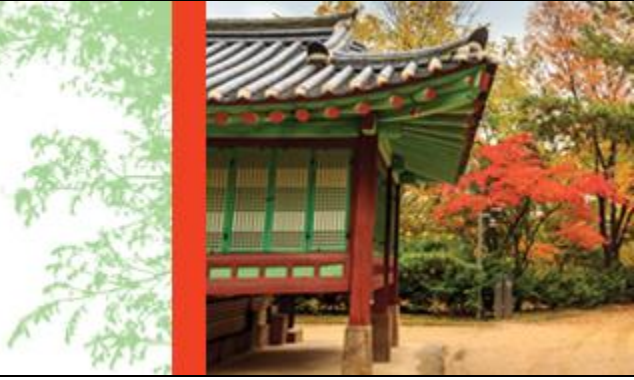
WAC 2015

XXIV World Allergy Congress
14–17 October 2015
Seoul, Korea



Pediatric Track 6: Environment and Pediatric Allergy
15th Oct 2015

Can the Human Microbiome be Targeted for Prevention/Therapy of Allergic Disease?

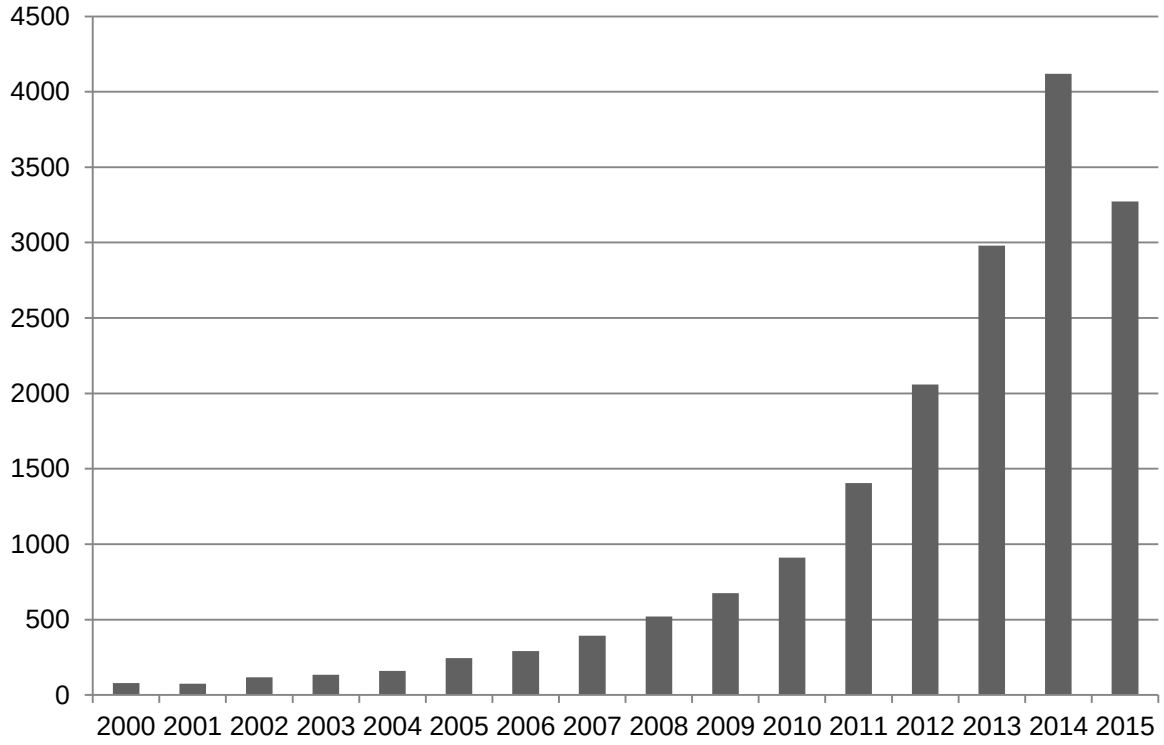
BW Lee, Dept Paediatrics
National University of Singapore

WORLD ALLERGY ORGANIZATION

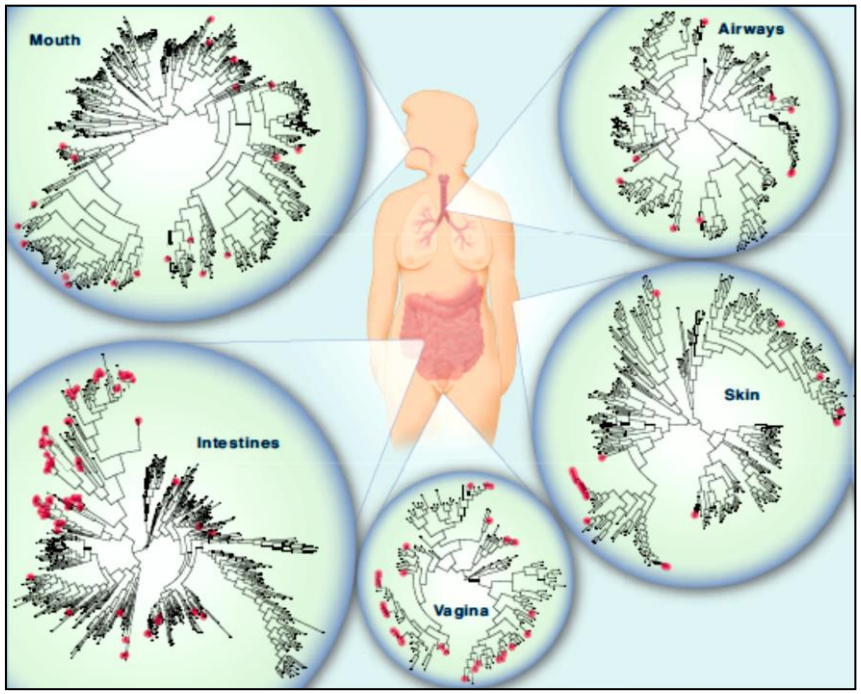
NUS National University of Singapore

Targeting the Human Microbiome for Allergies

Number Trends in Publications '*Human Microbiome*'



‘Cloak’ of Microbiota



MICROBIOME

Rethinking heritability of the microbiome

How should microbiome heritability be measured and interpreted?

By Edward J. van Opstal and Seth R. Bordenstein[1,2]

For almost a century, heritability has been routinely used to predict genetic influences on phenotypes such as intelligence, schizophrenia, alcoholism, and depression (*1*). However, there has been relatively little work on heritability of the human microbiome—defined here as the number and types of microorganisms and viruses present in or on the human body. This question has become increasingly more interesting as research reveals that humans and their microbial communities interact in complex and often beneficial networks. An underlying question is the degree to which environment versus human genotype influences the microbiome. A central goal of quantifying microbiome heritability is to discern genetic from environmental factors that structure the microbiome and to potentially identify functionally important microbial community members.

Twin-based studies provide one method for quantifying heritability (h^2) of microbial taxa. In such analyses, heritability is measured by comparing variation in microbial taxon abundances that is attributable to human genetics. This approach simplifies microbial abundances to continuously varying phenotypes, comparable to human height, weight, and eye color. In 2009 and 2012, studies of twins conducted in this manner concluded that there are no heritable gut microbial members (*2*), or low overall gut microbiome heritability (*3*), respectively. But in 2014, the largest twin cohort to date examined members of the gut microbiome and found that the bacterial family *Christensenellaceae* has the highest heritability ($h^2 = 0.39$), and associates closely with other heritable gut bacterial families (*4*). The groundbreaking discovery of a high heritability for members of the human microbiome raises specific questions about understanding the genetics of human-microbe symbioses: How should we interpret what heritability means for microbiome studies? Can microbiome heritability be viewed in a more comprehensive manner? Is h^2 the only term to measure and denote microbiome heritability?

Under a heritability analysis with standard statistical approaches (such as the Additive Genetics, Common Environment, Unique Environment (ACE) model), the abundance of each human-associated microbe is presented as a continuously varying, quantitative “trait” that is affected by host genetics—in other words, the host genome significantly dictates the abundance of a microbe. Although a suitable starting point, this host-centric interpretation of microbiome heritability tends to consider the human-microbiome interaction as unidirectional, in which the host regulates colonization. This view, however, is only half of the story. The microbiome is a collection of different organisms with genotypes that interact with each other as well as with the host to achieve colonization. A more comprehensive view is advisable in which both the host and the microbiome play a role in heritability. This view, based on community genetics principles, requires that studies adopt a conceptual foundation of interspecies (genotype-by-genotype) interactions that drive the assembly of the host and microbial consortia. It also necessitates the use of a measure—“community heritability” (H^2_c)—that reflects genetic variation underlying interactions with the entire (or portions of the) community—in this case, the microbiome together with its human host.

Human-associated microbes contain distinct genetic, transcriptomic, metabolic, and proteomic features that can reciprocally influence their own colonization of specific human genotypes. These features span competitive nutrient acquisition, mechanisms to evade the host immune system, and niche construction, among others. Thus, heritable taxa such as *Christensenellaceae* may be “recruited” by the human genome to perform beneficial functions in the microbial community, but they also may encode traits that enable them to circumvent host defenses and colonize susceptible genotypes. For example, commensal bacteria tolerate or evade human immune responses by modifying surface

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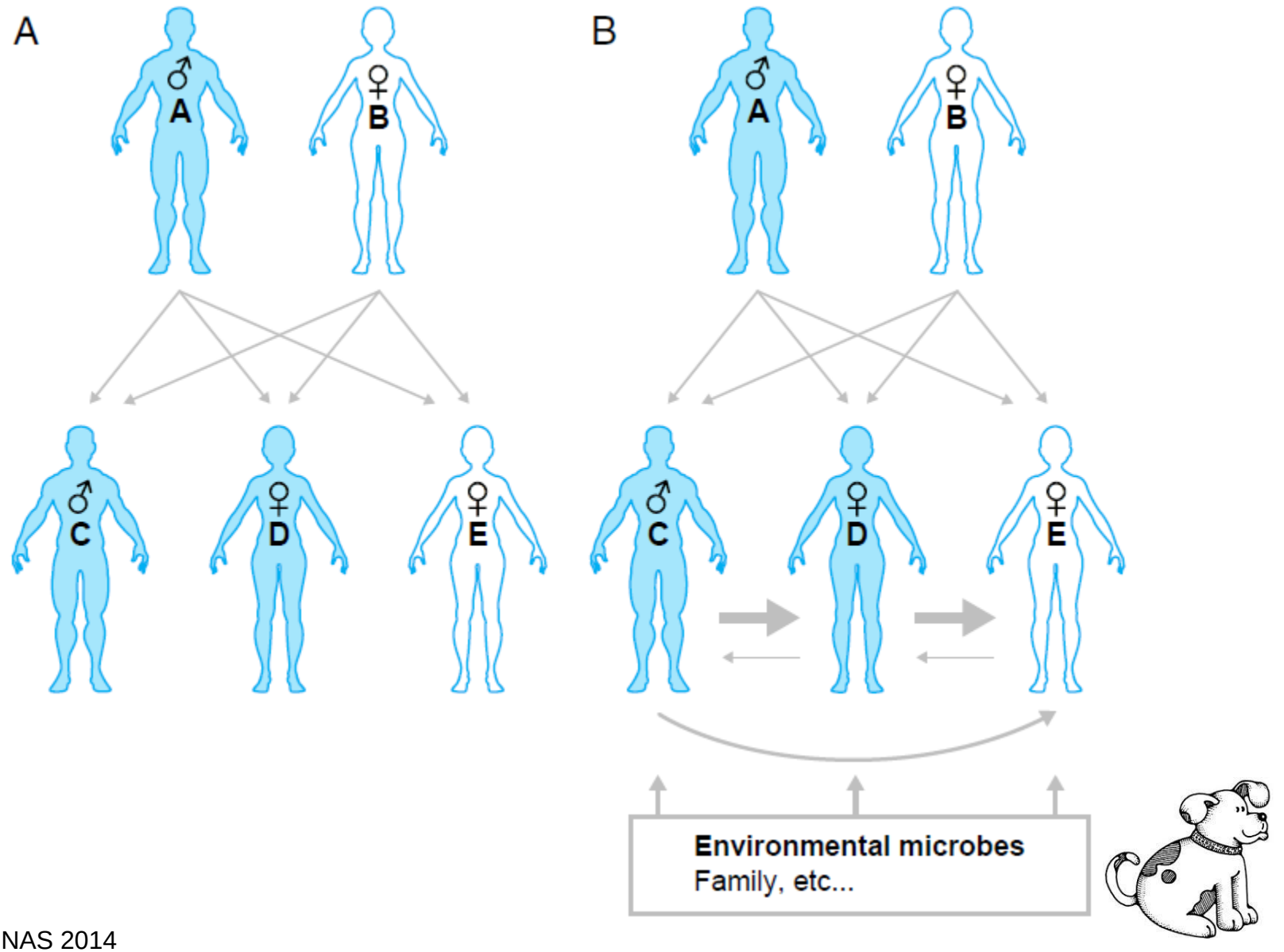
Lee YK, Data are from the NIH-funded Human Microbiome Project. Science 2007

Van Opstal and Bordenstein. Science 2015

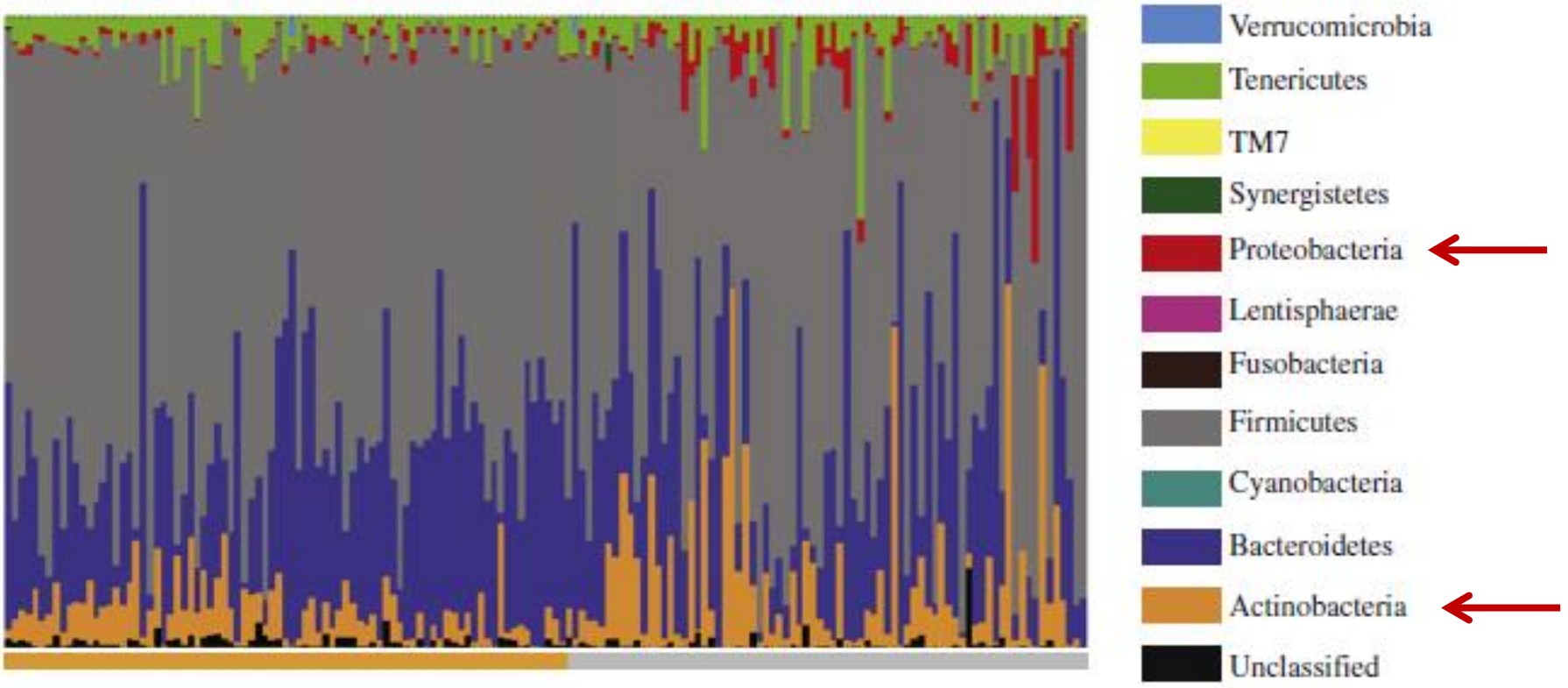
Human Genetic Inheritance

Microbial Inheritance



Faith JJ et al PNAS 2014

Abundances of Phyla of Bacteria Genera 1st and 3rd Trimester of Pregnancy



1st trimester

3rd trimester

Dramatic remodelling over the course of pregnancy

Koren O et al. Cell 2012

Cell Host & Microbe
Resource

Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life

Fredrik Bäckhed,[1,2,*] Josefine Roswall,[3,4] Yangqing Peng,[5] Qiang Feng,[5,6] Huijue Jia,[5] Petia Kovatcheva-Datchary,[1] Yin Li,[5] Yan Xia,[5] Hailiang Xie,[5] Huanzi Zhong,[5] Muhammad Tanweer Khan,[1] Jianfeng Zhang,[5] Junhua Li,[5] Liang Xiao,[5] Jumana Al-Aama,[5,7] Dongya Zhang,[5] Ying Shiuan Lee,[1] Dorota Kotowska,[6] Camilla Colding,[6] Valentina Tremaroli,[1] Ye Yin,[5] Stefan Bergman,[4,8] Xun Xu,[5] Lise Madsen,[6,9] Karsten Kristiansen,[5,6] Jovanna Dahlgren,[4,12,*] and Wang Jun[5,6,7,10,11,12,*]

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http://dx.doi.org/10.1016/j.chom.2015.04.004

SUMMARY

The gut microbiota is central to human health, but its establishment in early life has not been quantitatively and functionally examined. Applying metagenomic analysis on fecal samples from a large cohort of Swedish infants and their mothers, we characterized the gut microbiome during the first year of life and assessed the impact of mode of delivery and feeding on its establishment. In contrast to vaginally delivered infants, the gut microbiota of infants delivered by C-section showed significantly less resemblance to their mothers. Nutrition had a major impact on early microbiota composition and function, with cessation of breast-feeding, rather than introduction of solid food, being required for maturation into an adult-like microbiota. Microbiota composition and ecological network had distinctive features at each sampled stage, in accordance with functional maturation of the microbiome. Our findings establish a framework for understanding the interplay between the gut microbiome and the human body in early life.

INTRODUCTION

The human gut microbiota is an important environmental factor for human health (Clemente et al., 2012), having evolutionarily conserved roles in the metabolism, immunity, development, and behavior of the host (Cabreiro and Gems, 2013; Erkosar et al., 2013). Although considerable efforts have focused on cataloguing the adult human gut microbiome and its relationship to complex diseases (Human Microbiome Project Consortium, 2012; Karlsson et al., 2013; Li et al., 2014; Qin et al., 2010, 2012), studies on the infant gut microbiota have been restricted to culture-based enumeration, 16S-based profiling, and/or small sample sizes (Adlerberth et al., 2006; Brook et al., 1979; Dominguez-Bello et al., 2010; Eggesbø et al., 2011; Koenig et al., 2011; Palmer et al., 2007; Subramanian et al., 2014; Yatsunenko et al., 2012). Thus, factors that shape the gut microbiota in early infancy have not been satisfactorily examined.

From an ecological point of view, colonization of the infant's gut represents the de novo assembly of a microbial community (Costello et al., 2012) and is influenced by dietary and medical factors (Eggesbø et al., 2011; Koenig et al., 2011; La Rosa et al., 2014). However, it is not clear how these factors contribute to the overall composition and function of the infants' gut microbiome, and how different microbes cooperate or compete with one another as the gut environment changes.

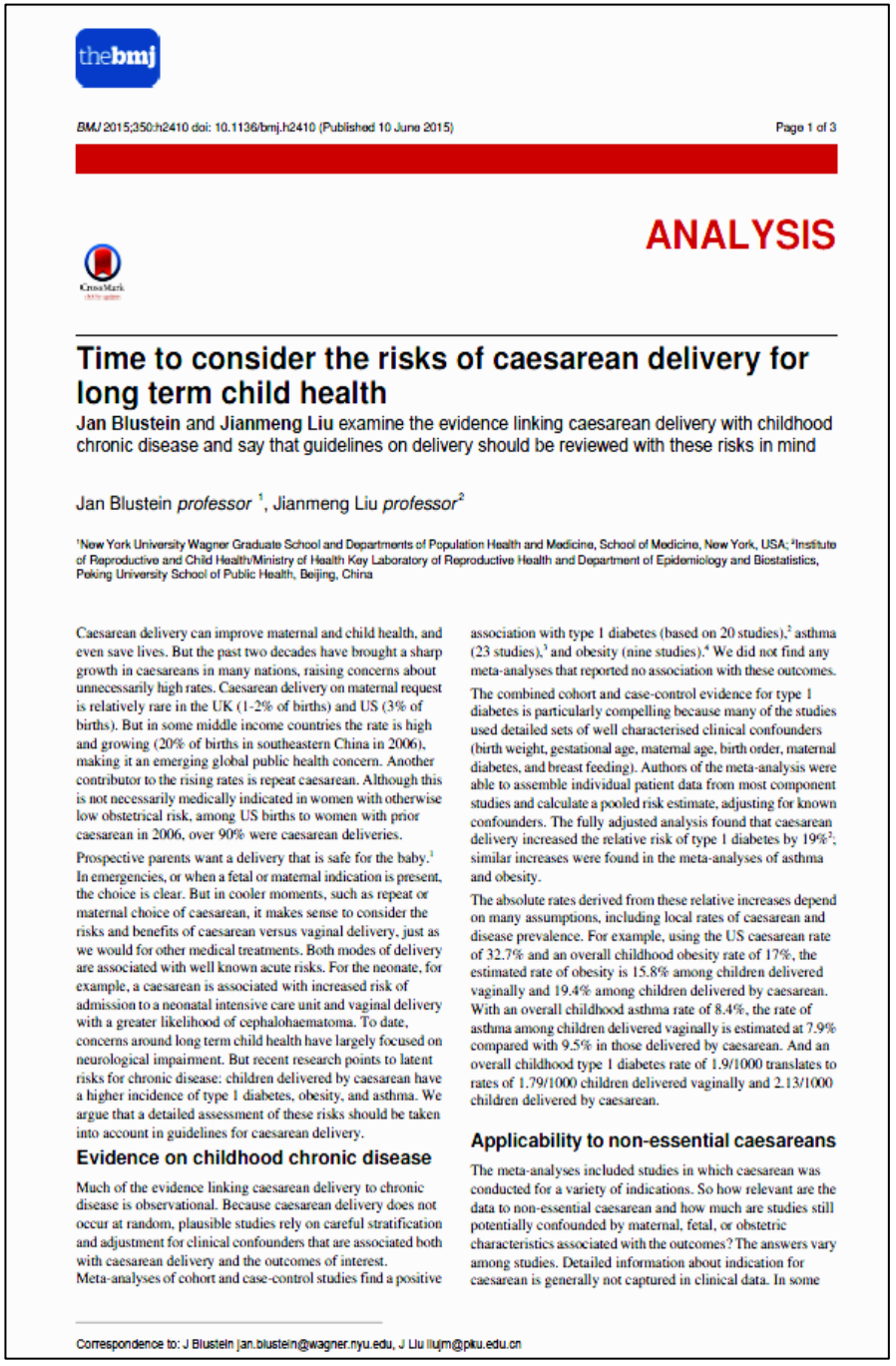
Here we performed metagenomic shotgun sequencing on fecal samples from 98 full-term Swedish infants and their mothers, assembled gut microbial genomes, and demonstrated gut microbiome signatures characteristic to each chronological and functional stage during the first year of life. In addition, we produced a gene catalog of the developing microbiome, which may constitute an important research tool.

RESULTS

Genomes Assembled from the Infants' Gut Microbiome

To characterize the infant gut microbiome, we shotgun-sequenced stool samples from 98 mothers at delivery after a

- Most of the early colonizers are derived from the mother
- Vertical mother-infant transmission was frequent for important intestinal microbes such as Bacteroides and Bifidobacterium



thebmj

BMJ 2015;350:h2410 doi: 10.1136/bmj.h2410 (Published 10 June 2015)

ANALYSIS

Time to consider the risks of caesarean delivery for long term child health

Jan Blustein and **Jianmeng Liu** examine the evidence linking caesarean delivery with childhood chronic disease and say that guidelines on delivery should be reviewed with these risks in mind

Jan Blustein *professor* [1], Jianmeng Liu *professor*[2]

[1]New York University Wagner Graduate School and Departments of Population Health and Medicine, School of Medicine, New York, USA; [2]Institute of Reproductive and Child Health/Ministry of Health Key Laboratory of Reproductive Health and Department of Epidemiology and Biostatistics, Peking University School of Public Health, Beijing, China

Caesarean delivery can improve maternal and child health, and even save lives. But the past two decades have brought a sharp growth in caesareans in many nations, raising concerns about unnecessarily high rates. Caesarean delivery on maternal request is relatively rare in the UK (1-2% of births) and US (3% of births). But in some middle income countries the rate is high and growing (20% of births in southeastern China in 2006), making it an emerging global public health concern. Another contributor to the rising rates is repeat caesarean. Although this is not necessarily medically indicated in women with otherwise low obstetrical risk, among US births to women with prior caesarean in 2006, over 90% were caesarean deliveries.

Prospective parents want a delivery that is safe for the baby.[1] In emergencies, or when a fetal or maternal indication is present, the choice is clear. But in cooler moments, such as repeat or maternal choice of caesarean, it makes sense to consider the risks and benefits of caesarean versus vaginal delivery, just as we would for other medical treatments. Both modes of delivery are associated with well known acute risks. For the neonate, for example, a caesarean is associated with increased risk of admission to a neonatal intensive care unit and vaginal delivery with a greater likelihood of cephalohaematoma. To date, concerns around long term child health have largely focused on neurological impairment. But recent research points to latent risks for chronic disease: children delivered by caesarean have a higher incidence of type 1 diabetes, obesity, and asthma. We argue that a detailed assessment of these risks should be taken into account in guidelines for caesarean delivery.

Evidence on childhood chronic disease

Much of the evidence linking caesarean delivery to chronic disease is observational. Because caesarean delivery does not occur at random, plausible studies rely on careful stratification and adjustment for clinical confounders that are associated both with caesarean delivery and the outcomes of interest. Meta-analyses of cohort and case-control studies find a positive association with type 1 diabetes (based on 20 studies),[2] asthma (23 studies),[3] and obesity (nine studies).[4] We did not find any meta-analyses that reported no association with these outcomes.

The combined cohort and case-control evidence for type 1 diabetes is particularly compelling because many of the studies used detailed sets of well characterised clinical confounders (birth weight, gestational age, maternal age, birth order, maternal diabetes, and breast feeding). Authors of the meta-analysis were able to assemble individual patient data from most component studies and calculate a pooled risk estimate, adjusting for known confounders. The fully adjusted analysis found that caesarean delivery increased the relative risk of type 1 diabetes by 19%[2]; similar increases were found in the meta-analyses of asthma and obesity.

The absolute rates derived from these relative increases depend on many assumptions, including local rates of caesarean and disease prevalence. For example, using the US caesarean rate of 32.7% and an overall childhood obesity rate of 17%, the estimated rate of obesity is 15.8% among children delivered vaginally and 19.4% among children delivered by caesarean. With an overall childhood asthma rate of 8.4%, the rate of asthma among children delivered vaginally is estimated at 7.9% compared with 9.5% in those delivered by caesarean. And an overall childhood type 1 diabetes rate of 1.9/1000 translates to rates of 1.79/1000 children delivered vaginally and 2.13/1000 children delivered by caesarean.

Applicability to non-essential caesareans

The meta-analyses included studies in which caesarean was conducted for a variety of indications. So how relevant are the data to non-essential caesarean and how much are studies still potentially confounded by maternal, fetal, or obstetric characteristics associated with the outcomes? The answers vary among studies. Detailed information about indication for caesarean is generally not captured in clinical data. In some

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Meta-analyses of cohort and case-control studies find a positive association with:

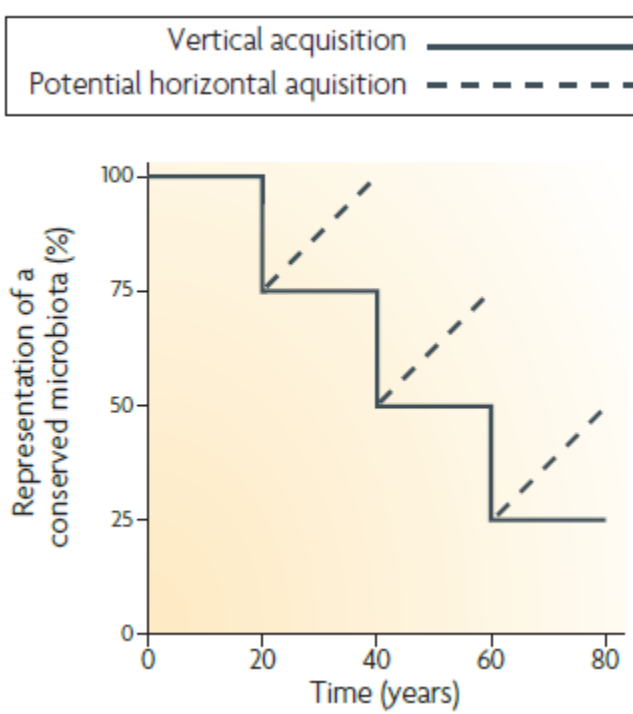
- type 1 diabetes (based on 20 studies),
- asthma (23 studies),
- obesity (nine studies).

We did not find any meta-analyses that reported no association with these outcomes.

ESSAY

What are the consequences of the disappearing human microbiota?

Martin J. Blaser and Stanley Falkow



'heirloom' microbes

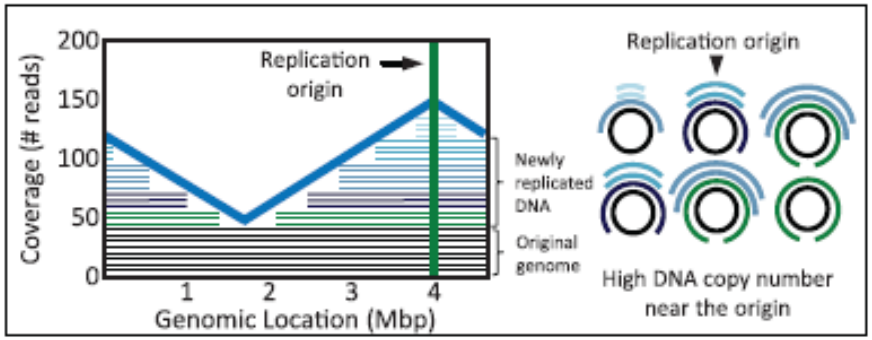
Nature Reviews Microbiology 2009

MICROBIOME

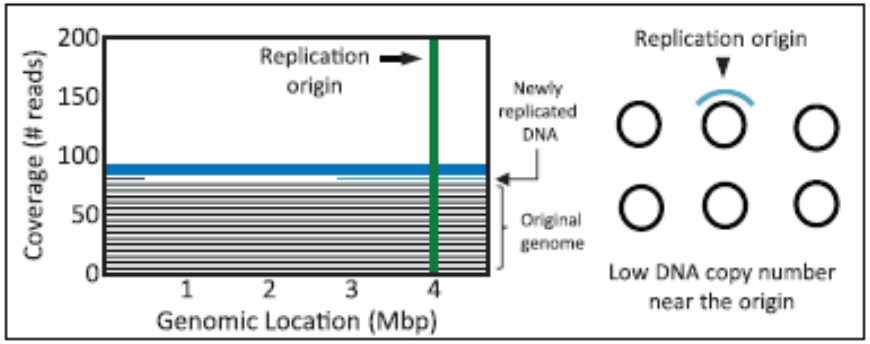
Growth dynamics of gut microbiota in health and disease inferred from single metagenomic samples

Peak:Trough ratio

A Growing bacterial population



Non-dividing bacterial population



New type of metagenomic analysis:

Provides an accurate quantitiative estimate of the growth dynamics of the microbiota

Korem et al, Science 2015

Growth dynamics vs Relative abundance

Tissue/organ "A"

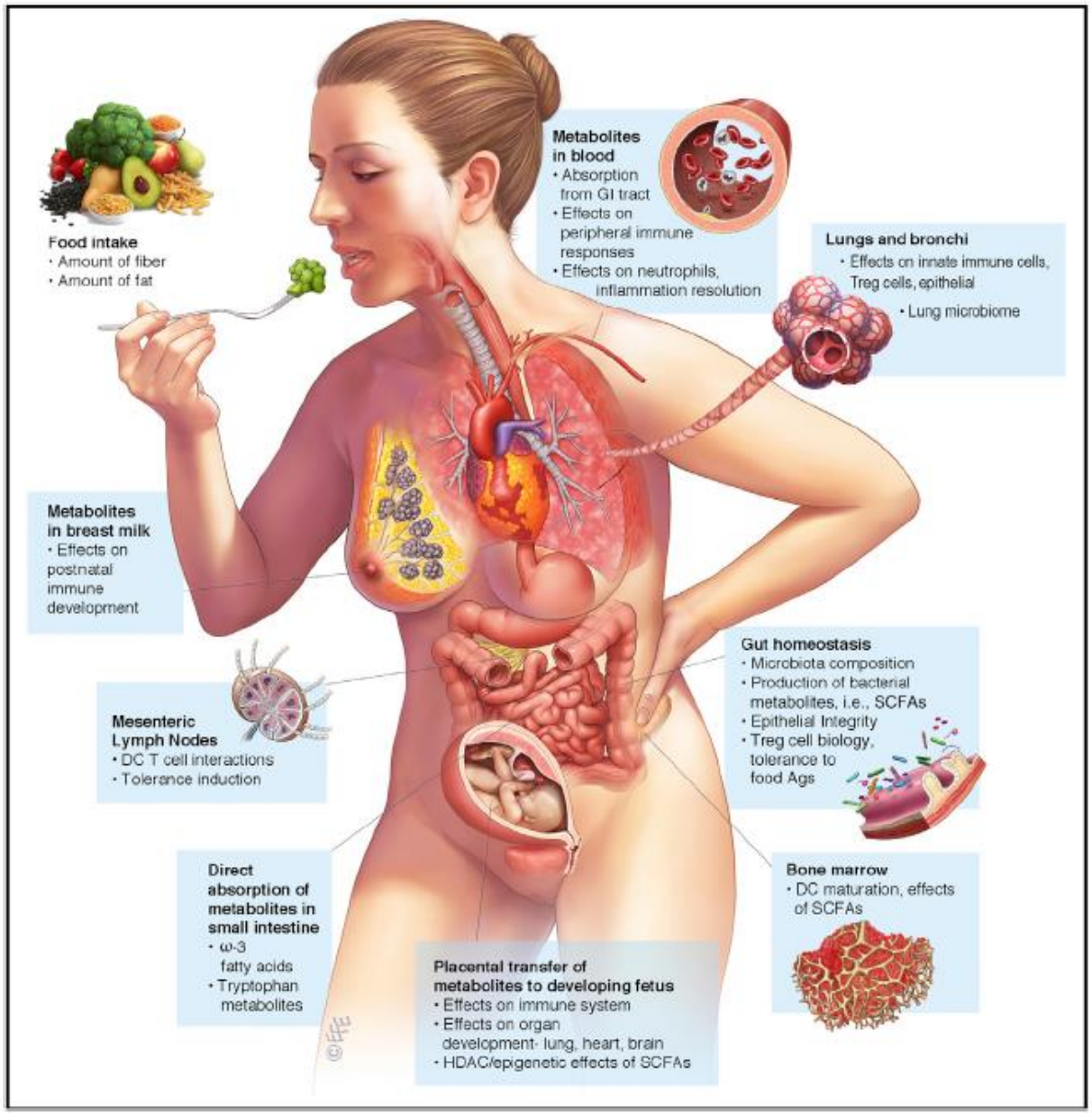
In a given tissue in an individual, an abundant microbial species may not necessarily be one with high metabolic activity (PTR value).

BACTERIA	ABUNDANCE	GROWTH RATE (PTR VALUE)	METABOLIC ACTIVITY	DISEASE CORRELATION
Species "1"	Highest	1.2	Lowest	No
Species "2"	Lowest	2.0	Highest	Yes

Segre. Science 2015

Diet, Metabolites and ‘Western Lifestyle’ Inflammatory Diseases

Maintaining the Microbiome?



Thorburn A et al Immunity 2014

Fiocchi et al. World Allergy Organization Journal (2015) 8:4
DOI 10.1186/s40413-015-0055-2

WAO journal
WORLD ALLERGY ORGANIZATION

POSITION ARTICLE AND GUIDELINES Open Access

World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics

Alessandro Fiocchi[1†], Ruby Pawankar[2†], Carlos Cuello-Garcia[3,4], Kangmo Ahn[5], Suleiman Al-Hammadi[6], Arnav Agarwal[3,7], Kirsten Beyer[8], Wesley Burks[9], Giorgio W Canonica[10], Motohiro Ebisawa[11], Shreyas Gandhi[3,7], Rose Kamenwa[12], Bee Wah Lee[13], Haiqi Li[14], Susan Prescott[15], John J Riva[16], Lanny Rosenwasser[17], Hugh Sampson[18], Michael Spigler[19], Luigi Terracciano[20], Andrea Vereda-Ortiz[22], Susan Waserman[21], Juan José Yepes-Nuñez[3], Jan L Brożek[3,21*] and Holger J Schünemann[3,21]

Abstract

Background: Prevalence of allergic diseases in infants, whose parents and siblings do not have allergy, is approximately 10% and reaches 20–30% in those with an allergic first-degree relative. Intestinal microbiota may modulate immunologic and inflammatory systemic responses and, thus, influence development of sensitization and allergy
propos

Probiotics of multiple strains analyzed

Object
recommendations about the use of probiotics in the prevention of allergy.

Methods: We identified the most relevant clinical questions and performed a systematic review of randomized controlled trials of probiotics for the prevention of allergy. We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop recommendations. We searched for and reviewed the evidence about health effects, patient values and preferences, and resource use (up to November 2014). We followed the GRADE evidence-to-decision framework to develop recommendations.

Results: Currently available evidence does not indicate that probiotic supplementation reduces the risk of developing allergy in children. However, considering all critical outcomes in this context, the WAO guideline panel determined that there is a likely net benefit from using probiotics resulting primarily from prevention of eczema. The WAO guideline panel suggests: a) using probiotics in pregnant women at high risk for having an allergic child; b) using probiotics in women who breastfeed infants at high risk of developing allergy; and c) using probiotics in infants at high risk of developing allergy. All recommendations are conditional and supported by very low quality evidence.

Conclusions: WAO recommendations about probiotic supplementation for prevention of allergy are intended to support parents, clinicians and other health care professionals in their decisions whether to use probiotics in pregnancy and during breastfeeding, and whether to give them to infants.

Keywords: Allergy, Prevention, Probiotics, Practice guidelines, GRADE

Probiotic supplementation **DOES NOT** reduce the risk of developing allergy in children

There is a likely net benefit from using probiotics resulting primarily from **prevention of eczema**

For at risk infants
a) in **pregnant women**;
b) in **women who breastfeed** infants
c) In **infants** at high risk of developing allergy.

All recommendations are **conditional** and supported by very **low quality evidence**.

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI
REVIEW ARTICLE

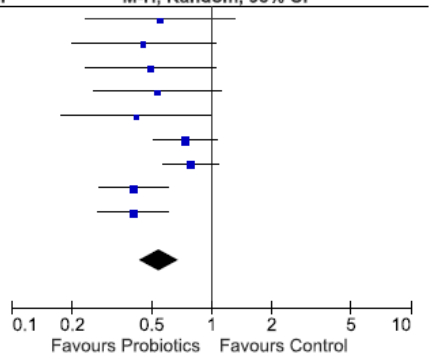
Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis

G. Zuccotti[1,*], F. Meneghin[2,*], A. Aceti[3,*], G. Barone[4,*], M. L. Callegari[5,*], A. Di Mauro[6,*], M. P. Fantini[7,*], D. Gori[7,*], F. Indrio[6,*,†], L. Maggio[4,*,†], L. Morelli[5,*] & L. Corvaglia[3,*,†,‡] on behalf of the Italian Society of Neonatology

A

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Huure 2008	7	72	12	68	5.5%	0.55 [0.23, 1.32]
Kim 2010	6	33	14	35	6.0%	0.45 [0.20, 1.04]
Kim 2010	7	35	17	42	6.9%	0.49 [0.23, 1.05]
Kim 2010	8	43	16	46	7.2%	0.53 [0.26, 1.12]
Niers 2009	6	50	15	52	5.6%	0.42 [0.18, 0.99]
Niers 2009	23	50	30	48	17.1%	0.74 [0.51, 1.07]
Niers 2009	27	50	33	48	19.6%	0.79 [0.57, 1.08]
Rautava 2012	21	73	44	62	16.2%	0.41 [0.27, 0.60]
Rautava 2012	20	70	44	62	15.8%	0.40 [0.27, 0.60]
Total (95% CI)		**476**		**463**	**100.0%**	**0.54 [0.43, 0.68]**
Total events	125		225			

Heterogeneity: Tau² = 0.04; Chi² = 12.86, df = 8 (P = 0.12); I² = 38%
Test for overall effect: Z = 5.34 (P < 0.00001)

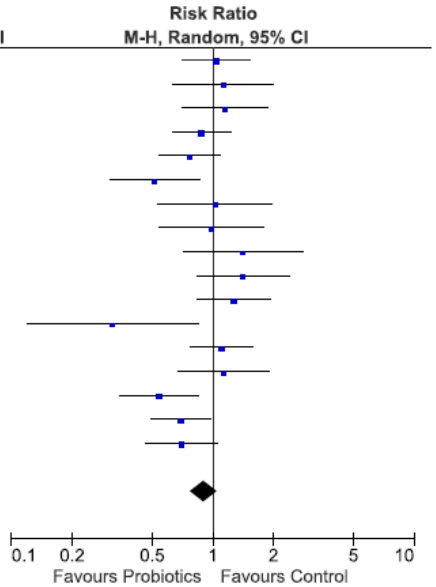


Probiotic mixture

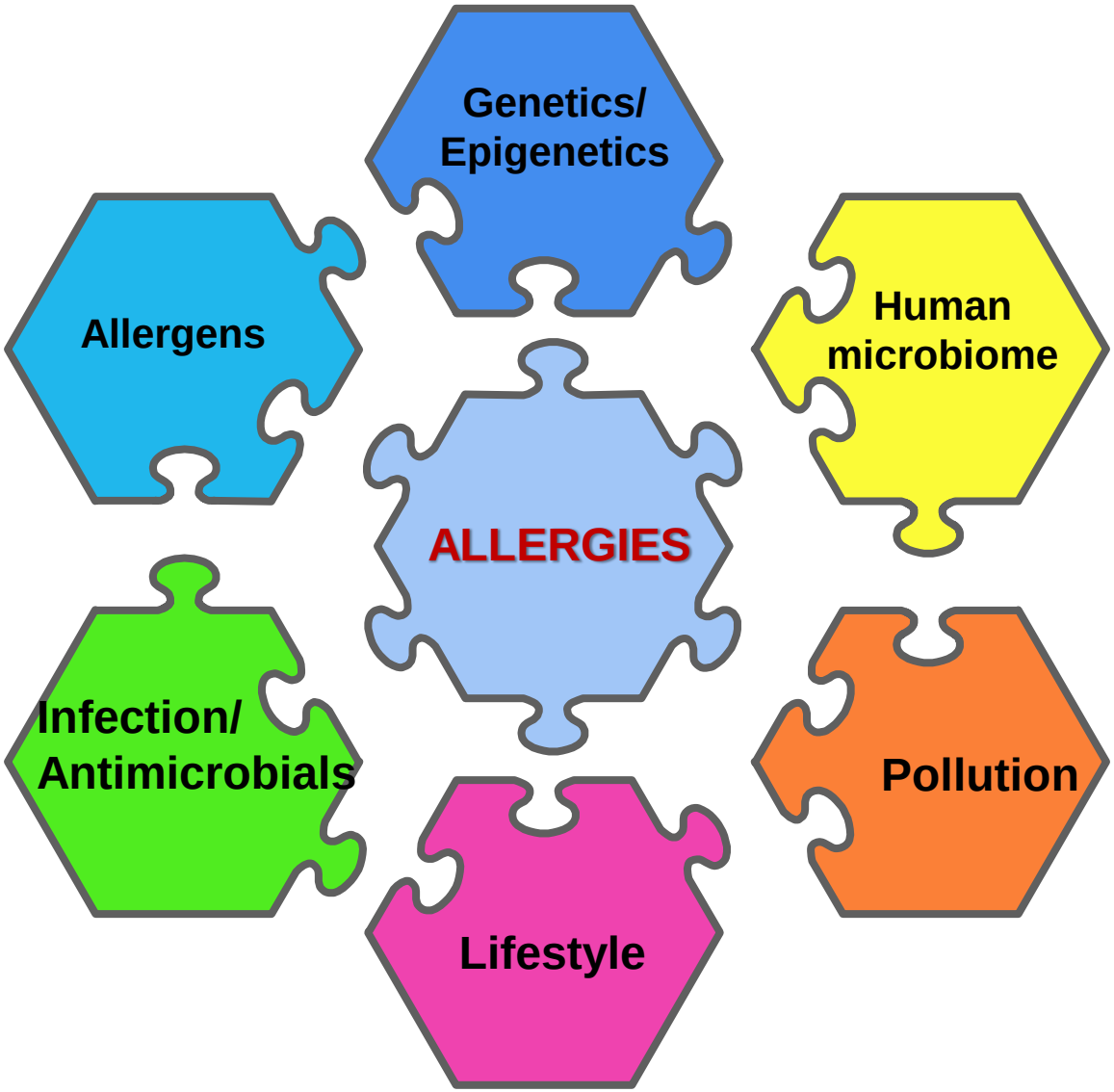
B

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abrahamsson 2007	34	95	32	93	7.3%	1.04 [0.70, 1.53]
Abrahamsson 2013	20	94	17	90	4.7%	1.13 [0.63, 2.01]
Bottcher 2008	21	51	19	53	5.8%	1.15 [0.71, 1.87]
Boyle 2011	42	122	47	120	8.3%	0.88 [0.63, 1.22]
Boyle 2011	35	108	43	102	7.9%	0.77 [0.54, 1.10]
Kalliomaki 2001	15	64	31	68	5.4%	0.51 [0.31, 0.86]
Kopp 2008	14	50	12	44	3.9%	1.03 [0.53, 1.98]
Ou 2012	16	65	16	64	4.4%	0.98 [0.54, 1.80]
Ou 2012	16	64	11	62	3.7%	1.41 [0.71, 2.79]
Ou 2012	24	72	17	72	5.2%	1.41 [0.83, 2.39]
Prescott 2008	31	74	25	76	6.8%	1.27 [0.84, 1.94]
Rautava 2002	4	27	14	30	2.1%	0.32 [0.12, 0.85]
Taylor 2007	38	88	34	87	7.9%	1.10 [0.77, 1.58]
Taylor 2007	23	89	20	88	5.3%	1.14 [0.67, 1.92]
Wickens 2008	23	157	43	159	6.2%	0.54 [0.34, 0.85]
Wickens 2012	37	136	56	143	8.1%	0.69 [0.49, 0.98]
Wickens 2013	26	112	43	129	6.8%	0.70 [0.46, 1.06]
Total (95% CI)		**1468**		**1480**	**100.0%**	**0.90 [0.77, 1.05]**
Total events	419		480			

Heterogeneity: Tau² = 0.05; Chi² = 29.60, df = 16 (P = 0.02); I² = 46%
Test for overall effect: Z = 1.34 (P = 0.18)



Single Probiotic


Genetics/
Epigenetics
Allergens
Human
microbiome
ALLERGIES
Infection/
Antimicrobials
Pollution
Lifestyle