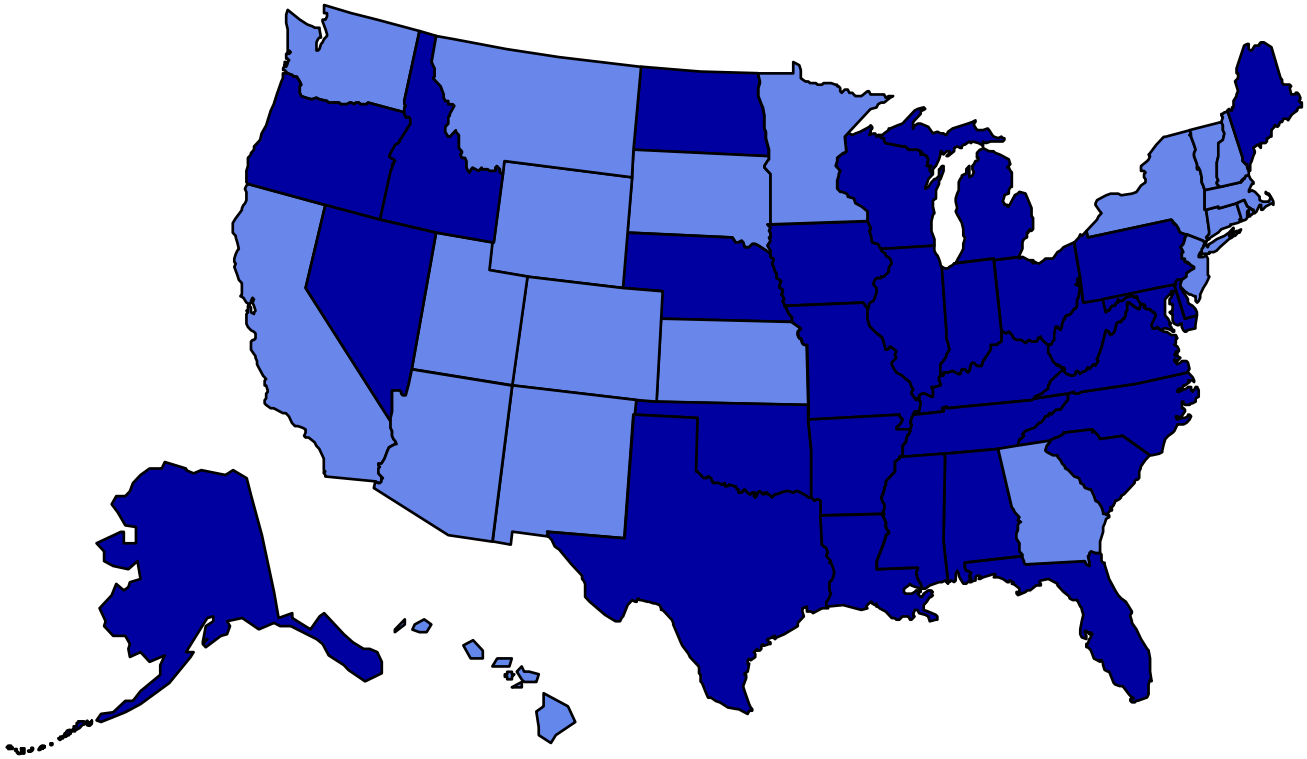




OBESITY IN THE US

BRSFF, 1996

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

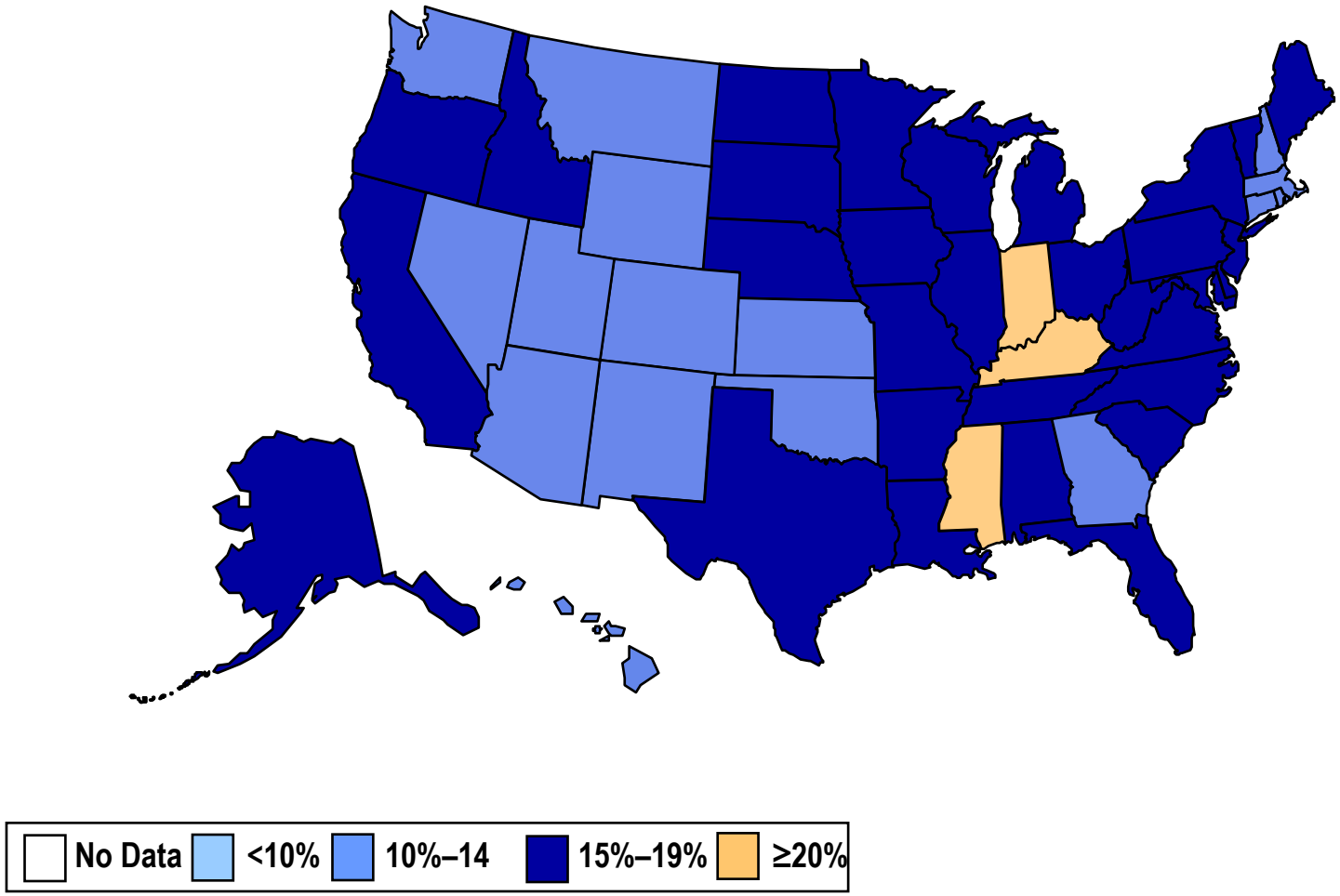


No Data | <10% | 10%–14 | 15%–19%

ההשמנה בארצות הברית

BRSFF, 1997

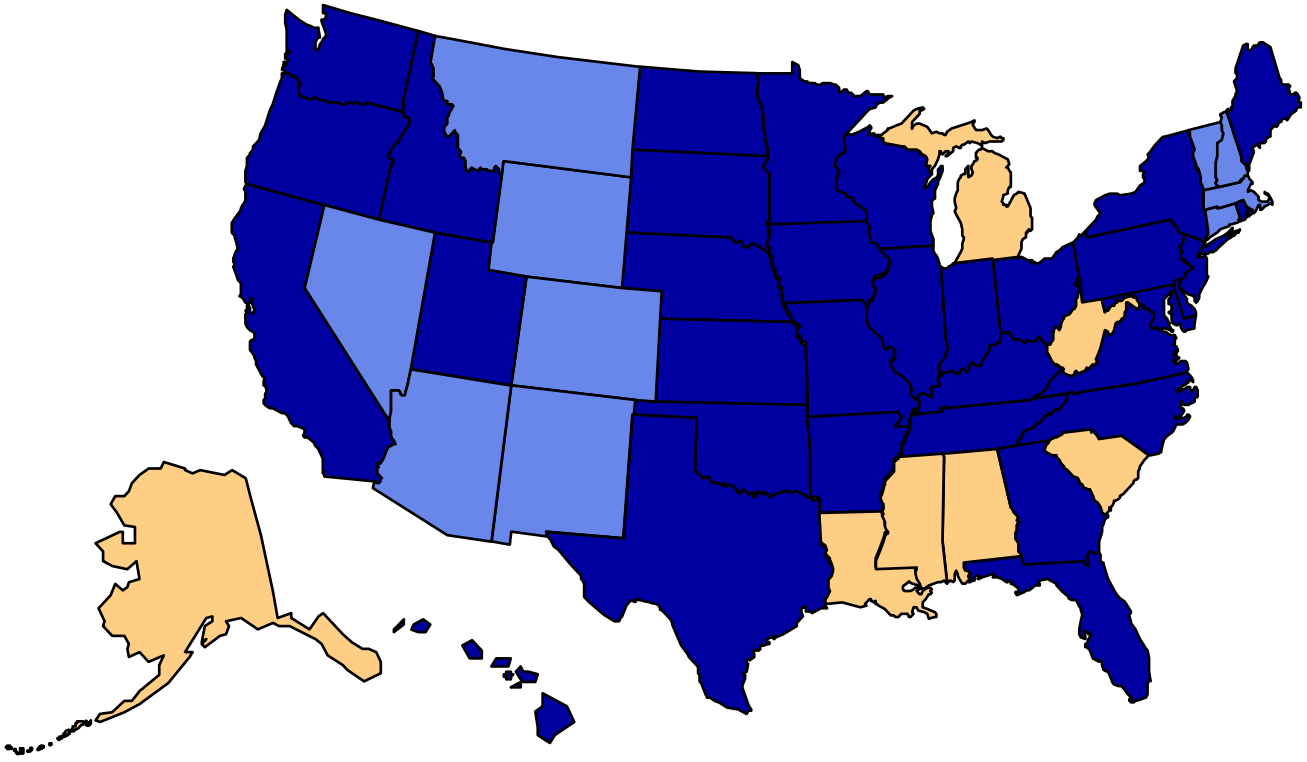
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



ההשמנה בארצות הברית

BRSFF, 1998

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

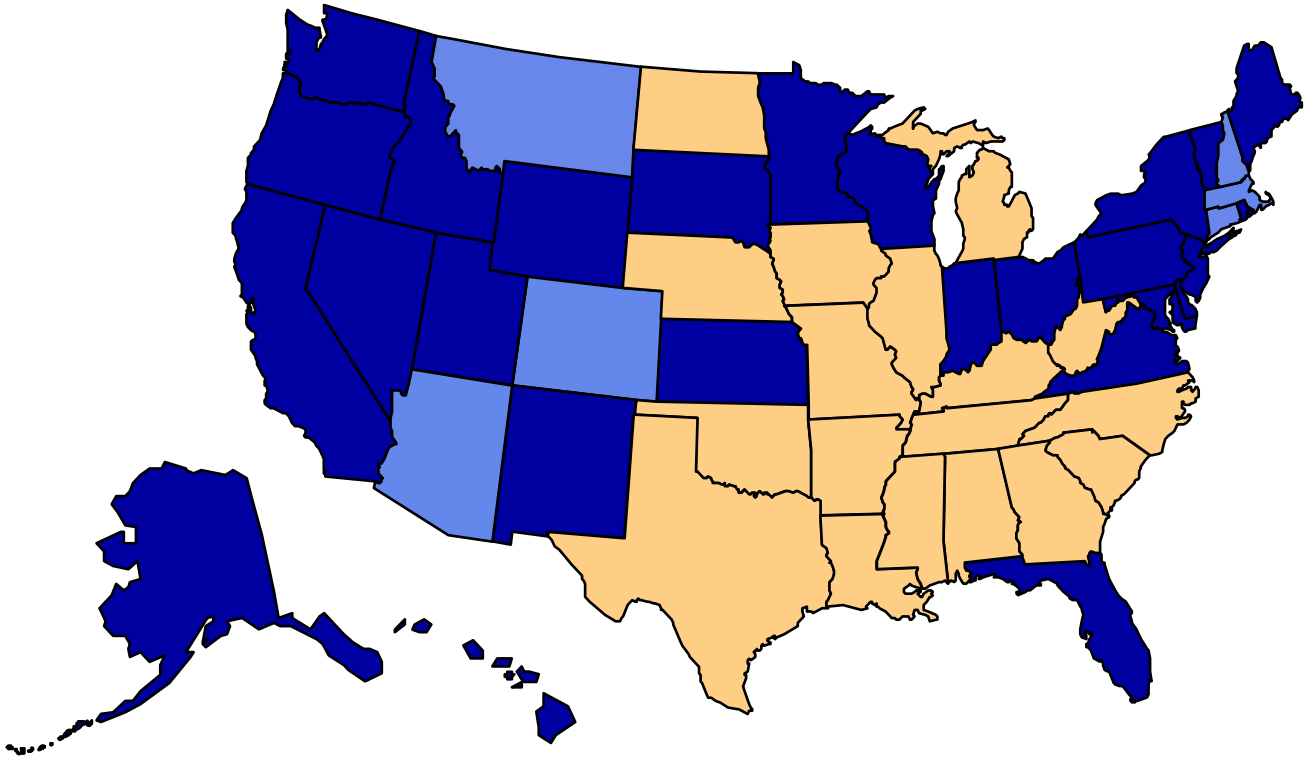


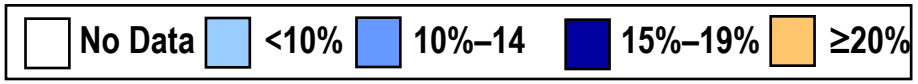
No Data | <10% | 10%–14 | 15%–19% | ≥20%

OBESITY IN THE US

BRSFF, 1999

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)





OBESITY IN THE US

BRSFF, 2000

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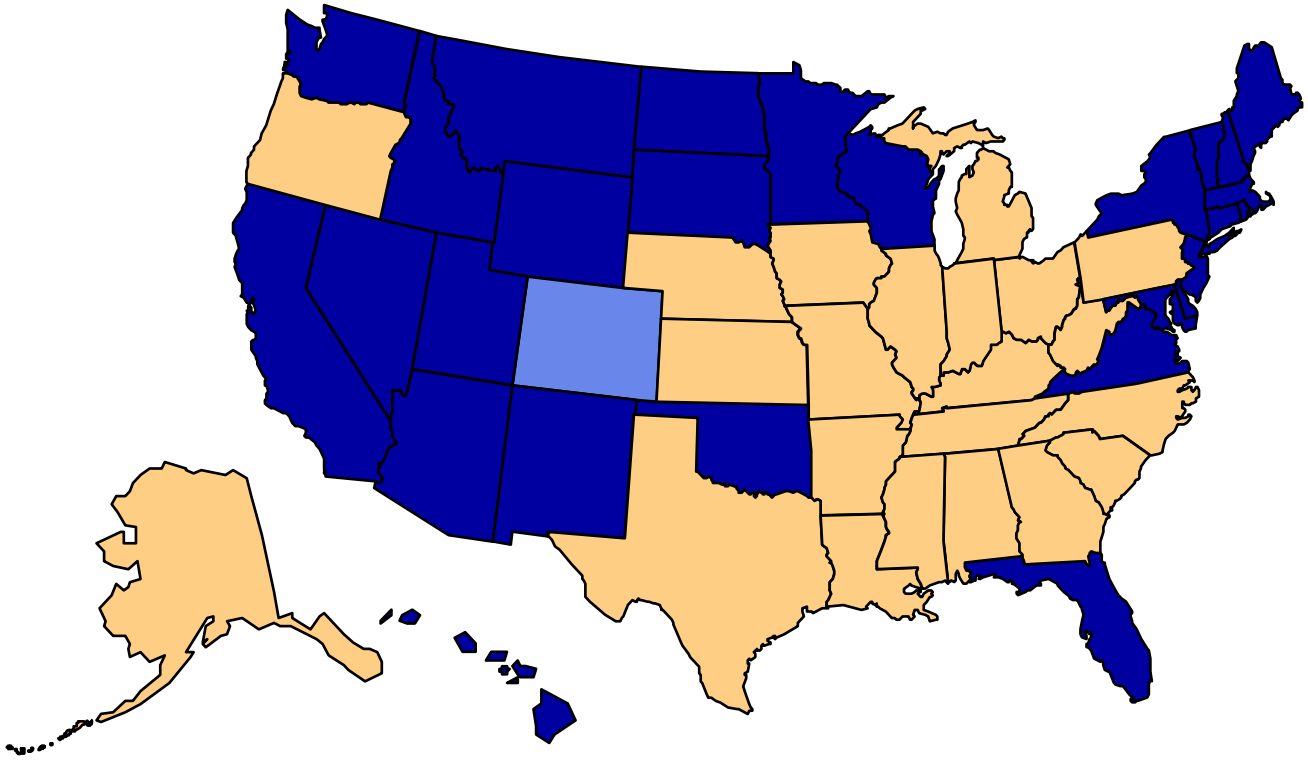
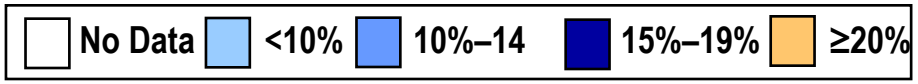
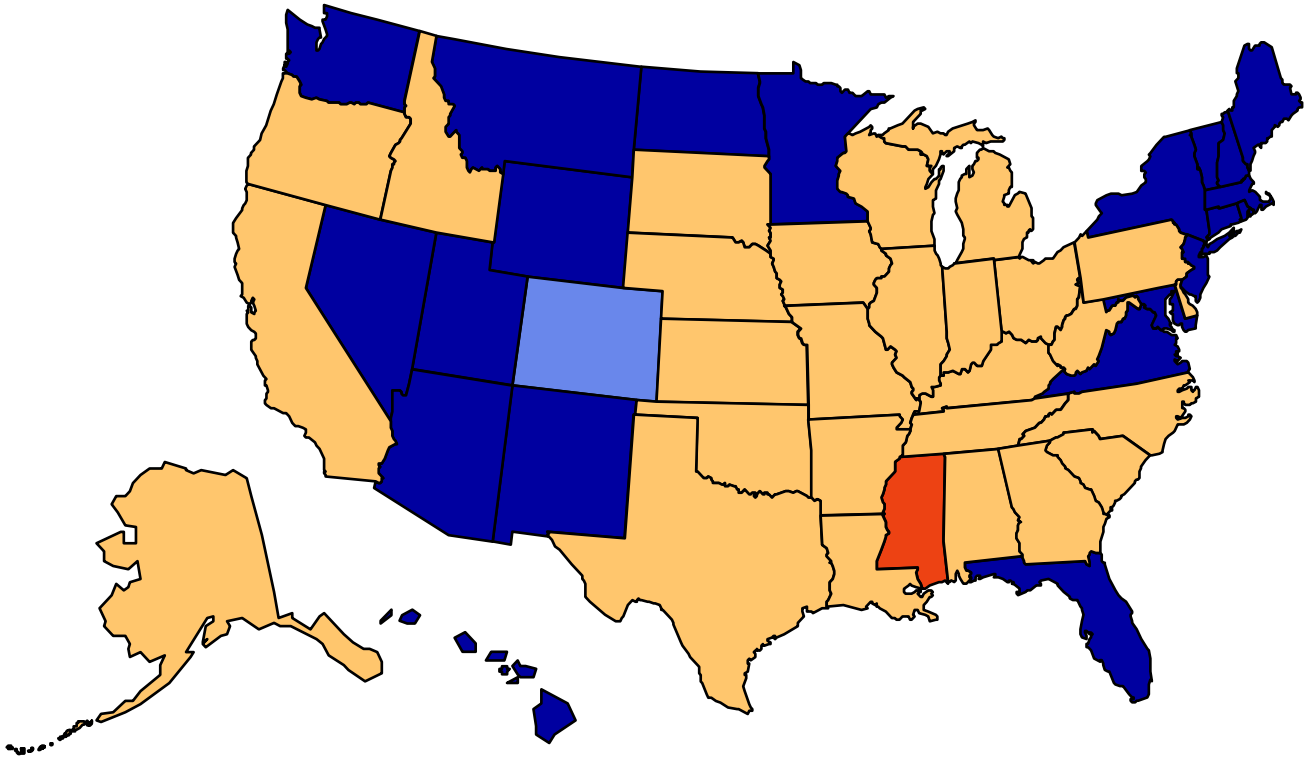


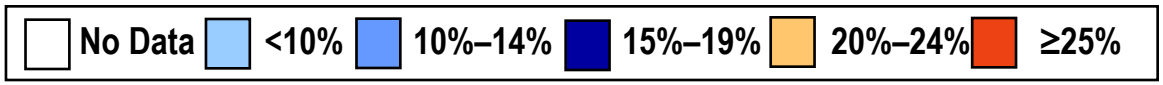


OBESITY IN THE US

BRSFF, 2001

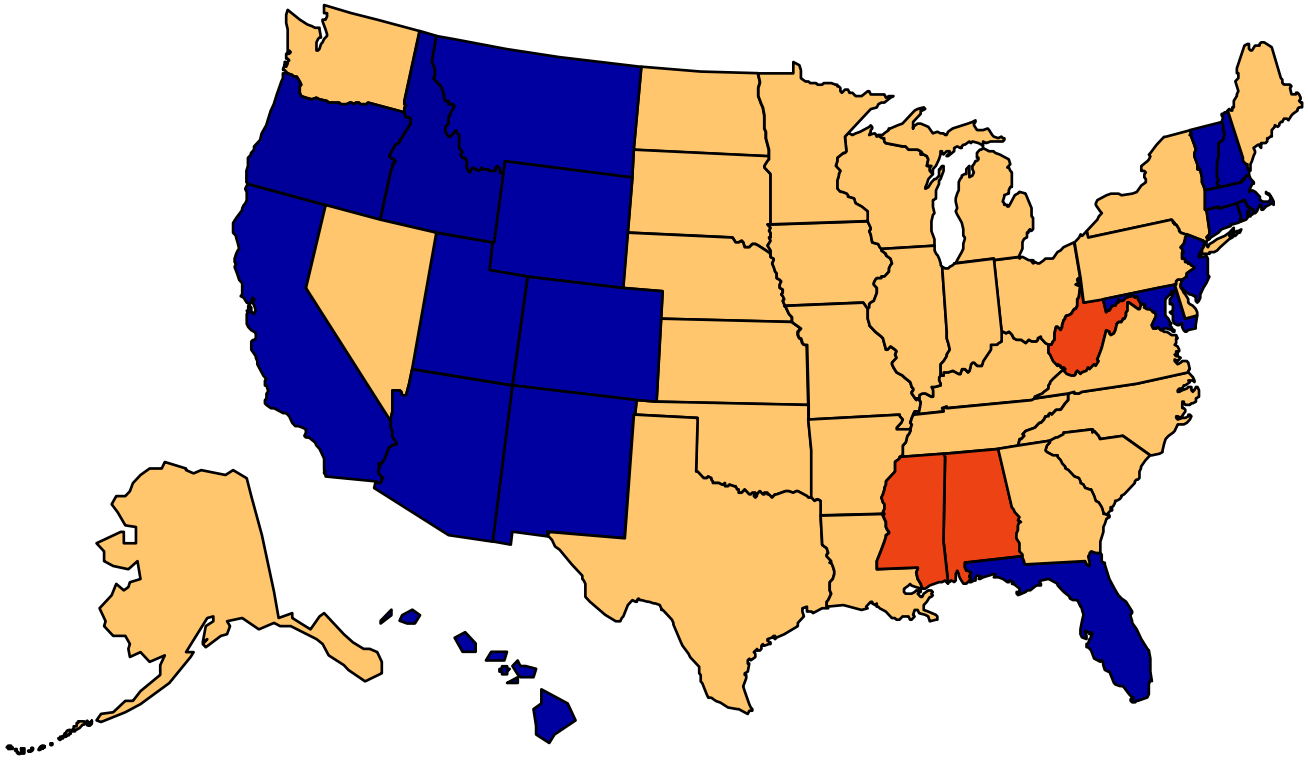
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

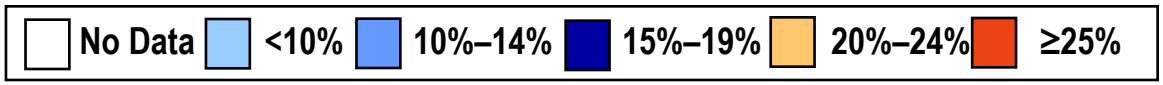




OBESITY IN THE US
BRSFF, 2002

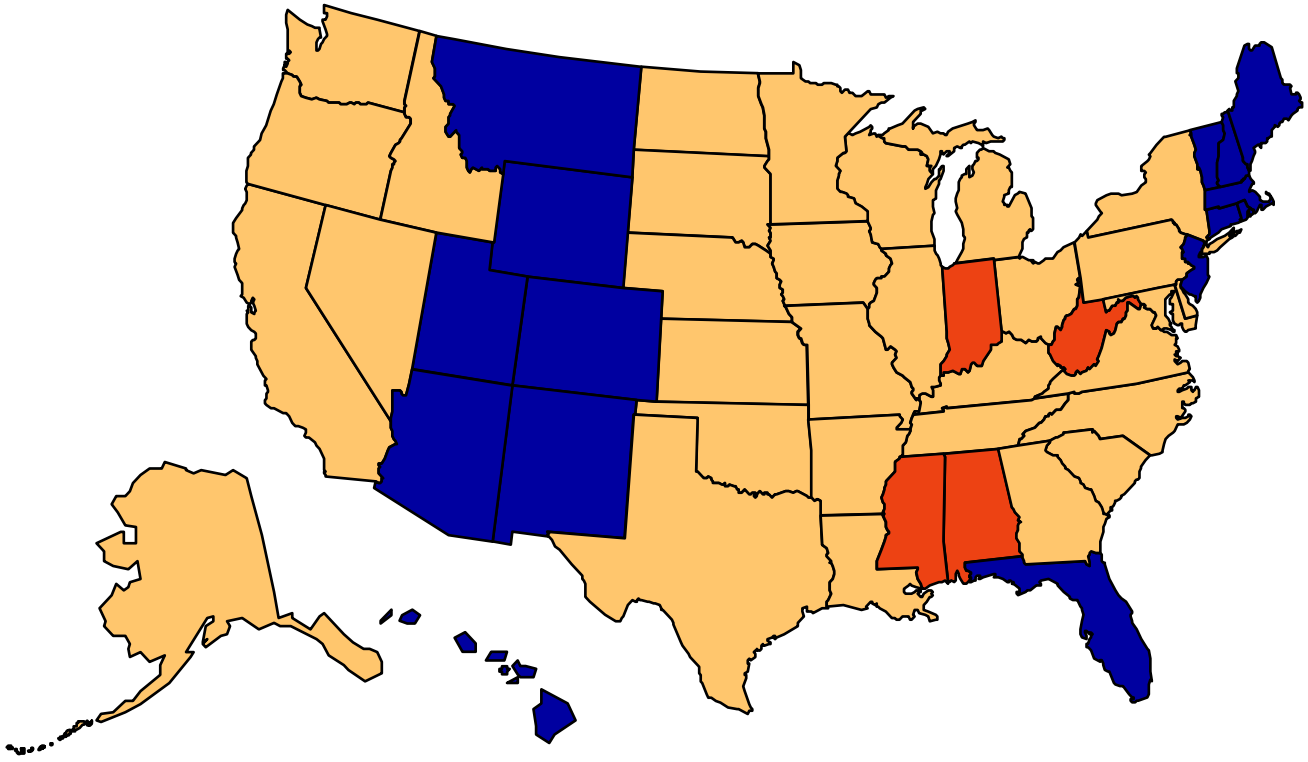
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

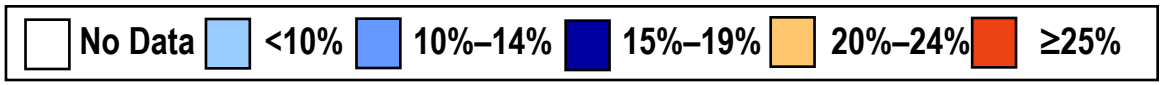




OBESITY IN THE US
BRSFF, 2003

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

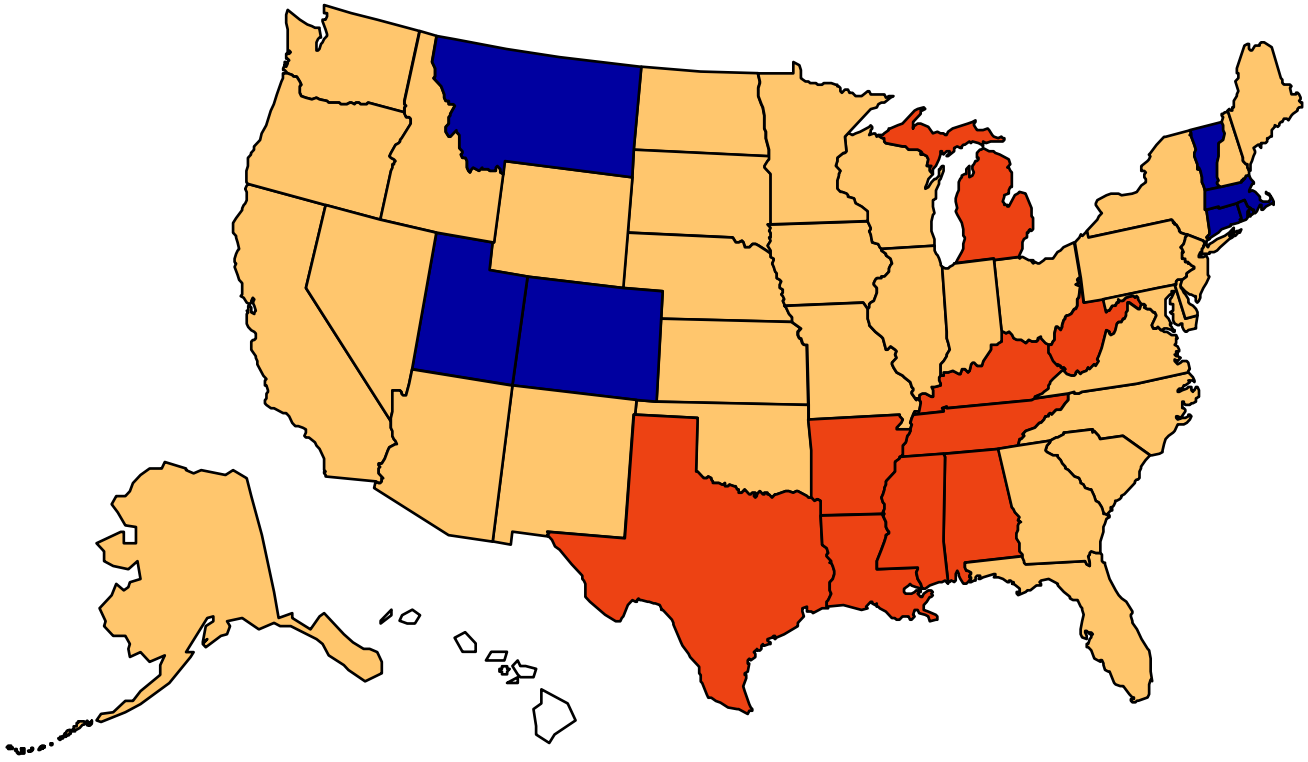


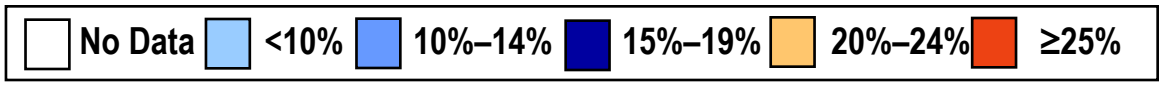


OBESITY IN THE US

BRSFF, 2004

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

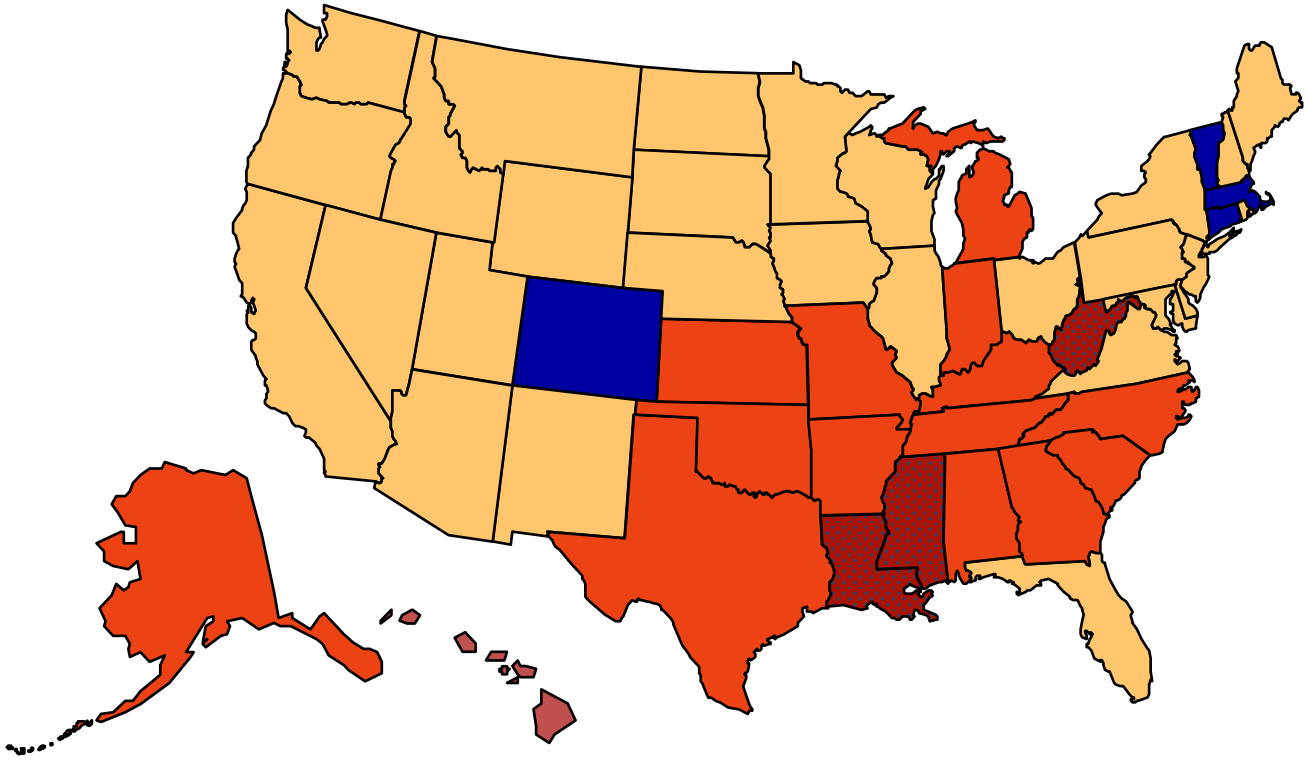


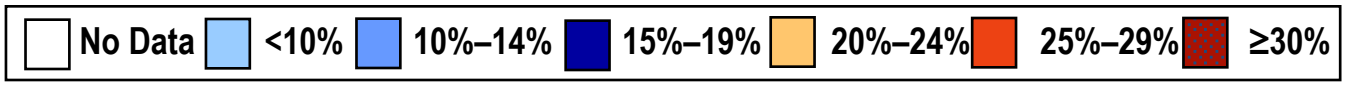


OBESITY IN THE US

BRSFF, 2005

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

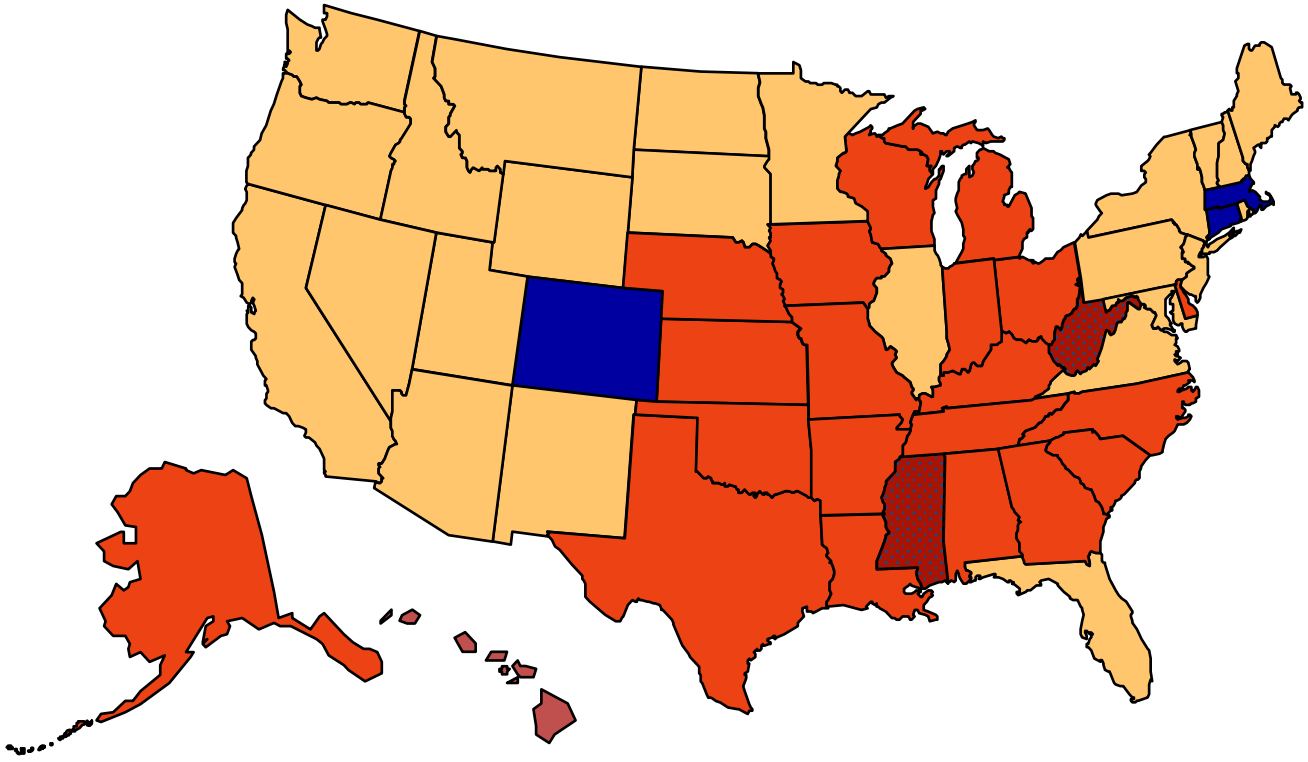


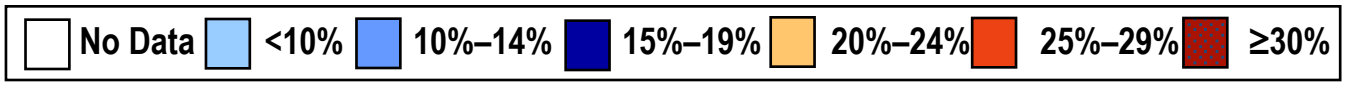


OBESITY IN THE US

BRSFF, 2006

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

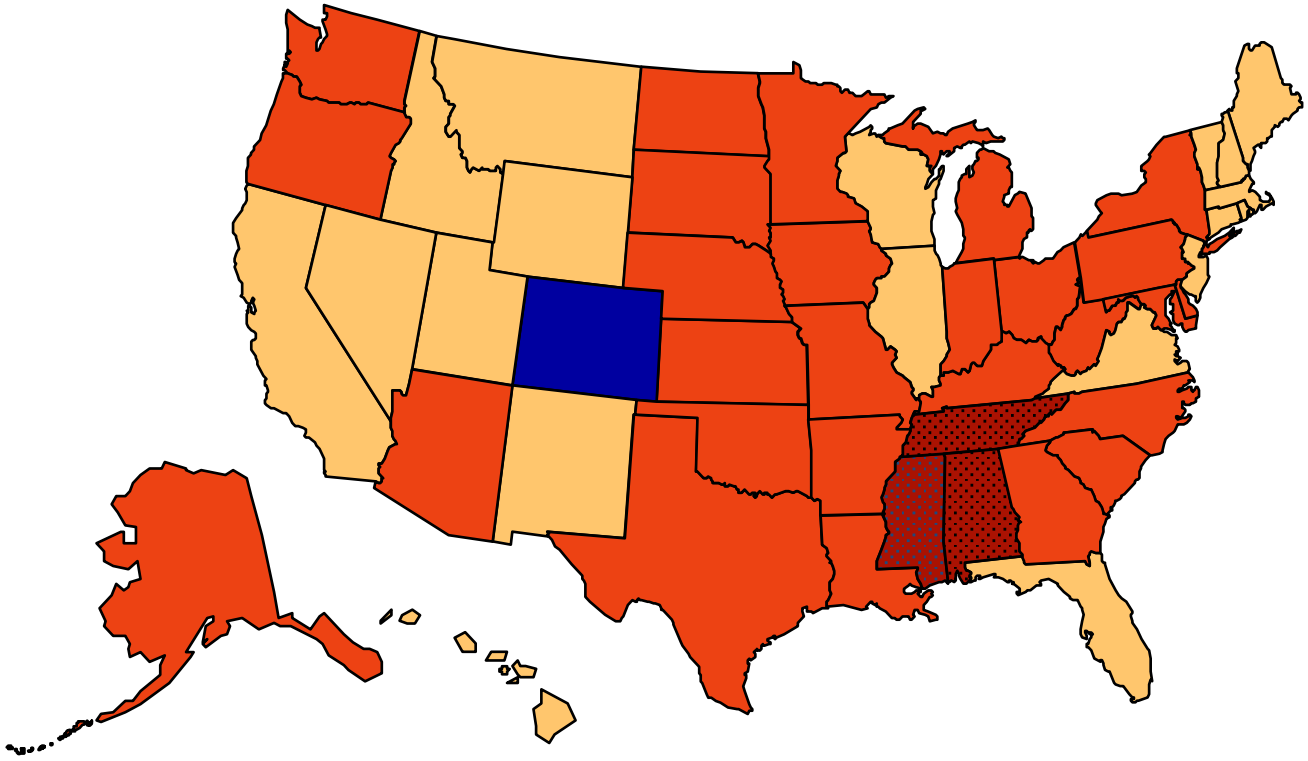


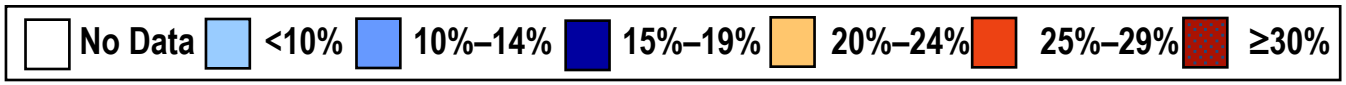


OBESITY IN THE US

BRSFF, 2007

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

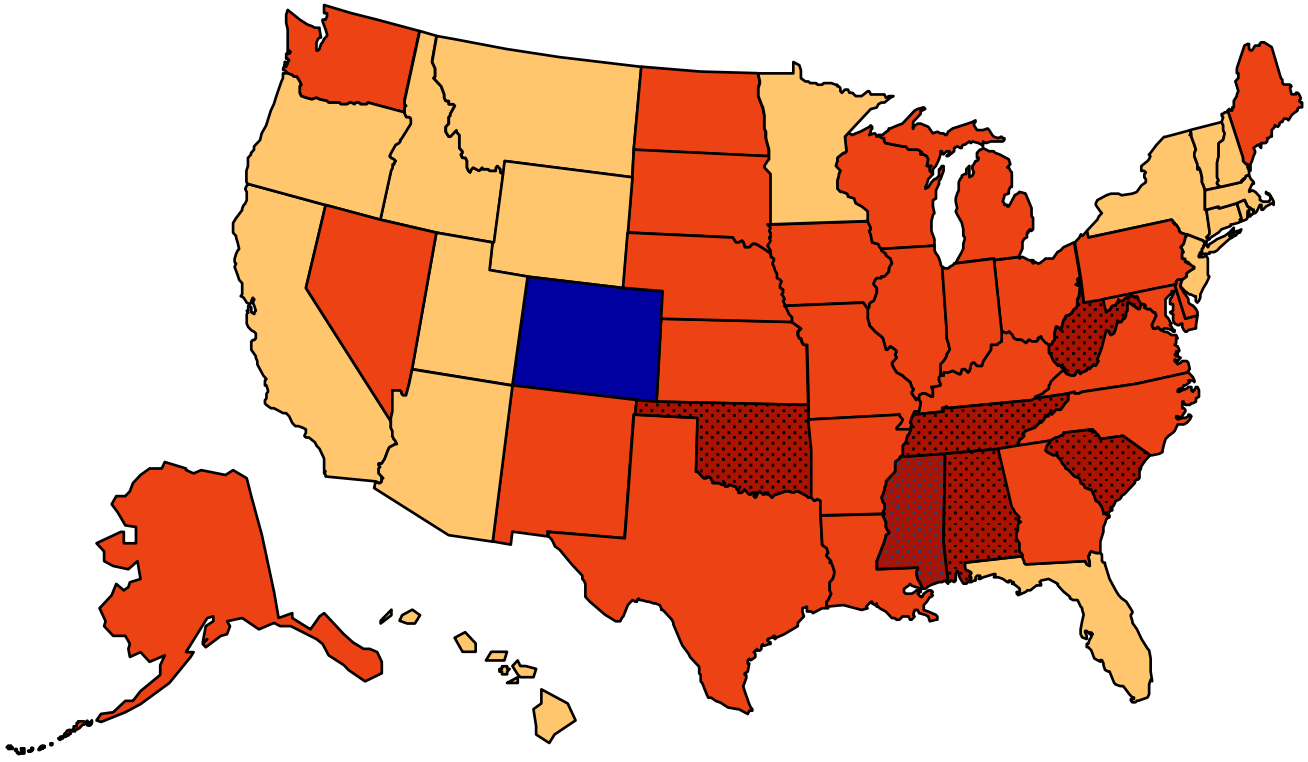


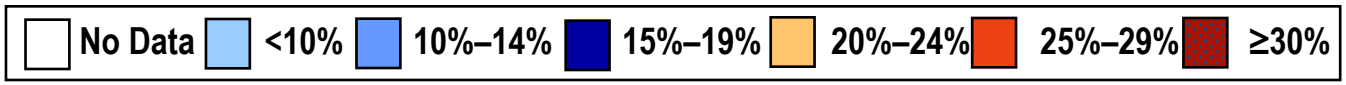


OBESITY IN THE US

BRSFF, 2008

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

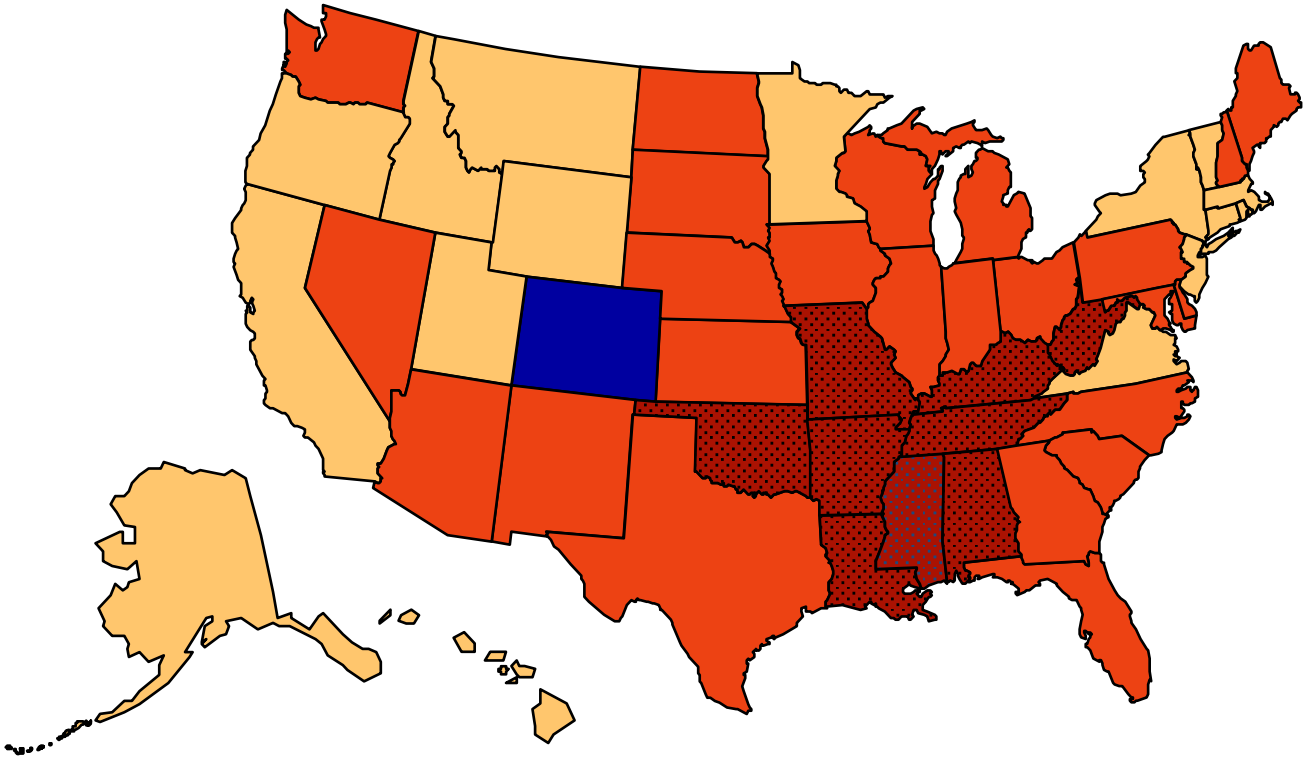




Obesity Trends* Among U.S. Adults

BRFSS, 2009

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

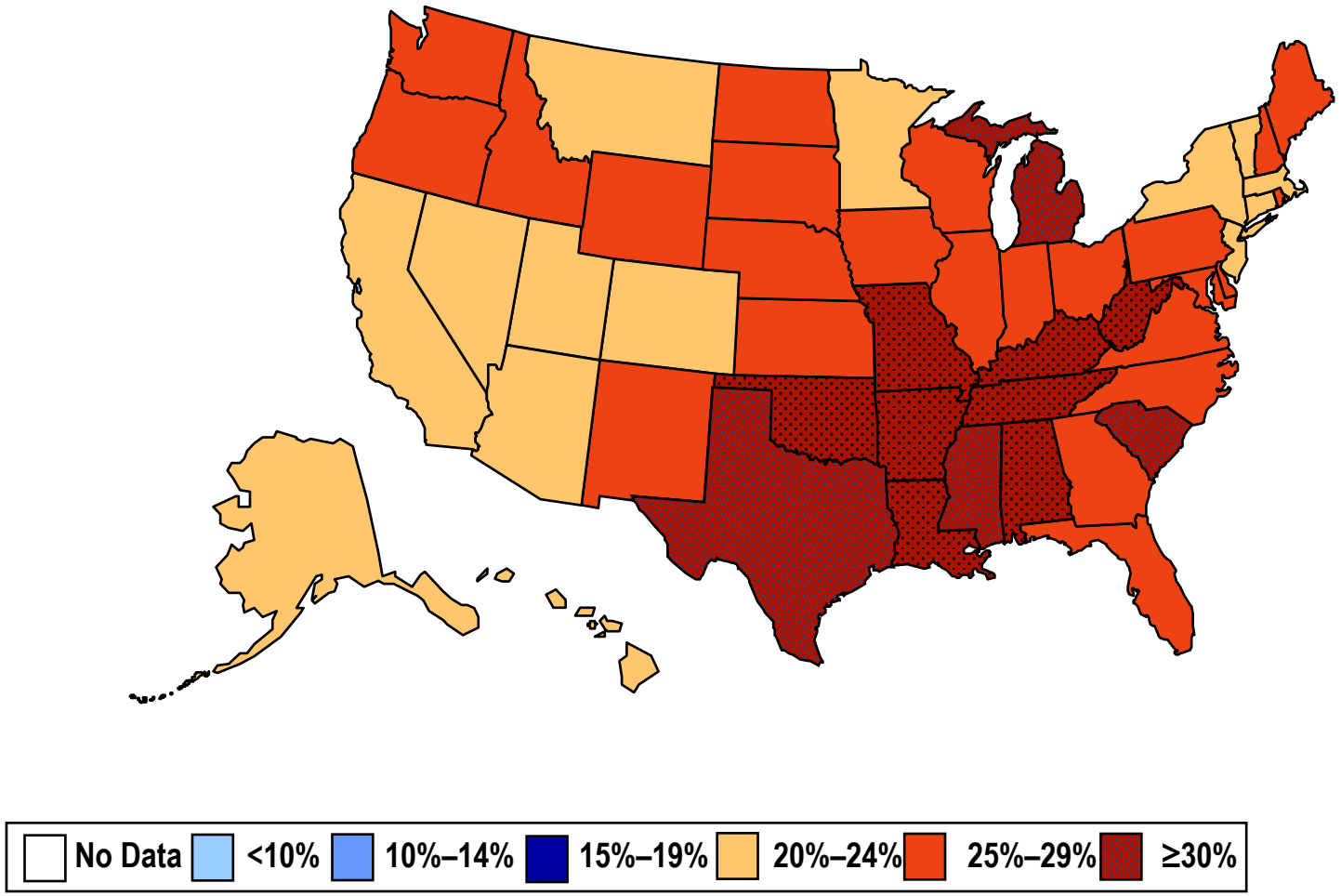


No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | ≥30%

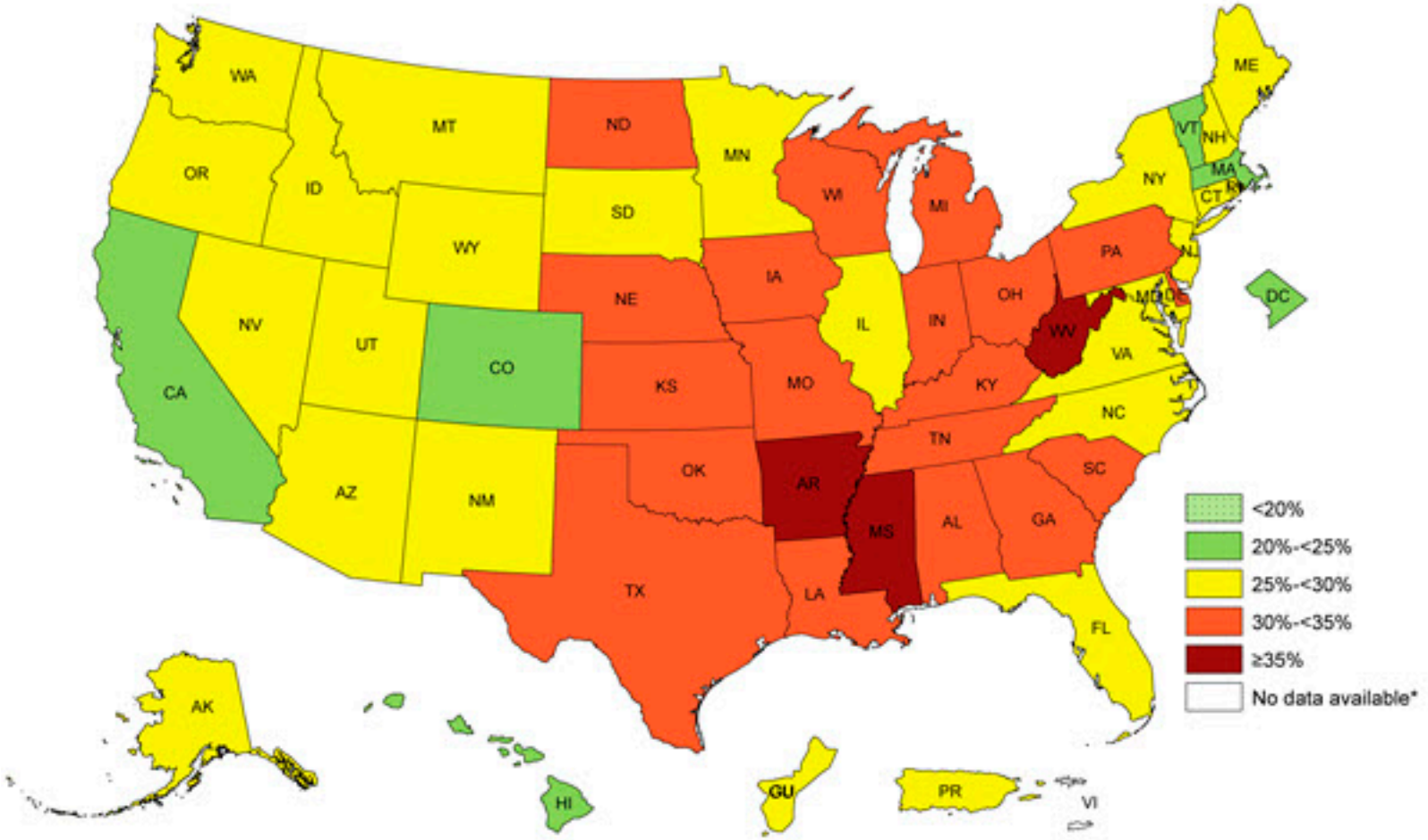
Obesity Trends* Among U.S. Adults

BRFSS, 2010

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

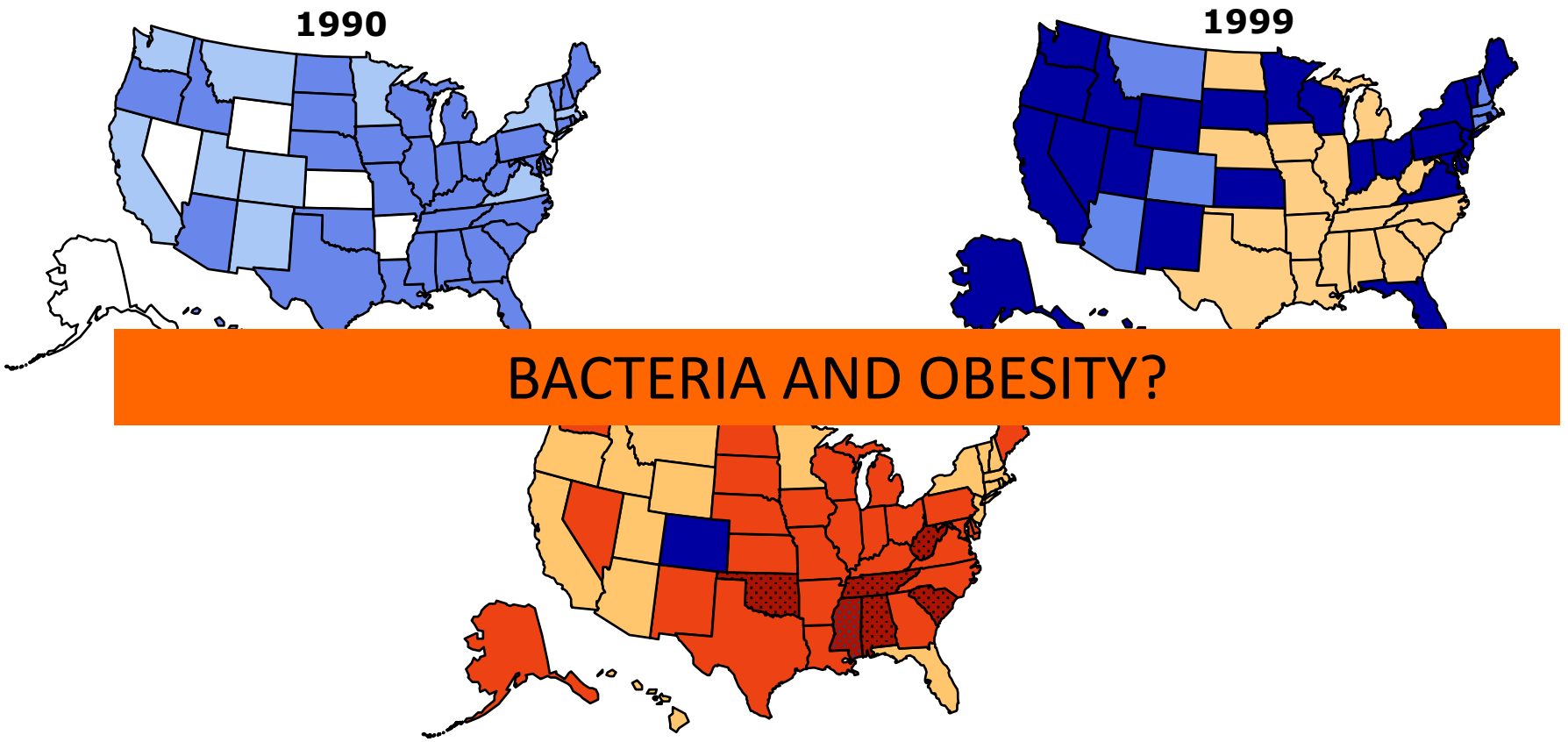


2014


WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
NY
MD
DC
NJ
CT
RI
MA
VT
NH
ME
AK
HI
GU
PR
VI
<20%
20%-<25%
25%-<30%
30%-<35%
≥35%
No data available*

BRFSS, 1990, 1999, 2008

(*BMI ≥30, or about 30 lbs. overweight for 5’ 4” person)

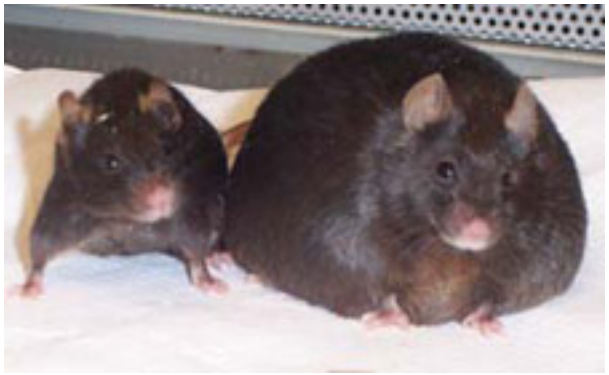


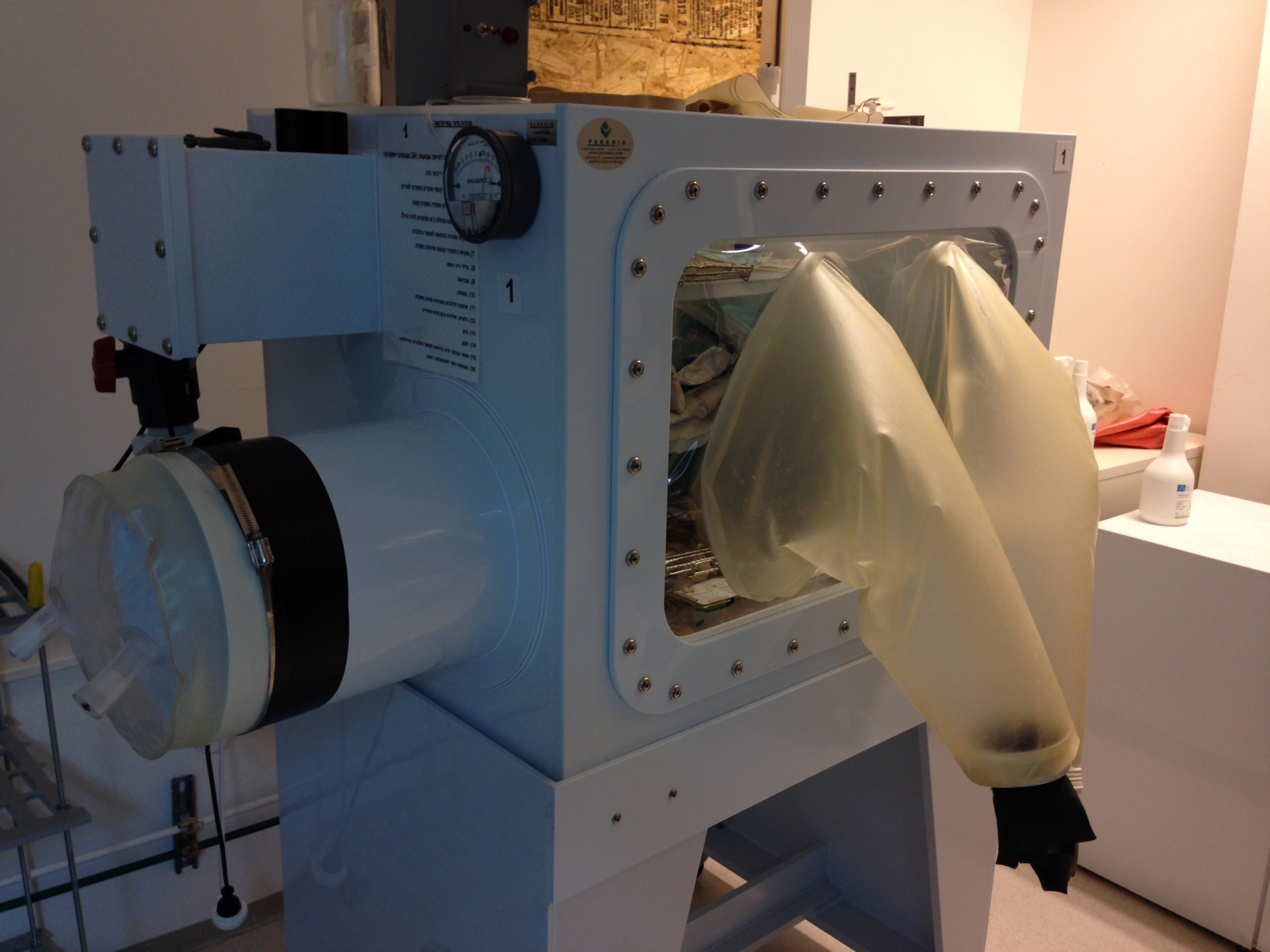
Mouse Models Help Us Learn More

Leptin: A hormone, produced by adipose tissue, that plays a key role in regulating appetite and metabolism

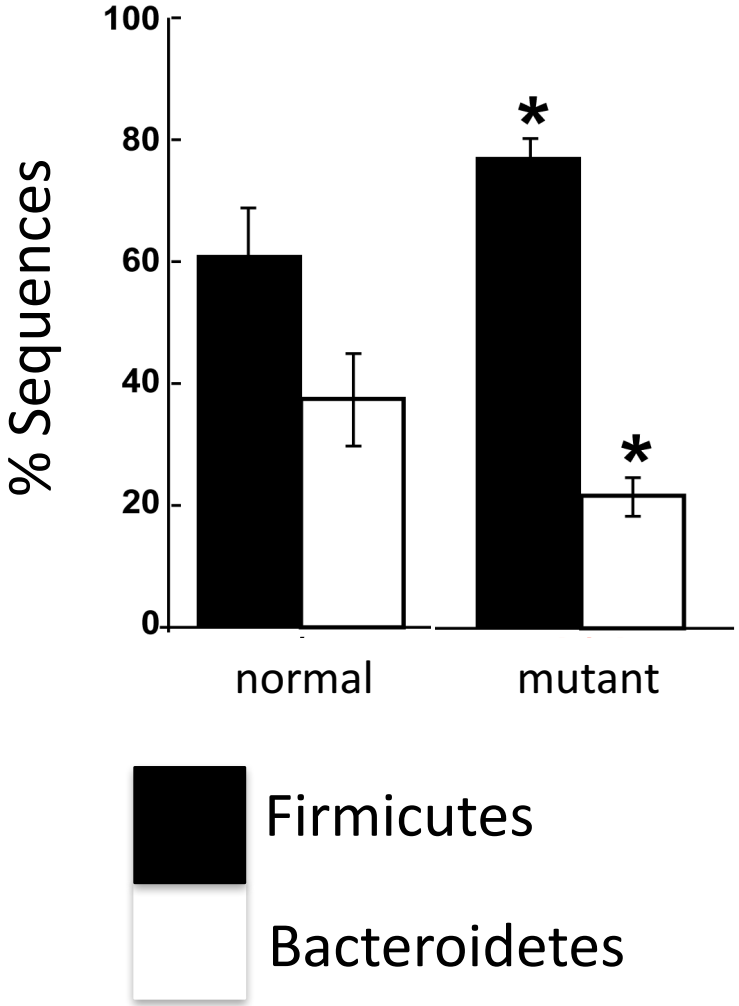
normal (with leptin)

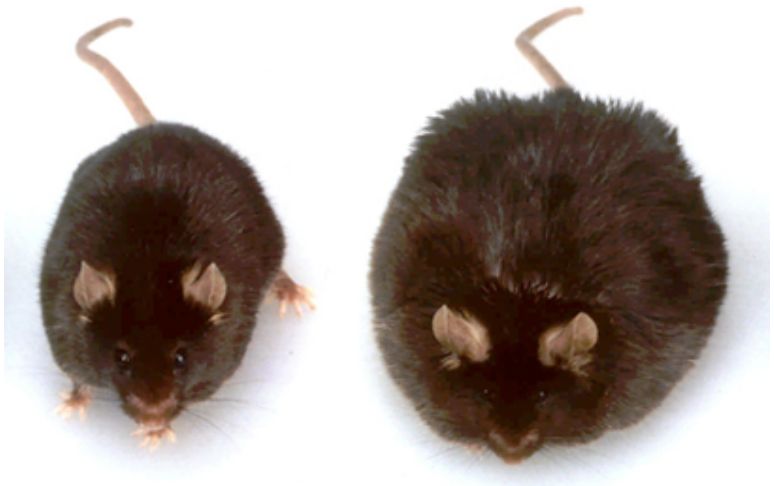
mutant (without leptin)





Altered gut microbiome in leptin-deficient mice



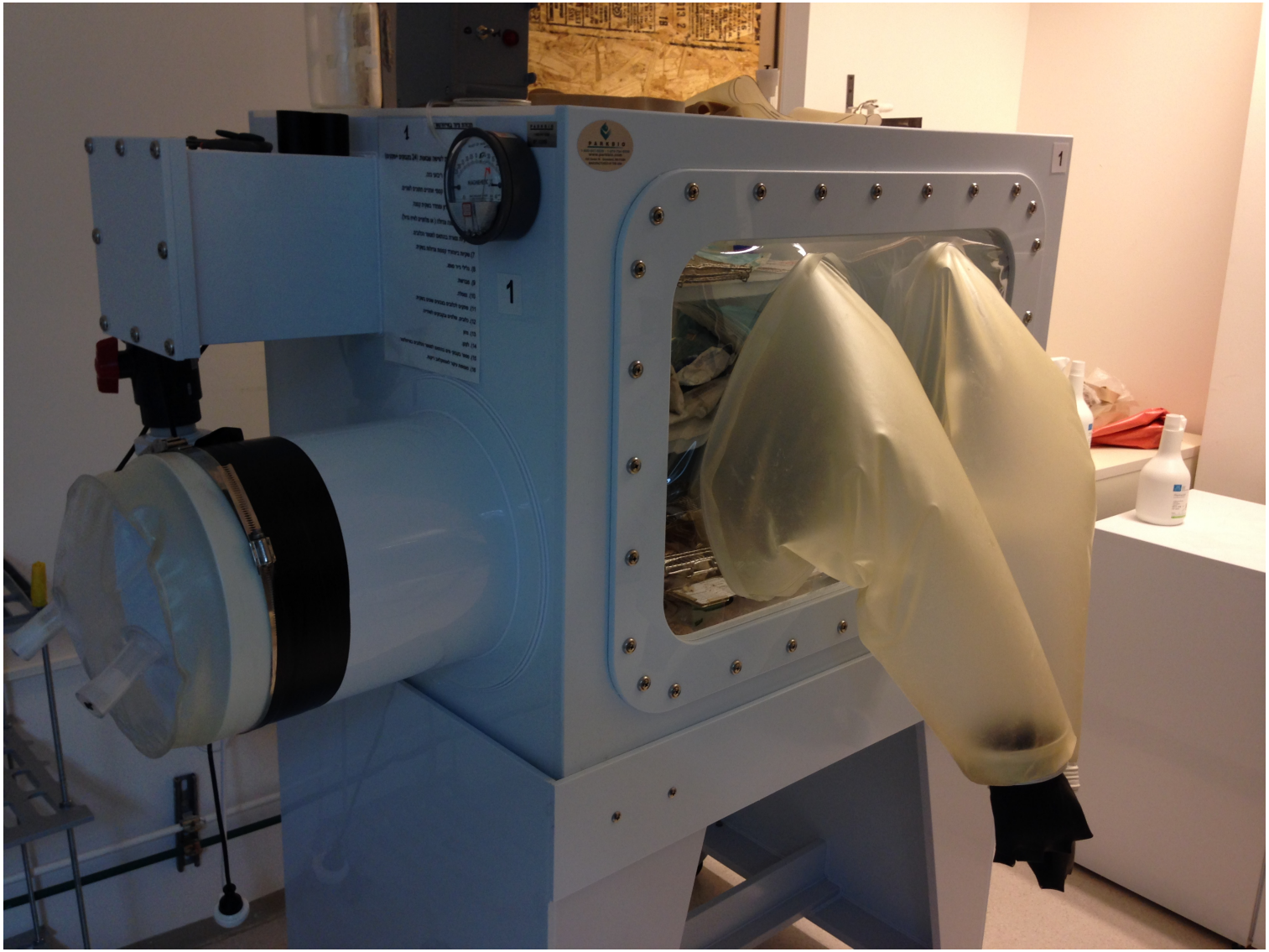


normal
(with leptin)

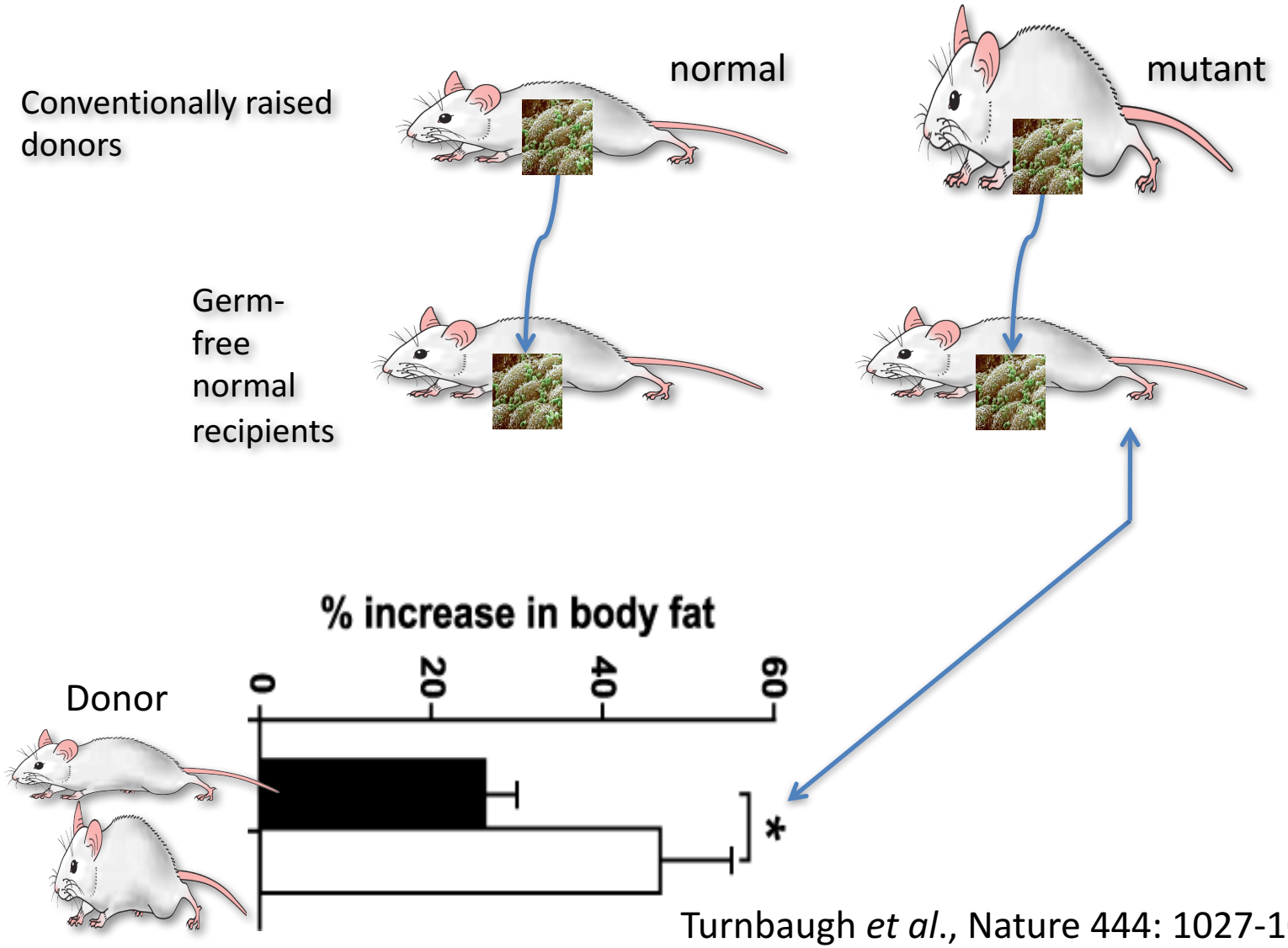
mutant
(without leptin)

Ley *et al*., PNAS 102: 11070-5 (2005)

Microbiome Transplants – a Powerful Tool

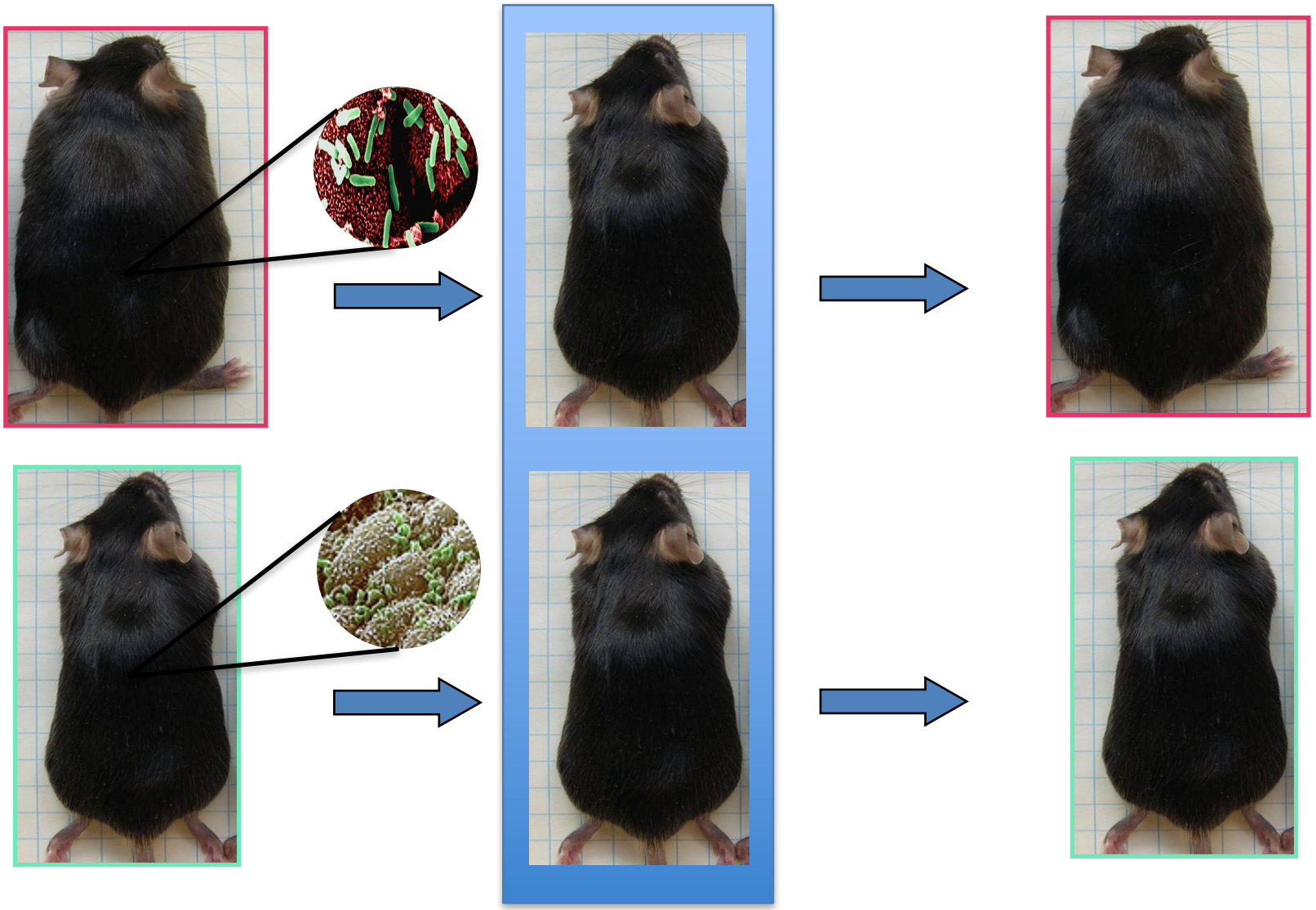


Microbiota transplantation experiments



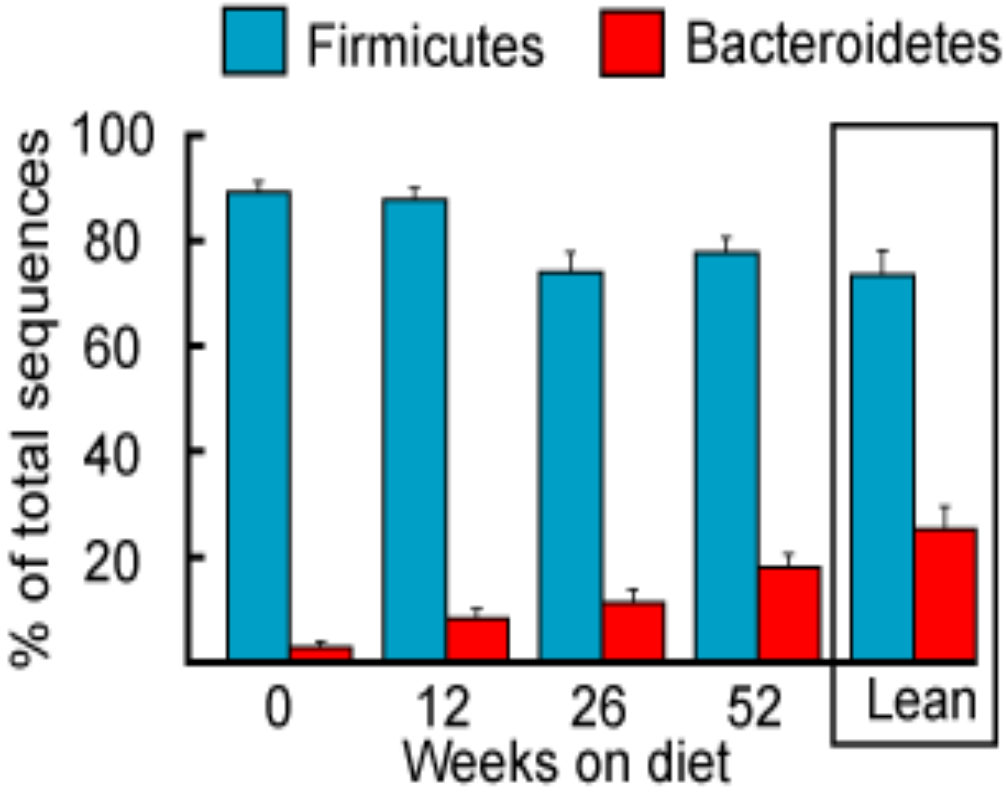
Turnbaugh *et al*., Nature 444: 1027-1031 (2006

Metabolic syndrome phenotype transferred



Vijay-Kumar et al. Science

An altered microbiome in obesity

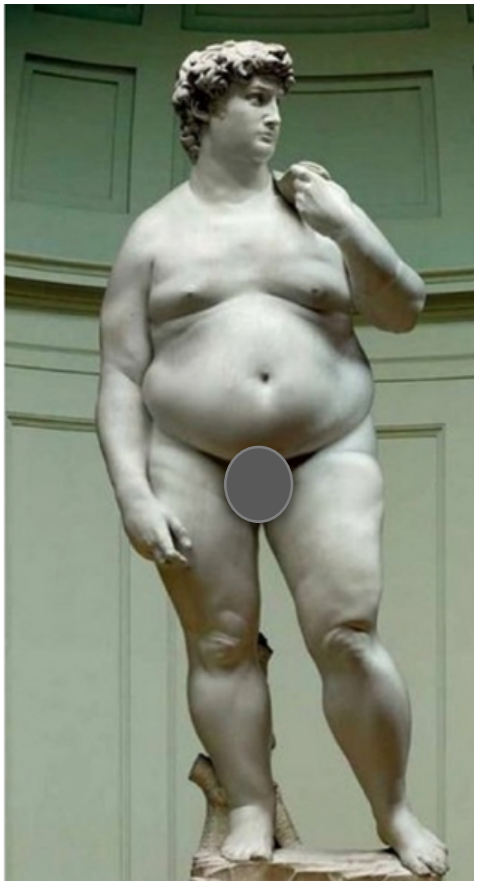


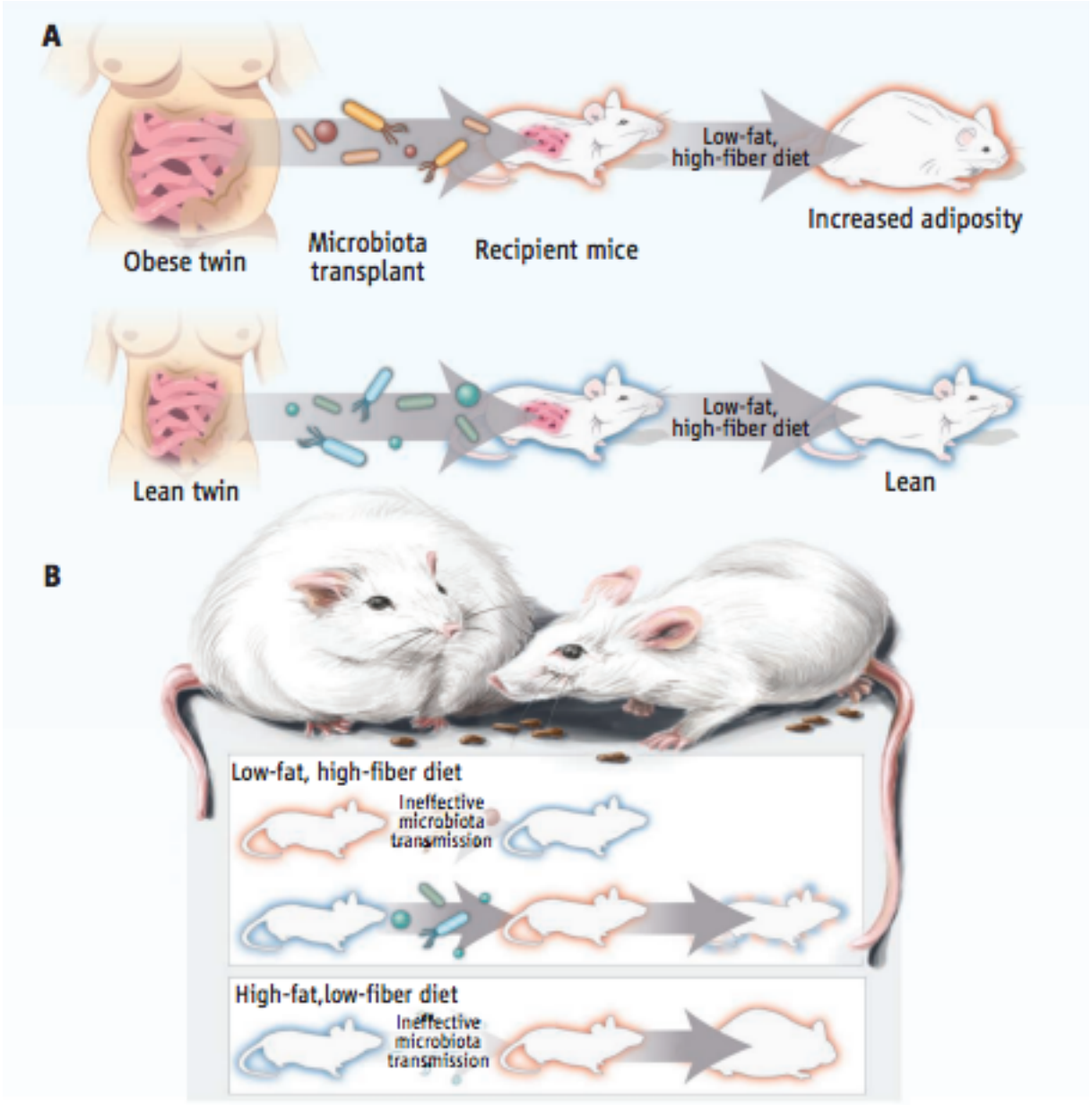
12 HUMANS

1-year (4 time points)

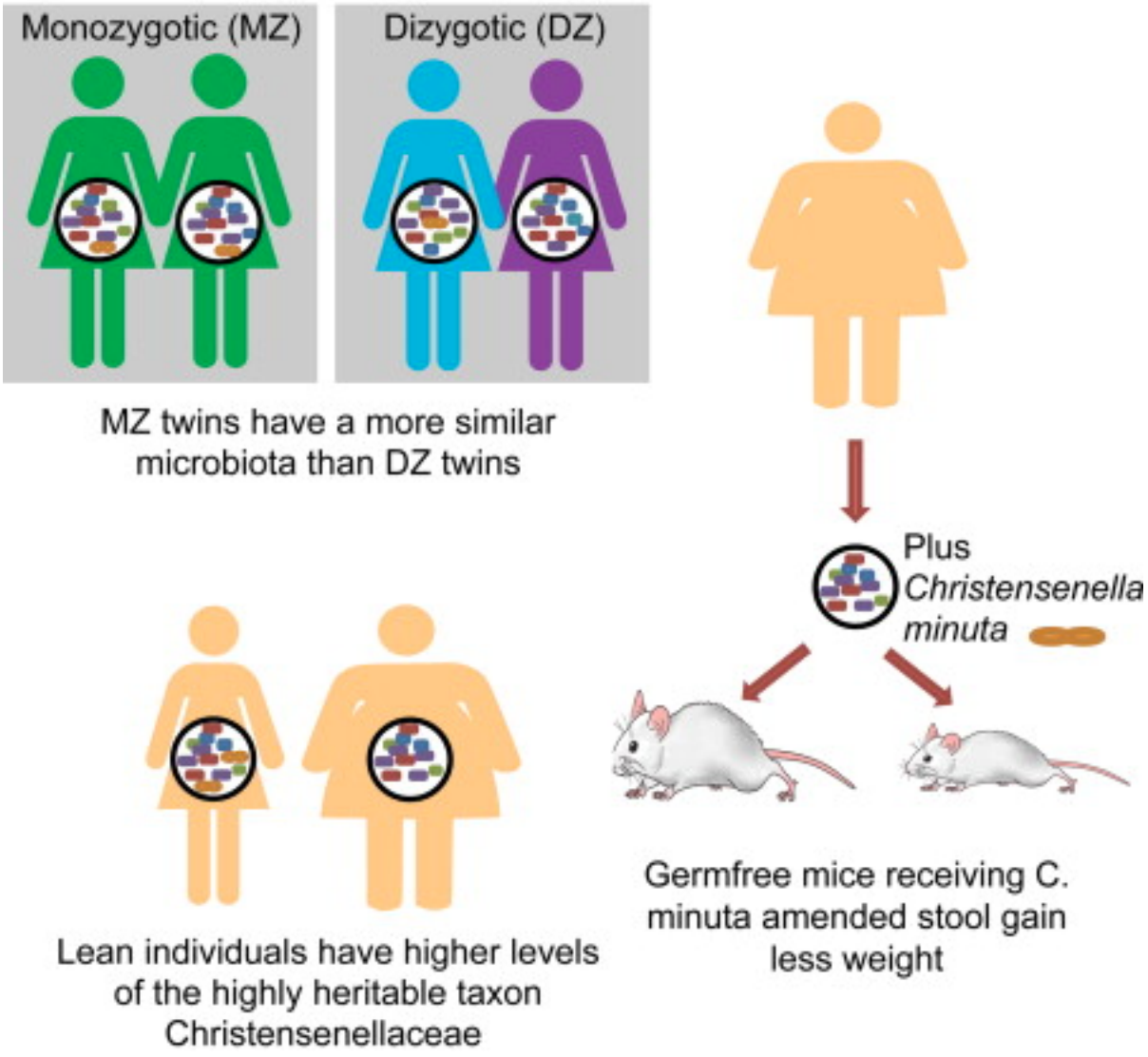
Ley, 2006

Twins

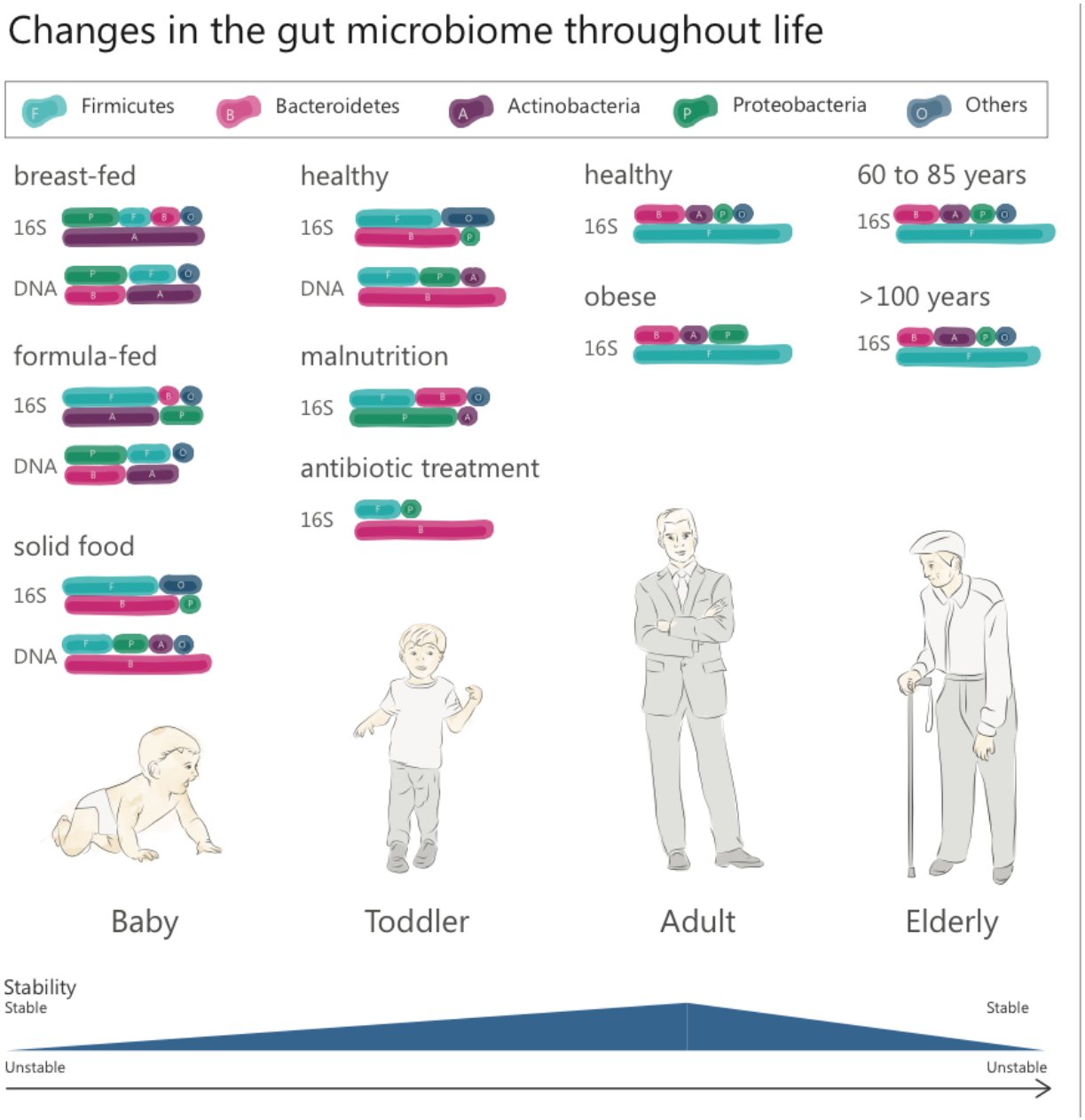



A
Low-fat,
high-fiber diet
Increased adiposity
Obese twin
Microbiota
transplant
Recipient mice
Low-fat,
high-fiber diet
Lean twin
Lean
B
Low-fat, high-fiber diet
Ineffective
microbiota
transmission
High-fat,low-fiber diet
Ineffective
microbiota
transmission

Bacteria may help keep you lean

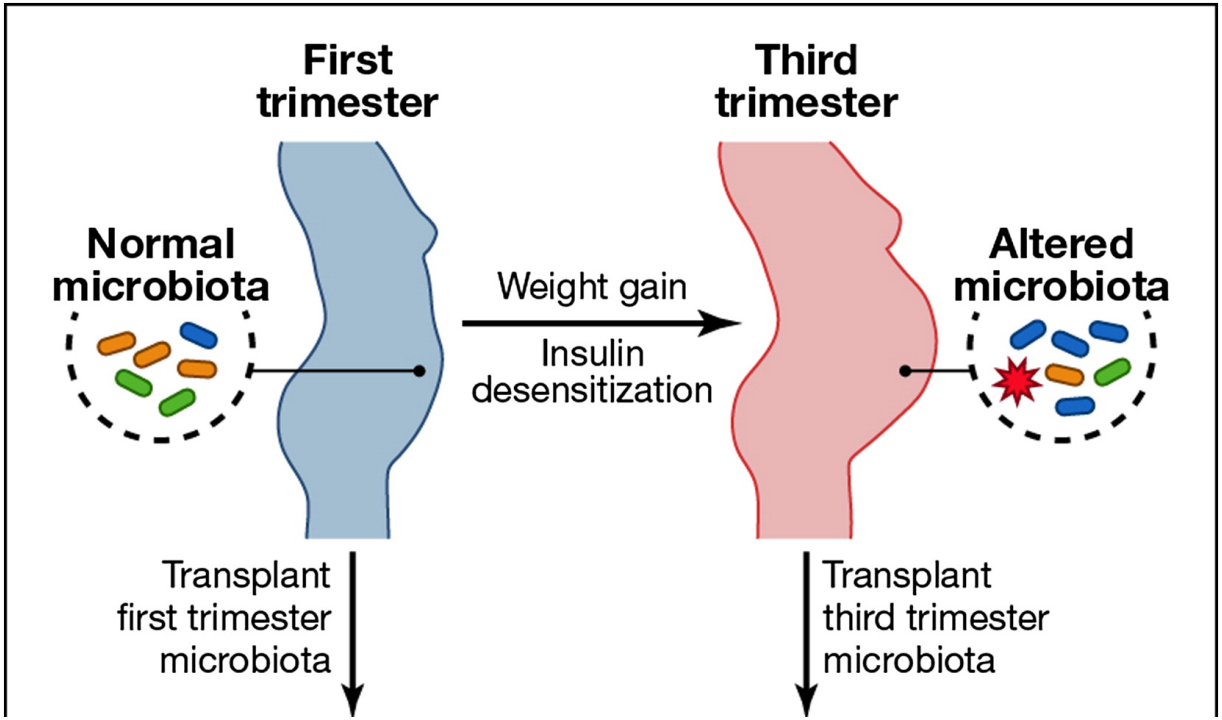


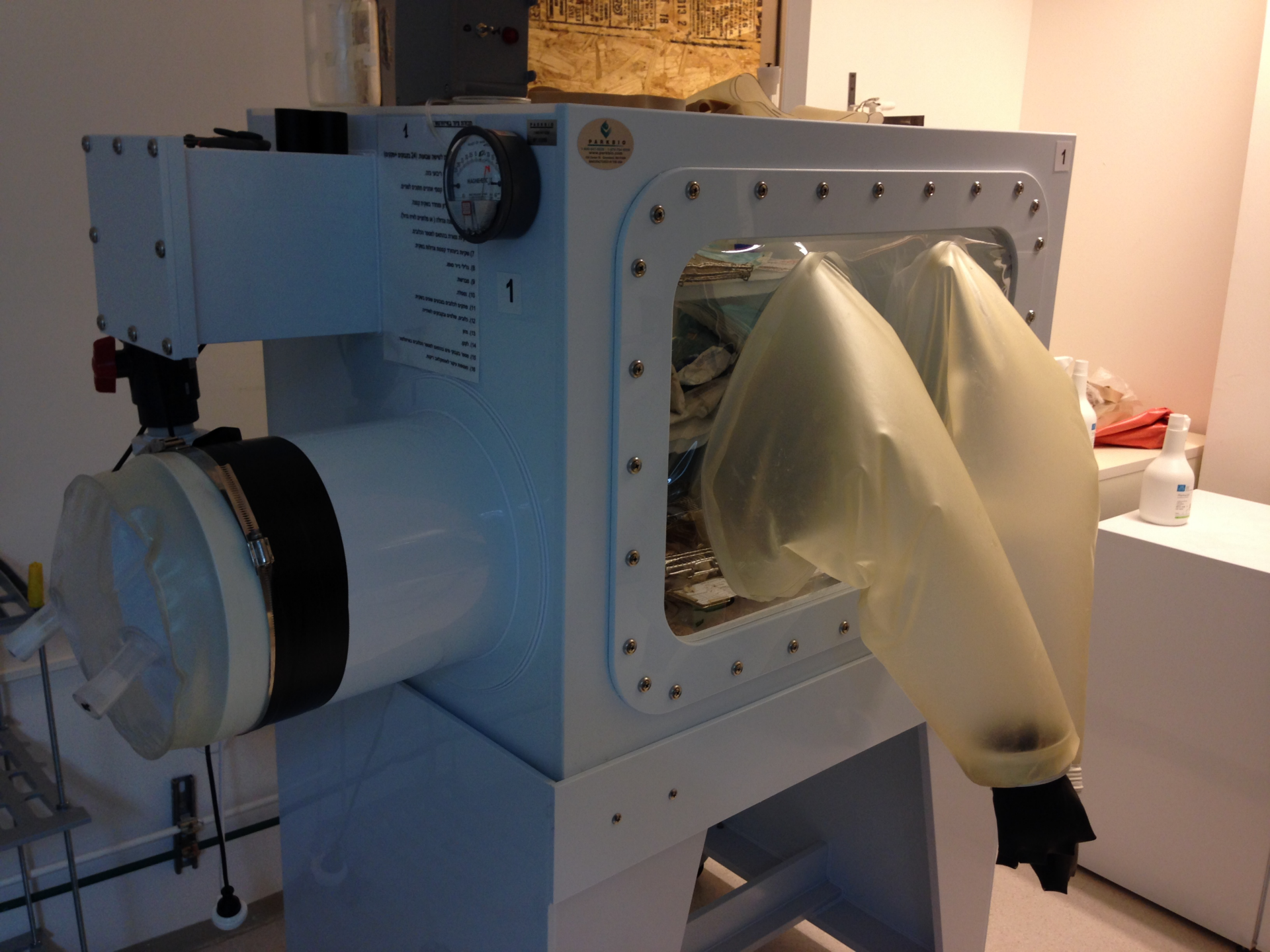
Goodrich et al. Cell, 2014



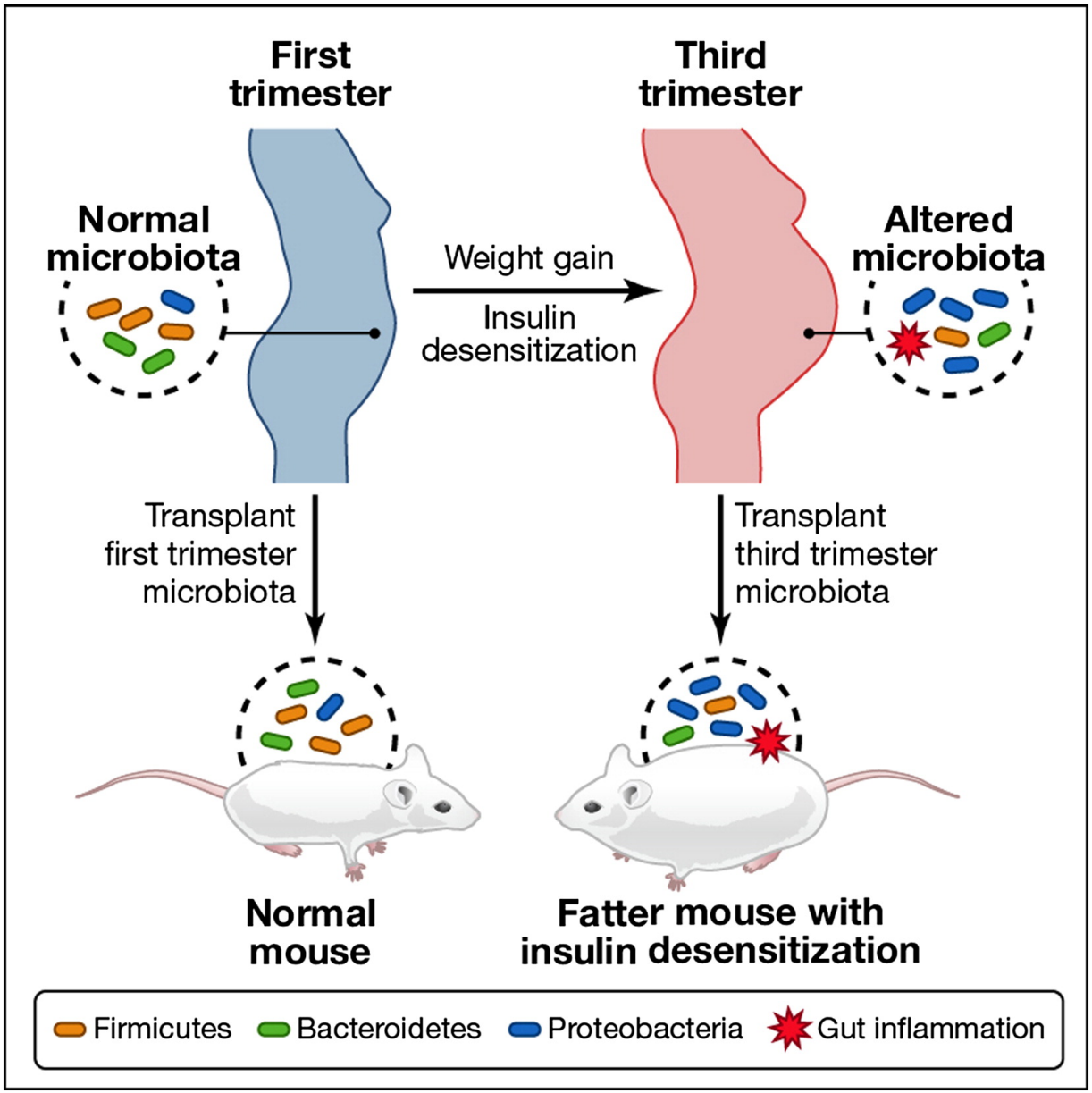
Neuman and Koren, In press

Phenotype Effect: Microbiota Transfer

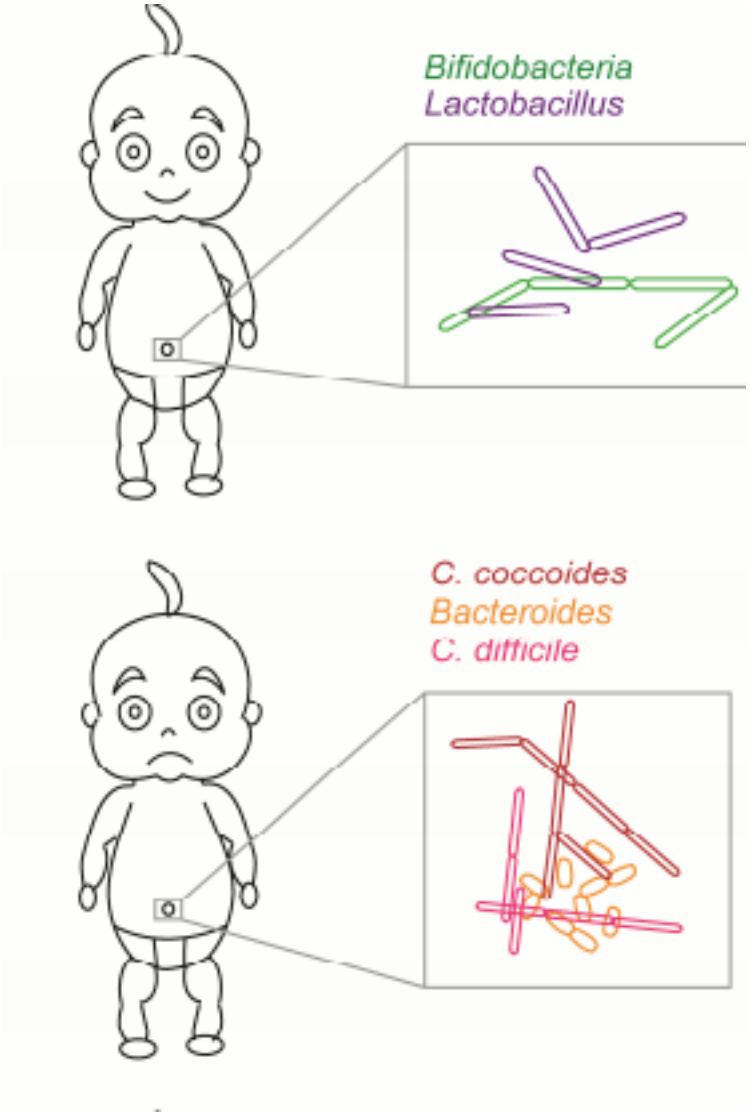




Phenotype Effect: Microbiota Transfer



What about the kids?

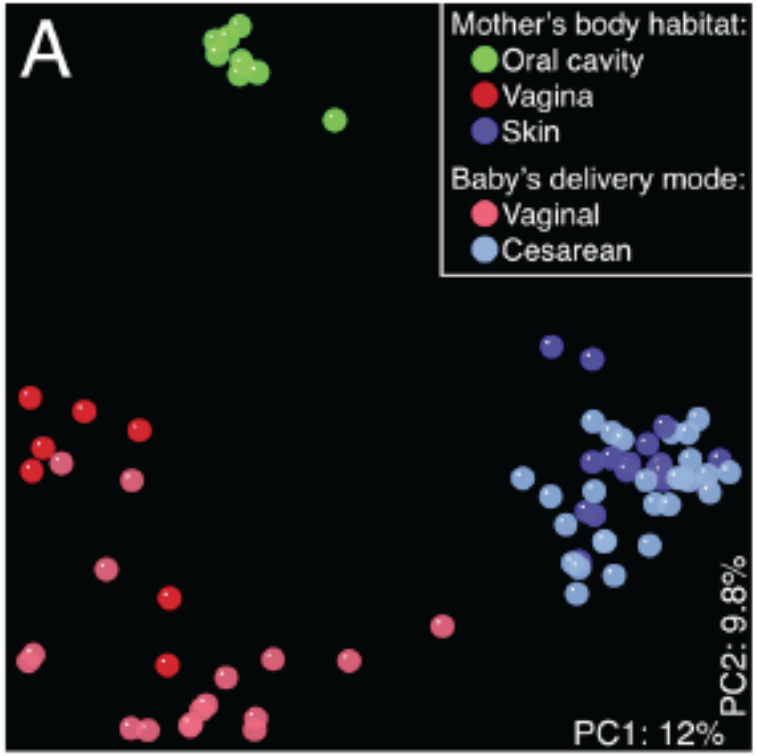


Adapted from Fischer *et al*. 2012

THE MICROBIOME STARTS AT BIRTH. AS BABIES PASS THROUGH THE BIRTH CANAL, THEY PICK UP THE BACTERIA FROM THE MOTHER'S VAGINAL MICROBIOME.

PRI

We are inoculated at birth


A
Mother's body habitat:
Oral cavity
Vagina
Skin
Baby's delivery mode:
Vaginal
Cesarean
PC1: 12%
PC2: 9.8%

nature medicine

Home | Current issue | News & comment | Research | Archive ▾ | Authors & referees ▾ | About the journal

home ▸ advance online publication ▸ full text

NATURE MEDICINE | BRIEF COMMUNICATION

Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

Maria G Dominguez-Bello, Kassandra M De Jesus-Laboy, Nan Shen, Laura M Cox, Amnon Amir, Antonio Gonzalez, Nicholas A Bokulich, Se Jin Song, Marina Hoashi, Juana I Rivera-Vinas, Keimari Mendez, Rob Knight & Jose C Clemente

Affiliations | **Contributions** | **Corresponding authors**

Nature Medicine (2016) | doi:10.1038/nm.4039

Received 03 July 2015 | Accepted 22 December 2015 | Published online 01 February 2016

Restoring the Newborn Microbiota

3

1. Sample mom.
2. Incubate gauze in vagina for 1h.
3. Extract gauze before C-section.
4. Expose newborn to the vaginal gauze.
5. Swab- sample newborn.

5

4

Mouth first...

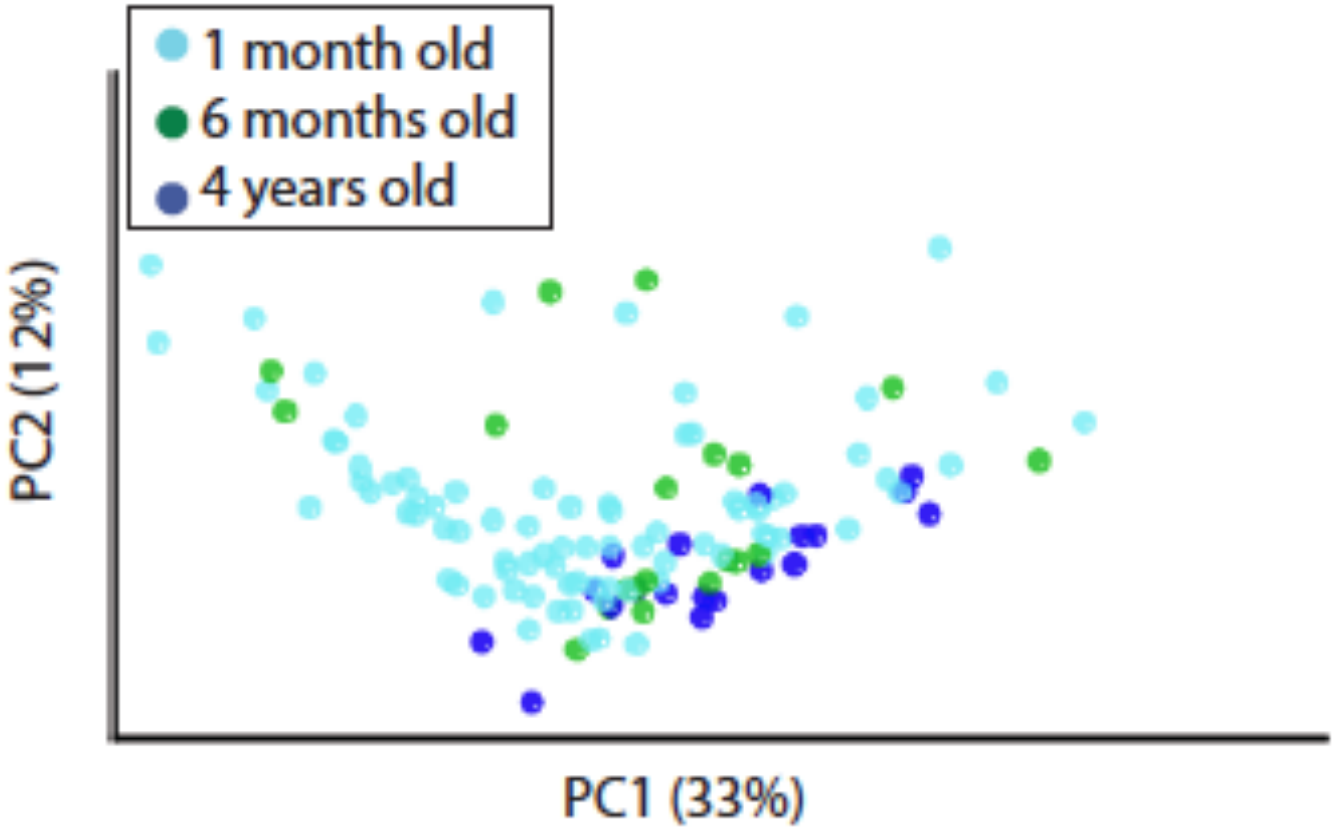
then face...

and rest of the body

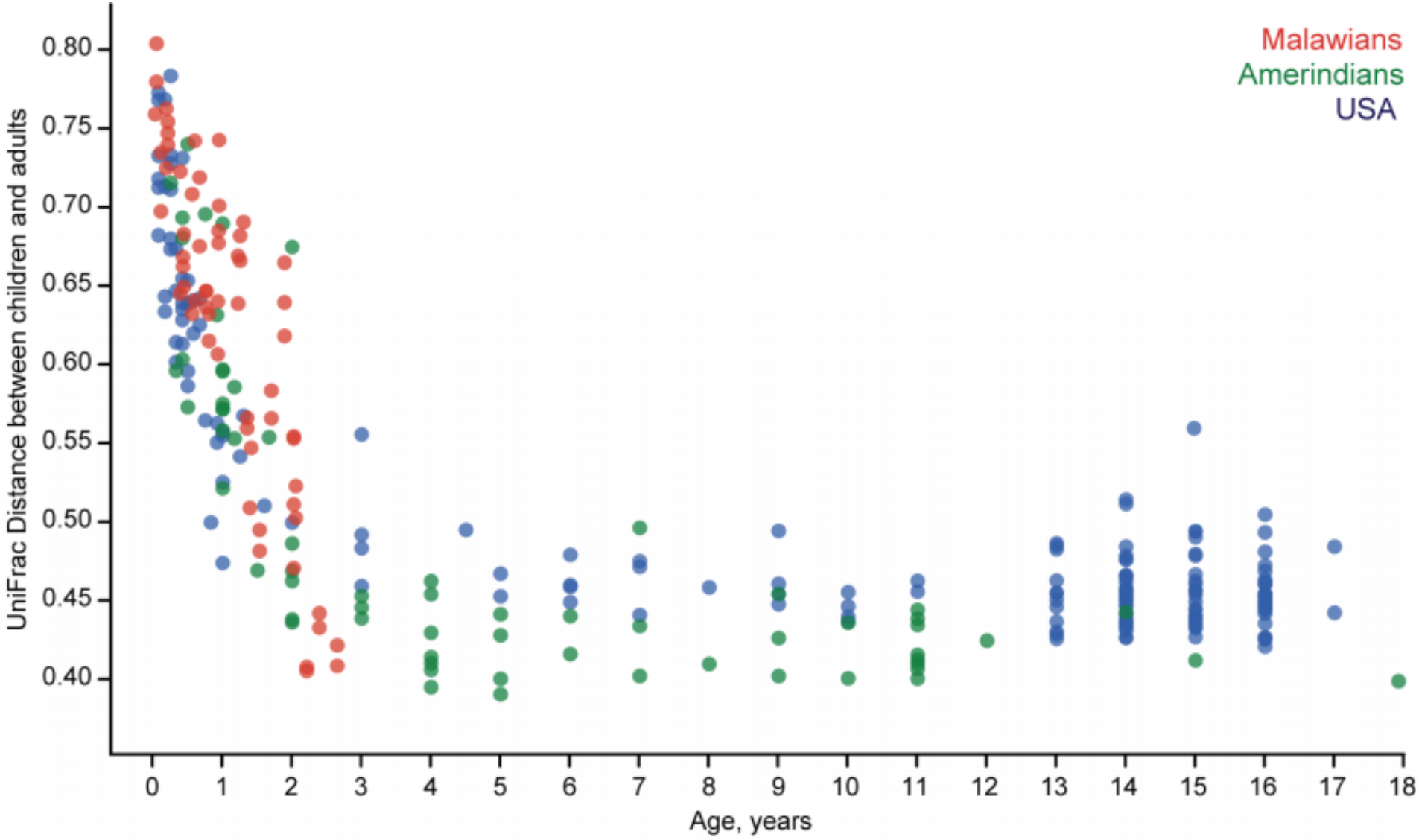
BABIES ARE MICROBE MAGNETS.

FOR 2-3 YEARS THEIR MICROBIOMES GROW WHILE THEIR IMMUNE SYSTEMS DEVELOP, LEARNING NOT TO ATTACK FRIENDLY BACTERIA.

PRI



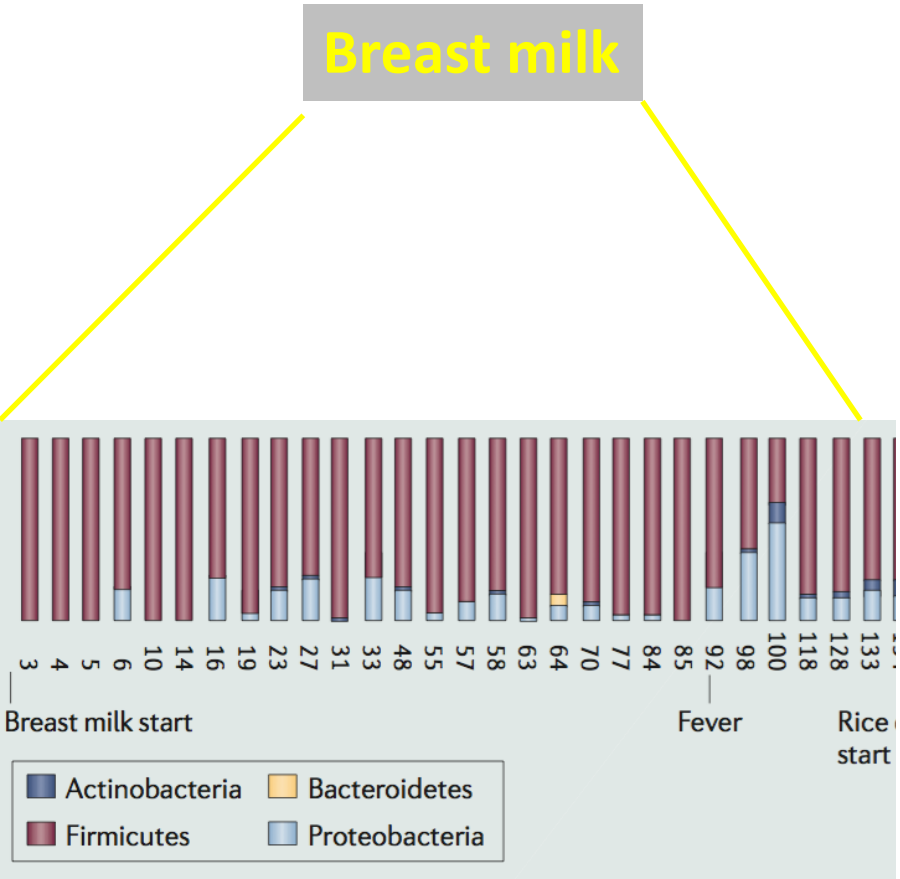
Koren, 2012



UniFrac distances between children and adults decrease with increasing age of children in each population. Each point shows an average distance between a child and all adults unrelated to that child but from the same country.

Yatsunenko et al., 2012

Timeline of gut colonization by microbes

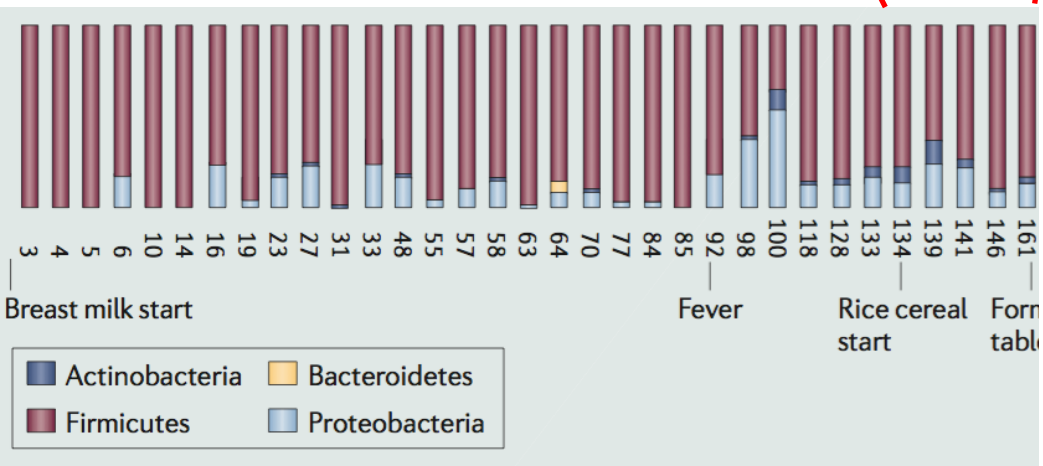


Spor*, Koren* and Ley. 2011. NRM

Timeline of gut colonization by microbes

Breast milk

Rice cereal



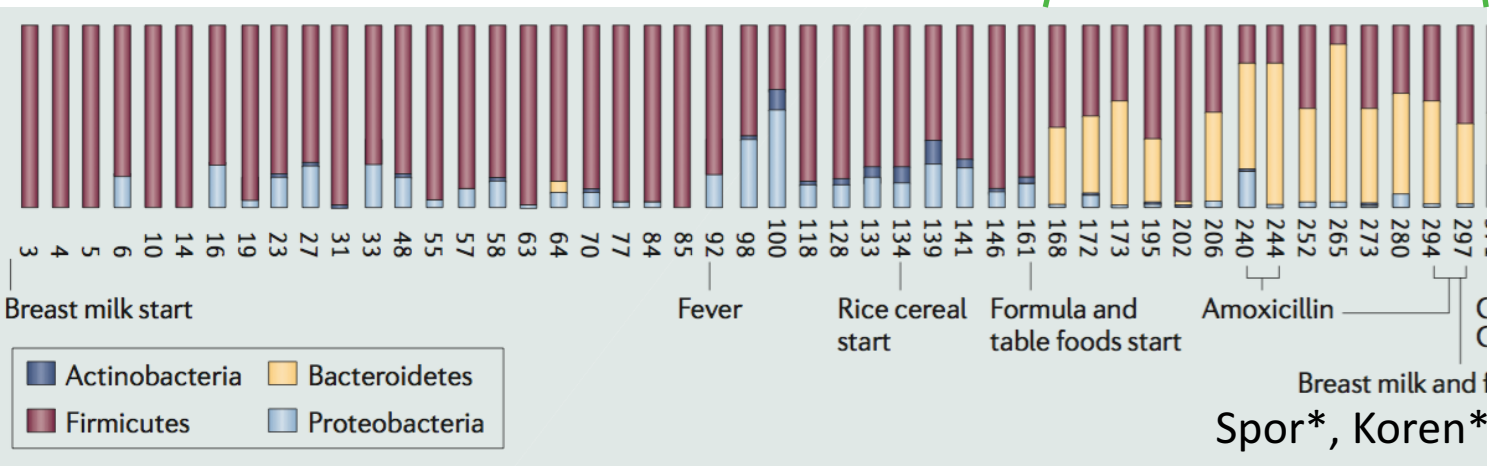
Spor*, Koren* and Ley. 2011. NRM

Timeline of gut colonization by microbes

Breast milk

Rice cereal

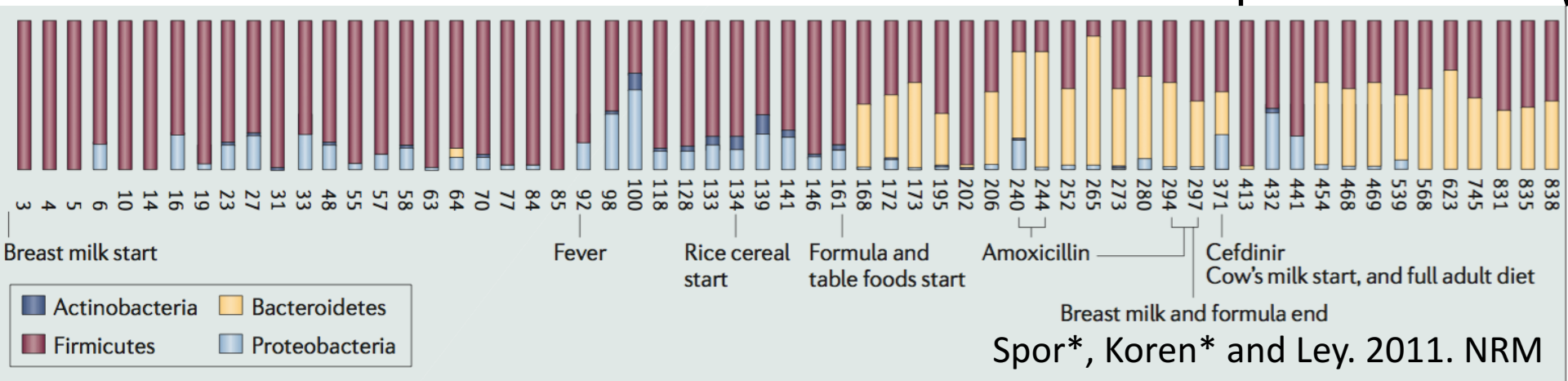
Table foods



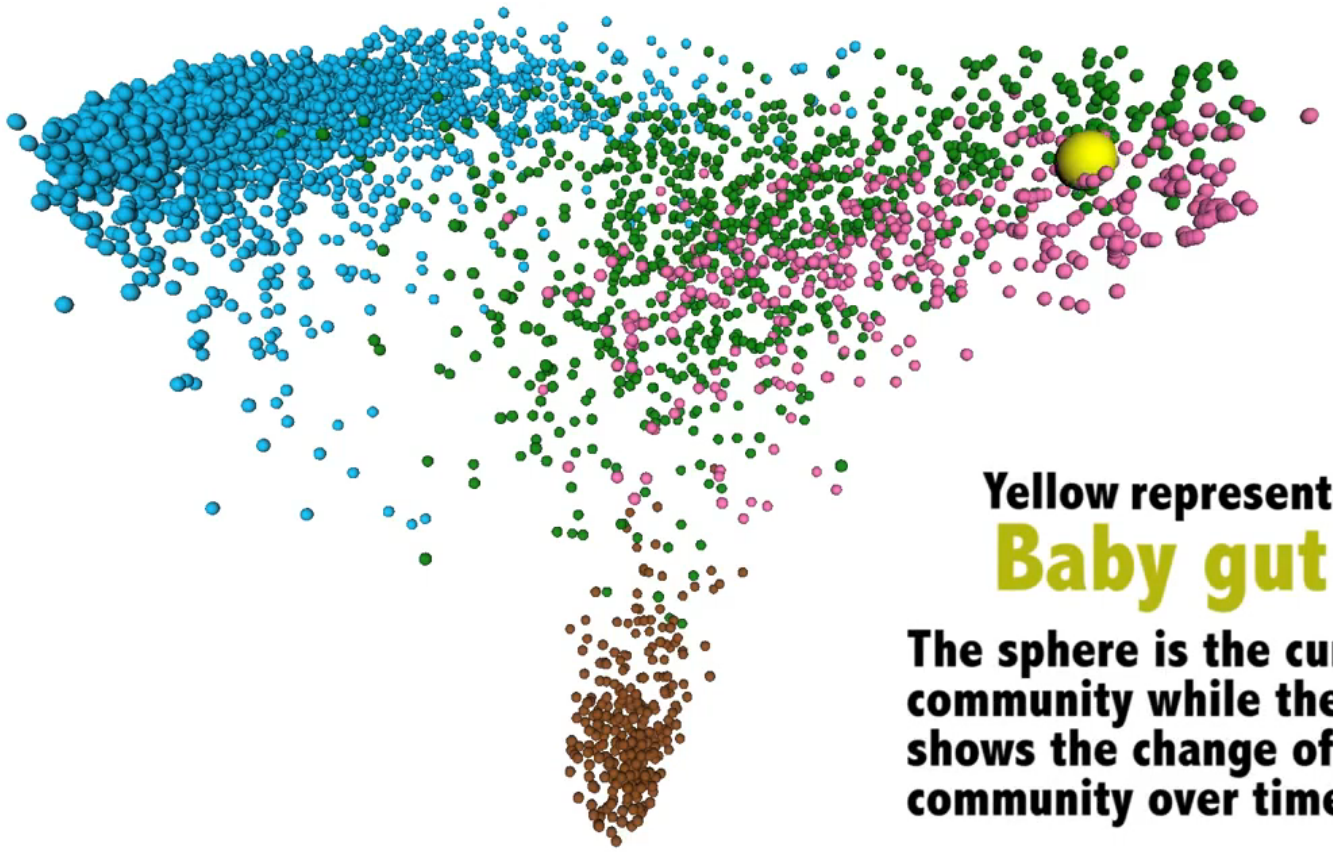
Spor*, Koren* and Ley. 2011. NRM

Timeline of gut colonization by microbes

Breast milk | Rice cereal | Table foods | Adult diet



Spor*, Koren* and Ley. 2011. NRM



Yellow represents

Baby gut

The sphere is the current community while the path shows the change of the community over time

Dr. Henry Cotton

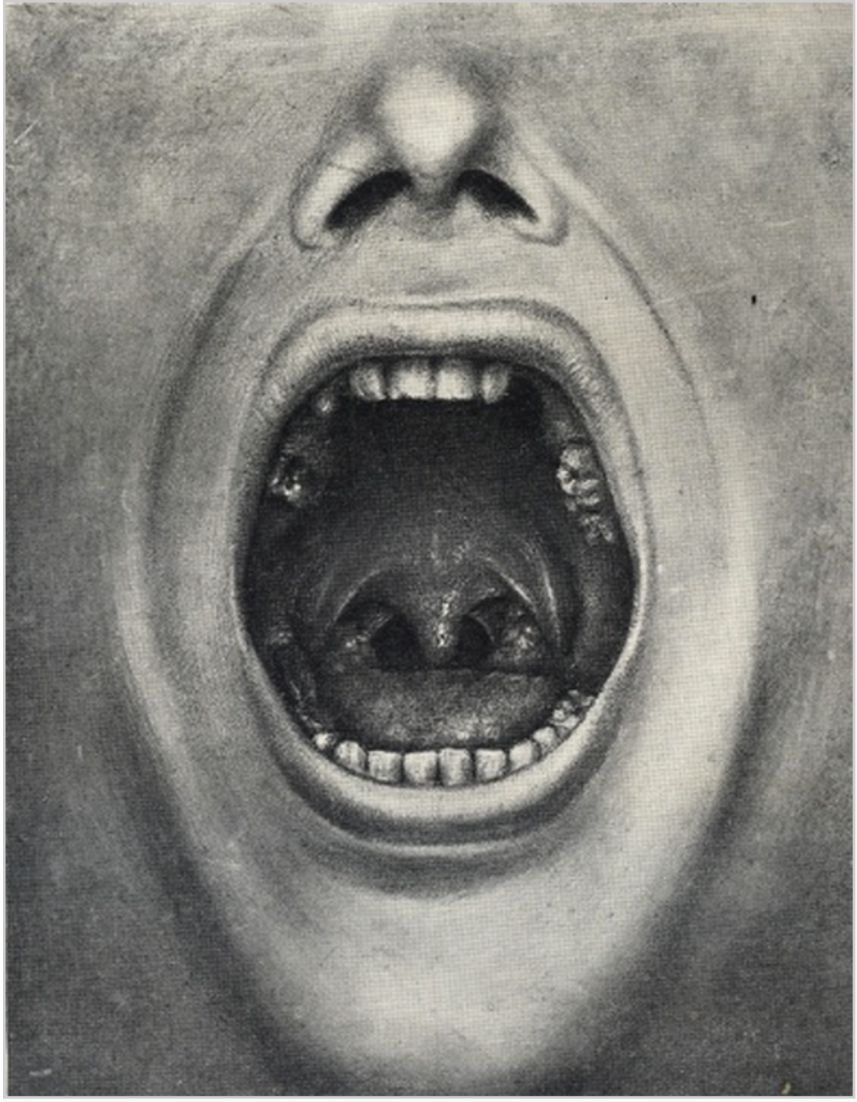


Illustration of a mouth with teeth removed from Cotton's book *The defective delinquent and insane: the relation of focal infections to their causation, treatment and prevention.*

The microbiome alters behavior

Microbiomes impact behaviors

Animal	Microbial species or consortium	Interaction with behavior	Implication
 Fruit fly (*Drosophila melanogaster*)	Gut microbiota	Diet-specific microbiota influence mating preferences	Microbes could drive speciation
 Mosquito (*Anopheles gambiae*)	Human skin microbiota	Skin microbes of humans influence attraction to mosquitoes	Differential attraction could impact disease spread
 Mouse (*Mus musculus*)	*Lactobacillus rhamnosus*	The probiotic *L. rhamnosus* decreases anxiety in mice	Suggests bacteria can alter mood

Science, 2012


I brought them together

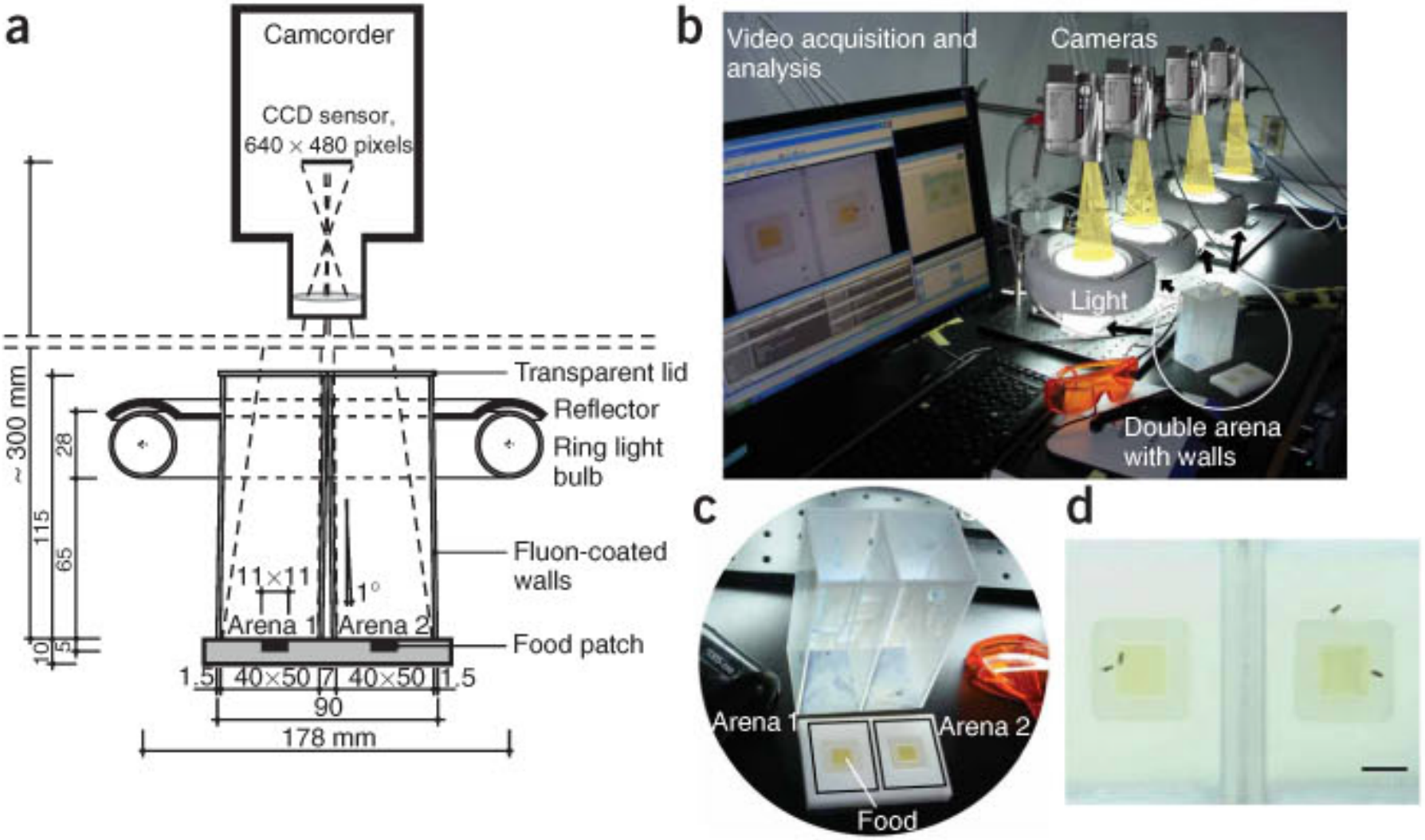

a
Camcorder
CCD sensor,
640 × 480 pixels
~ 300 mm
28
115
65
10
5
Transparent lid
Reflector
Ring light
bulb
Fluon-coated
walls
11×11
1°
Arena 1
Arena 2
Food patch
1.5
40×50
7
40×50
1.5
90
178 mm
b
Video acquisition and
analysis
Cameras
Light
Double arena
with walls
c
Arena 1
Arena 2
Food
d

Figure 3 | Detectable actions. (**a**–**d**) Single images of side and top views showing lunging (**a**), tussling (**b**), wing threat (**c**) and copulation (**d**). (**e**,**f**) Sequential images showing wing extension and circling (**e**) and chasing (**f**). Scale bars, 1 mm. Times shown are relative to the first frame in each movie.

Psychobiotics and the gut–brain axis: in the pursuit of happiness

Table 1. Psychobiotic Studies

	Findings
Preclinical	
Germ Free Studies	↓ behavioral but ↑ endocrine response to stress (62)
	Altered serotonergic development (63), BDNF, and glutamate expression (62)
	Partial reversal by *B. Infantis* (64) or fecal ingestion (62)
Maternal Separation Model of Depression	*B. Infantis* normalizes behavior (68)
	Contradictory findings for psychobiotic effects on corticosterone (68–70)
Restraint Stress and Social Stress	Altered microbiota and ↑ proinflammatory cytokines (66,67)
Acute Stressors (e.g., Elevated Plus Maze)	*L. Rhamnosus* is anxiolytic and acts via the vagus nerve to produce changes in GABAA and GABAB expression (75)
Human Studies	
Irritable Bowel Syndrome	*B. Infantis* effective and alters plasma pro-inflammatory to anti-inflammatory cytokine ratio (77)
Chronic Fatigue Syndrome	↓ anxiety in those given *L. casei* relative to placebo (80)
Healthy Volunteer Studies	*L. Helveticus* together with *B. longum* ↓ psychological distress relative to placebo and ↓ urinary free cortisol output (71)

BDNF, brain-derived neurotrophic factor; GABAA, gamma-aminobutyric acid type A; GABAB, gamma-aminobutyric acid type B.

Dinan et al, BPS 2013

FDA אישר: בנק השתלות צואה לטיפול בזיהומי מעיים

צפו: כך נראה בנק השתלות הצואה החדש באיכילוב

בנק הצואה באיכילוב

אלפי אמריקאים משתילים לעצמם צואה של אחרים כטיפול במחלות מעיים

בעידוד מחקרים המצביעים על למעלה מ-90% הצלחה, אך בהיעדר אישור מהרשויות, מתפשטת תופעת ההשתלה בשיטת "עשה זאת בעצמך"

THE NEW YORKER

NEWS CULTURE BOOKS & FICTION SCIENCE & TECH BUSINESS HUMOR MAGAZI

MEDICAL DISPATCH | DECEMBER 1, 2014 ISSUE

THE EXCREMENT EXPERIMENT

Treating disease with fecal transplants.

Early History of FMT

- 4th Century:
  - Oral human fecal suspension ("yellow soup") for severe diarrheal illnesses

- 17th Century: Veterinary medicine
  - Fecal transfer for horses with diarrhea

- 1958: FMT enema
  - Eismann, et al. 4 patients with pseudomembranous colitis
  - "Dramatic" response within 48 hours

Coprophagy

- Many vertebrates have specific behaviors that direct the assembly of the gut microbiota. For instance, the juveniles of some animals (such as horses and iguanas) consume the feces of the adults, ensuring that the guts of the young are colonized by appropriate microorganisms.

- In other animals, mothers deliberately feed feces to their offspring: koalas inoculate their young directly with a special faecal pellet (a pap) to colonize the infant gut with bacteria that can detoxify secondary compounds of eucalyptus

Gut Ecosystem Restoration via Fecal Transplantation

University of Colorado **Boulder**

knightlab

Thanks