8

A microbiome record for life

8.1 Proactive sampling of the microbiome at important time periods

From birth to old age, the microbiome in various body sites contains important information that could predict disease risks in the future (Fig. 8.1). Colonization of microbes in early life leads to trafficking of microbial antigens to the thymus by antigen-presenting cells in the intestine, skin, and probably other mucosal sites, and the T-cells induced can then protect the host against related pathogens, and go awry at times [1–3].

8.1.1 A microbiome record from birth

Hospital records are really impressive in some countries already. If an infant is born preterm or full term, will there be microbiome samples for the feces, the oropharynx, and the skin? Were there antibiotics, oxytocin (to stimulate labor) [4], or other medication given to the mother before birth? Should the infants' microbiome be followed afterward (Table 8.1)? In extremely preterm infants, the difference between delivery modes was no longer a big deal. Infants born through vaginal delivery were more colonized by *Bacteroides* spp. and *Bifidobacterium* spp. from the mother [19,28,29], but what about the father and the grandparents, and the natural playgrounds that are also contributing some good bacteria [30]?

Vaginal microbes from the mother, including bacterial vaginosis (BV)-related *Gardnerella vaginalis* (now formally in the *Bifidobacterium* genus, as *Bifidobacterium vaginalis* [31]) and *Atopobium vaginae* (renamed as *Fannyhessea vaginae*) could be detected in the infant's gut in the first week after delivery [32]. Emerging from the amniotic fluid into a dry environment, does the ambient temperature influence the maturation of the newborn's respiratory microbiome, skin microbiome, and gut microbiome? Are there pets in the house [33,34]? How many hours did the baby sleep, before and after a stable rhythm has been established [35] (Table 8.1)?

Newborns have a continuous airway optimized for sucking and breathing, with the larynx high up in the mouth like that in chimpanzees.

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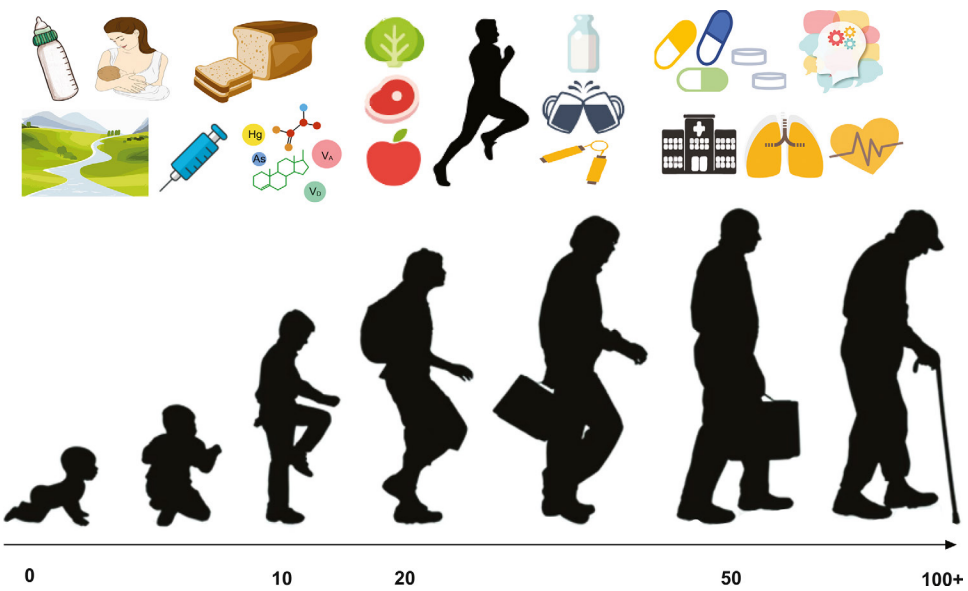


Fig. 8.1 Monitoring the microbiome in different age groups. Credit: Huijue Jia, Xin Tong, Fei Li.

The larynx gradually moves down to an adult-like position (Chapter 3, Fig. 3.5), swallowing more solid food instead of breastmilk (swallowing interrupts breathing), and beginning to speak [36,37]. We do not know yet, how this series of remodeling affect the oral, respiratory, and gastrointestinal microbiome. As the infant begins to produce its own antibodies, instead of depending on the mother's antibodies through the placenta and in the milk (and sometimes from the mouth) [38,39], how do the antibodies and the microbes coevolve into an appropriate affinity (weak binding help retain the commensals, Chapter 2) that could sufficiently protect the infant against pathogens? The infant liver shifts from the hematopoietic function in embryos to the (circadian) metabolic and immune functions more similar to adults [40,41]. Besides the human genome-encoded amylase that gives the sweet taste when we chew on starchy food such as rice, do the oral and gastrointestinal microbiome influence taste and food preference? Pectin-degrading *Bacteroides thetaiotaomicron*, for example, might contribute to a preference for oranges and peas [42]?

The baseline for a healthy infant microbiome may need to be established for each ethnic group [43,44], depending on the local habits. As mentioned in Chapter 2, human genetics contribute to the microbiome composition. The alleles associated with more fecal *Prevotella* spp. instead of *Bacteroides* spp. are more prevalent in African and East Asian populations compared to European populations [45,46]. *Prevotella* spp. were more prevalent in the airway of children without

Table 8.1 A metagenomic record from birth.

Age	Event	Oral	Fecal	Airway	Skin	Conditions to watch for	Reference
0	Exposure to antibiotics at delivery or during infancy	?	Y		?	Childhood obesity; impaired antibody induction after vaccination, but enhanced T cell responses	[5–7]
0	Exposure to oxytocin at delivery	?	Y		?	Supplements the endogenous oxytocin to reduce anxiety and autism risk, or reduce the risk of over-feeding and obesity?	[8–10]
1–2 months	Preterm birth, C-section, antibiotics, lack of elder siblings, lack of dog, etc.		Y	Y	?	Risk of asthma in the following years	[11–14]
Any age	Vaccination	?	Y			Prediction of vaccination efficacy depending on the microbiome, and use of additional ways if possible	[14]
2–6 months	Hospitalized for bronchiolitis with more nasal *Moraxella* and *Streptococcus*	Y	?	Y		Recurrent wheezing by 3 years old	[15]
3–6 months	Milk allergy	?	Y		?	Prediction of resolved allergy in childhood	[16–18]
0–12 months	Lack of breastfeeding	Y	Y	?		Lack of *Bifidobacterium* from the mother, and consequently difference in immune development	[19–22]
4–11 months	Introduction of solid food	Y	Y		?	Early exposure to solid food before cessation of breasting-feeding, to prevent food allergy	[23,24]
4–12 months	More regular sleep and feeding	?	Y			Establishment of a diurnal gut microbiome rhythm?	[19], Chapter 2, Box 2.5
Childhood to adolescence	Rural environment	Y	Y	Y	Y	Difference in microbiome composition with potential long-lasting consequences	[25–27]

The associations are not necessarily causal (Chapter 6) and would need to be further elucidated. This is not meant to be an exhaustive list, but it serves to illustrate the range of conditions and samples to consider. Y, samples strongly recommended; ?, evidence needed.
Credit: Huijue Jia.

asthma and in healthy adults [47]. *Bifidobacterium* spp., for example, are not so prevalent in the gut microbiome of infants in some Asian, African, or Latin American regions [48,49]; multiple alleles other than the lactase *LCT* also associate with *Bifidobacterium* [45,46]. Proteobacteria such as *Escherichia coli* and *Klebsiella* sp., for example, encodes enzymes that could metabolize sulphoquinovose (6-deoxy-6-sulphoglucose), which takes up at least 10 mg/g of plant leaf dry weight [50,51]. The local grain, soil, and water are important sources of micronutrients and heavy metals that could influence the microbiome [46,52–54] (Fig. 8.1). Water in developed countries such as the United States are not necessarily all at the healthy standards [55].

8.1.2 Immediate and historical events for a wholesome microbiome

For the mother, many kinds of precious samples could also be collected (Table 8.2). Factors that shape the vaginal microbiome span from puberty to postmenopausal years. Vaccination would not be sufficient to prevent all infections and tumors. Microbiome samples collected during the first pregnancy could also take better care of things the next time. But the mother's microbiome is going to be different for the subsequent children, with less *Lactobacillus crispatus* in the vagina [54], more *Prevotella copri* in the gut (and possibly the amniotic fluid [69]). *Prevotella copri* in the pregnant mother's fecal microbiome associated with a lower risk of food allergy for the kids [70]. A lower BMI (body mass index) before pregnancy relates to more *Bifidobacterium* in breast milk [71]. Fecal microbiome markers for gestational diabetes are partly similar to those for T2D [69,72], consistent with a family history of T2D and heightened risk for subsequent T2D in women who had gestational diabetes during pregnancy [73,74]. Women with menstrual pains (dysmenorrhea) showed more Pseudomonadales, *Acinetobacter,* and *Moraxellaceae* in the cervicovaginal microbiome, while lower in plasma level of histidine; The relative abundances of *Acinetobacter* and *Moraxellaceae* were indeed lower in married women [54]. In vitro fertilization (IVF) is rather common nowadays. In addition to contributing to a higher success rate of consumption and term pregnancy (Table 8.2), the vaginal, oral and gut microbiome could also contain information for disease risks much later in life. For example, can we predict risk for breast cancer according to the fecal and the milk microbiome (Chapter 2, Table 2.1; Chapter 4, Fig. 4.2)? Recovery of the fecal, cervical, urinary, and other microbiome after each pregnancy may be more difficult in some people than others, which necessitates additional effort. Hip fractures due to osteoporosis is a life-threatening incident in postmenopausal women, and the fecal microbiome markers for bone mineral density

Table 8.2 A metagenomic record for women.

Event	Sample					Microbes	Reference
	Vaginocervical	Oral	Fecal	Urine	Breastmilk		
Menstrual cycle	Y					More *Lactobacillus iners* and bacterial vaginosis-related bacteria during menses; More *L. crispatus* in the secretory phase	[54,56]
		Y				More bacterial cells before menses, bad breath; *Streptococcus*?	
Sexual debut	Y					More susceptible to bacterial vaginosis right after menses; Older age at sexual debut associated with *Bifidobacterium breve*	[54,57]
Contraception	Y					More *G. vaginalis* for no contraception; Oral contraceptives appeared to associate with cervical *L. iners*, *Ureaplasma parvum* and *Comamonas*, and some associations in the fecal microbiome	[54]
Pregnancy	Y			?		More Lactobacilli during pregnancy	[58]
In vitro fertilization	Y			?		Endometrium (or fallopian fluid) samples to test for Lactobacilli and other bacteria, in correlation with successful pregnancy	[59–61]
Spontaneous abortion	Y			?		*L. iners* negatively associated with spontaneous abortion	[54]
		Y	Y			Mouse gavaged with *Fusobacterium* showed preterm birth	[62]
Preterm birth	Y			?		A diverse vaginal microbiome lacking Lactobacilli	Many studies

Continued

Table 8.2 A metagenomic record for women—cont'd

Event	Sample					Microbes	Reference
	Vaginocervical	Oral	Fecal	Urine	Breastmilk		
Delivery	Y					Less *L. crispatus* for mothers who had given birth in the past; *Streptococcus anginosis* (GBS), *Ureaplasma*, etc. screened to prevent infection of newborns	[54,56]
			Y			Likely more obesity-related bacteria for mothers who deliver by C-section; Risks for diseases such as (gestational) diabetes and hypertension monitored during and after pregnancy	Follow up studies needed
Breastfeeding	Y					Recovery to a Lactobacilli-dominated microbiota, perhaps shifting to *L. iners*	[54,56]
			Y		Y	Monitor risk of breast cancer in the years to come; *Bifidobacterium* and other bacteria match those in the baby?	[63–66]
Menopause	Y	Y	Y	Y		Maintaining a healthy bone mineral density, metabolic health and urinary function, free of HPV and other pathogens	Prospective cohorts needed
Hysteromyoma (uterine fibroids)	Y			Y		More *L. iners* instead of *L. crispatus*?	[67,68]
Rheumatoid arthritis	Y	Y	Y	Y		Fungal infection in synovial fluid matches that in the vagina? Bacteria in synovial fluid matched that in the mouth and in the gut? More effective medication	Chapter 4

The associations are not necessarily causal (Chapter 6) and would need to be further elucidated. This is not meant to be an exhaustive list, but it serves to illustrate the range of conditions and samples to consider. Y, samples strongly recommended. *HPV*, human papillomavirus.
Credit: Huijue Jia.

(BMD) should be a target for early intervention through measures such as probiotics and tea (Intervention evidence needed) [75–78]. Like the skin [79], the vaginal metabolome also include compounds that likely come from cosmetic products [80].

In developed countries such as the U.S., a lot of food allergy cases start in adulthood (Table 8.3), and more commonly in women [81]. The comorbidities such as asthma, allergic rhinitis, are also known to involve the gut microbiome and the respiratory microbiome.

We do not know as much for men. Infant boys already differed in gut microbiome composition and functional capacity compared to girls [19]. An allele between *NEGR1* and *LINC01360* that has been implicated in autism spectrum disorder (ASD) and schizophrenia showed a significant M-GWAS (Metagenome-genome-wide association study) association with the gut bacterium *Acidaminococcus* (e.g., *Acidaminococcus intestinalis*) only in males [45,82]. Hyperuricemia (high level of blood uric acid) and gout are more prevalent in men, and the gut and oral microbiome are heavily involved [45,83,84]. *Anaerococcus* and *Prevotella* in semen are associated with low sperm quality, while *Pseudomonas* correlated with total sperm count [85,86]. There were microbial differences between subtypes of male infertility, e.g., nonobstructive and obstructive azoospermia (no sperm) [87], with and without varicocele (bulging blood vessels) [86]. *Staphylococcus* has been reported to be enriched in prostate cancer tissues [88]; both *Staphylococcus* and the more abundant *Cutibacterium acnes* (renamed from *Propionibacterium acnes*) implicated in chronic prostatitis showed a reduced level in the seminal fluid of *Estrogen Receptor*-α (*ESR1*) knockout mice [89]. A wild speculation would be to modulate hormone levels with physical fitness training and see how the microbiome improves throughout the body.

We mentioned biological aging in Chapter 2. To better understand the process, keeping a good record of the microbiome at each stage (Fig. 8.1), along with other omics such as hormone levels, trace metals, physical activity, would also be useful for the general population [53,90]. Handgrip strength lower than people of the same age group, a known epidemiological factor for cardiovascular events, associated with fecal relative abundance of *E. coli* [83], which was shown by Mendelian Randomization (MR, Chapter 6) to promote Type 2 diabetes, congestive heart failure, colorectal cancer [46] and could mediate the disease risks for the years to come. Sleeping for longer than average (> 9 or 10 h) is epidemiologically linked to a reduced lifespan [91][92], and it remains to be seen whether that has something to do with lack of saliva secretion while asleep, hypoxia, and the accumulation of oral and lung microbes. Effects of intervention, e.g., dietary fibers (Table 8.4) [42,94,95], dairy products, vitamins, high-intensity interval training, going to bed earlier, could be quickly assayed with

Table 8.3 Overall and age-specific prevalence of specific food allergies among all US adults.

Specific food allergy	Prevalence, % (95% confidence interval (CI))					
	All ages	18–29 years	30–39 years	40–49 years	50–59 years	≥ 60 years
Any food allergy	10.8 (10.4–11.1)	11.3 (10.5–12.2)	12.7 (11.8–13.7)	10.0 (9.2–10.9)	11.9 (11.0–12.8)	8.8 (8.2–9.4)
Peanut	1.8 (1.7–1.9)	2.5 (2.2–2.8)	2.9 (2.5–3.3)	1.8 (1.5–2.1)	1.4 (1.1–1.7)	0.8 (0.7–1.0)
Tree nut	1.2 (1.1–1.3)	1.6 (1.3–1.9)	1.7 (1.4–2.1)	1.1 (0.9–1.4)	1.2 (0.9–1.5)	0.6 (0.4–0.7)
Walnut	0.6 (0.6–0.7)	0.8 (0.7–1.1)	0.9 (0.7–1.3)	0.6 (0.5–0.8)	0.7 (0.5–0.9)	0.3 (0.2–0.4)
Almond	0.7 (0.6–0.8)	0.9 (0.7–1.2)	1.0 (0.7–1.3)	0.7 (0.6–1.0)	0.7 (0.5–0.9)	0.3 (0.2–0.4)
Hazelnut	0.6 (0.5–0.7)	0.7 (0.5–0.9)	0.9 (0.6–1.2)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.3 (0.2–0.4)
Pecan	0.5 (0.5–0.6)	0.6 (0.5–0.8)	0.8 (0.5–1.1)	0.6 (0.5–0.8)	0.5 (0.4–0.8)	0.5 (0.4–0.8)
Cashew	0.5 (0.5–0.6)	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.5 (0.4–0.7)	0.5 (0.3–0.7)	0.2 (0.1–0.3)
Pistachio	0.4 (0.3–0.5)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.5 (0.3–0.6)	0.4 (0.3–0.6)	0.1 (0.1–0.2)
Other tree nut	0.2 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.0–0.2)	0.3 (0.2–0.6)	0.2 (0.1–0.5)	0.1 (0.1–0.2)
Milk	1.9 (1.8–2.1)	2.4 (2.0–2.9)	2.3 (1.9–2.8)	2.0 (1.6–2.4)	1.9 (1.6–2.2)	1.9 (1.6–2.2)
Shellfish	2.9 (2.7–3.1)	2.8 (2.4–3.2)	3.6 (3.1–4.2)	2.5 (2.2–3.0)	3.3 (2.8–3.8)	2.6 (2.2–3.0)
Shrimp	1.9 (1.8–2.1)	1.8 (1.5–2.1)	2.5 (2.1–3.0)	1.8 (1.4–2.1)	2.2 (1.8–2.6)	1.6 (1.3–1.9)
Lobster	1.3 (1.2–1.4)	1.2 (1.0–1.5)	1.6 (1.3–2.0)	1.3 (1.0–1.5)	1.4 (1.1–1.7)	1.1 (0.9–1.3)
Crab	1.3 (1.2–1.5)	1.2 (1.0–1.5)	1.6 (1.3–2.0)	1.3 (1.0–1.6)	1.6 (1.3–2.0)	1.1 (0.9–1.4)
Mollusk	1.6 (1.4–1.7)	1.6 (1.3–2.0)	2.0 (1.7–2.5)	1.3 (1.1–1.7)	1.7 (1.4–2.0)	1.2 (1.0–1.5)
Other shellfish	0.3 (0.2–0.3)	0.3 (0.1–0.5)	0.1 (0.1–0.2)	0.3 (0.2–0.4)	0.3 (0.2–0.5)	0.3 (0.2–0.4)
Egg	0.8 (0.7–0.9)	1.1 (0.7–1.5)	1.1 (0.9–1.3)	0.7 (0.5–0.9)	0.8 (0.6–1.1)	0.5 (0.3–0.7)
Fin fish	0.9 (0.8–1.0)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	0.8 (0.6–1.1)	1.0 (0.7–1.3)	0.6 (0.4–0.7)
Wheat	0.8 (0.7–0.9)	1.0 (0.7–1.3)	1.0 (0.8–1.3)	0.8 (0.6–1.0)	0.7 (0.5–0.9)	0.6 (0.4–0.8)
Soy	0.6 (0.5–0.7)	0.7 (0.5–0.9)	0.8 (0.6–1.0)	0.6 (0.5–0.8)	0.7 (0.5–0.9)	0.4 (0.3–0.6)
Sesame	0.2 (0.2–0.3)	0.3 (0.2–0.4)	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.3 (0.2–0.5)	0.1 (0.0–0.2)

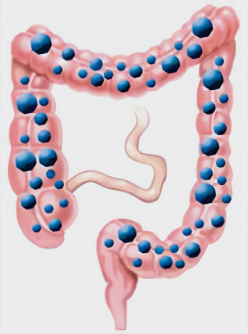
Credit: Table 2 of Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. JAMA Netw Open 2019;2:e185630. https://doi.org/10.1001/jamanetworkopen.2018.5630.

Table 8.4 Naturally occurring fibers according to solubility and fermentation properties.

Fiber type	Chain length	Sources	Potential benefits for IBS[a]	Potential risks for IBS[a]
Soluble highly fermentable oligosaccharides (includes FOS,GOS) 	Short-chain carbohydrates	• Legumes/pulses, nuts and seeds • Wheat, rye • Onions, garlic, artichoke	• Laxation: weak laxative effect • Transit time: does not hasten transit time • Balance of bacteria: selective growth of certain microbiota, e.g., Bifidobacterium • SCFA: very rapidly fermented in terminal ileum and proximal colon to produce SCFA • Gas production: high	• In patients with IBS the rapid fermentation may contribute to gas, flatus and gastrointestinal symptoms • A number of studies have been undertaken in IBS—with mixed results [98]
Soluble highly fermentable "fiber" (e.g., RS, pectin, guar gum, and inulin) 	Long-chain carbohydrates	• Legumes/pulses • Rye bread, barley • Firm bananas • Buckwheat groats (kashi), millet, oats • Cooked and cooled-pasta, potato and rice	• Laxation: mild laxative effect • Transit time: does not hasten gut transit. Can slow absorption from the small intestine • Balance of bacteria: increases overall bacterial species but not selective for bifidobacteria • SCFA: rapidly fermented in proximal colon to produce SCFA. RS is good an excellent substrate for the production of the SCFA butyrate • Gas production: moderate	• In patients with IBS the rapid fermentation may contribute to gas, flatus, and gastrointestinal symptoms • No well-designed studies have been undertaken in IBS

Continued

Table 8.4 Naturally occurring fibers according to solubility and fermentation properties—cont'd

Fiber type	Chain length	Sources	Potential benefits for IBS[a]	Potential risks for IBS[a]
Intermediate soluble fermentable "fiber" (psyllium/ispaghula) and oats 	Long-chain carbohydrates	Seed of the plant *Plantago ovata*, and oats	• Laxation: good laxative effect • Transit time: does hasten transit time • Balance of bacteria: increases overall bacterial species but little evidence for selective growth • SCFA: moderately fermented along length of colon to produce SCFA • Gas production: moderate	• In patients with IBS studies have shown some positive effect on laxation • Side-effects of gas/flatus has produced mixed results for some patients with IBS [99]
Insoluble slowly fermentable "fiber" (e.g., wheat bran, lignin (flax), fruit, and vegetables) 	Long-chain carbohydrates	• Some vegetables and fruit • Wheat bran • Wholegrain cereal • Rye • Brown rice, wholemeal pasta, quinoa • Flax seed	• Laxation: good laxative effect • Transit time: does hasten transit time • Balance of bacteria: increases overall bacterial species but little evidence for selective growth • SCFA: slowly fermented to produce SCFA along the length of the colon • Gas production: moderate-high	• In patients with IBS wheat bran has not been shown to be effective. A major side-effect has been excessive gas/wind and bloating [100]. This may be due to the presence of high quantities of fructans also associated with the wheat bran [101] • Symptoms associated with wheat bran may not be acceptable to many patients

Insoluble, nonfermentable "fiber" (e.g., cellulose, sterculia, and methylcellulose) 	Long-chain carbohydrates	• High fiber grains and cereals • Nuts, seeds • Skins of fruit and vegetables	• Laxation: good laxative effect • Transit time: does hasten transit time • Balance of bacteria: no evidence for selective growth • SCFA: poorly fermented • Gas production: low	• Less gas/wind forming properties • This fiber type may have better characteristics for treating constipation in IBS patients. However, few well designed studies have been conducted	

FOS, fructo-oligosaccarides; *GOS*, galacto-oligosaccarides; *IBS*, irritable bowel syndrome; *RS*, resistant starch; *SCFA*, short-chain fatty acids. Information given in this table is a simplified overview that summarizes the different physiological effects of the different fiber types. More detailed information about this area may be obtained by key reviews cited in [94]. The microbiome is sufficiently versatile that these are only general categories of fibers, especially regarding what is "nonfermentable."

[a] Using standard (not excessive) doses of these carbohydrates. Now, there are more emerging evidence for differential growth of bacteria induce by dietary fibers (e.g., [42][93]), but the dose is sometimes excessive compared to population-wide standard recommendations from nutritional experts.

Credit: Table 1 of Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. Am J Gastroenterol 2013;108:718–27. https://doi.org/10.1038/ajg.2013.63.

microbiome composition and functional capacity. The association between milk consumption and fecal microbiome may have something to do with estrogen exposure from the cow milk, in addition to IBS (irritable bowel syndrome) risk in some individuals [90]. Microbiome associations with more local habits, such as the types of tea, soy milk, plants used for bathing, can also be validated with more volunteer participation.

As we take measures to better protect the ecosystems on our planet Earth, gases and particles in the air, metals and organic compounds in water and soils will also be changing [96,97]. Exposure to climate change-related events such as wildfires could have long-term effects on the microbiome and the immune system. The microbiome records now may then be historic.

8.2 From genetic risk to the prevention of diseases

We discussed metagenomics-based diagnosis and treatment in Chapter 7. For infants, airway microbiome at 1 month could predict asthma at 6 years old [13] (Table 8.3), and there might be ways to amend for preterm birth and Cesarean section early on (e.g., Probiotics [102], Facilitated microbial colonization [103]; Cortisols and catecholamine exposure, Chapter 6, Fig. 6.4). Large cohorts have been followed to understand the microbiome during the onset of Type 1 diabetes [22,104–106].

Trends for many diseases could be seen decades before clinical symptoms, and the microbiome adds a key dimension for visualizing such early trends. For example, fecal bacterial and plasma metabolomic markers for colorectal cancer, hyperuricemia (high level of urate in the blood, which does not necessarily lead to painful gout) and meat consumption are visible in a cohort with a mean age of 30 years old, with some individuals at a higher risk than others [53]. Poly-genetic risk scores (PRS) for periodontal diseases and dental caries already showed an area under the (receiver operating) curve (AUC) of more than 0.8, suggesting that some people would always have to take better care of their oral microbiome [84]. PRS for diseases such as breast cancer, cardiovascular diseases, Alzheimer's diseases are promising for preventive medicine [107], and the fecal or oral microbiome could add an important dimension. Progression of Parkinson's disease and Alzheimer's disease might be slowed with proper management of risk factors [108,109]. The intervention can simply be dietary changes, exercise, or quit smoking, which would be a wise thing to do before it is too late. Plasma biomarkers for metabolic syndrome and Alzheimer's disease, e.g. branched-chain amino acids (BCAAs) and

acylcarnitines, could be metabolized by leg muscles and the kidneys [110–112]. Frequent moderate-intensity physical activity, e.g., brisk walking, is associated with lower risk and mortality for major diseases such as cancer and cardiovascular diseases [113,114]. The gut microbiome and inflammatory markers change after sprinting [115]. Dairy products are known as a protective factor for gout [90,116]. So if we compute from the fecal and/or oral microbiome that the urate level is not low [45,83,84], and the risk for Parkinson's disease is not high (fecal microbiome studies tend to be complicated by medication and disease duration, but useful biomarkers would still emerge) [117,118], maybe people with a genetic risk for Parkinson's disease can consume dairy products just fine [108].

Digitalizing the dietary information as nitrogen source (e.g., shifting from nitrite to amines), amino acids, metals, vitamins, etc. instead of crude questionnaires, would be a long-term effort for each culture. Sodium benzoate, a preservative that used to be widely present in pickled vegetables and in soda, is recently in clinical trials to see if it might help treat negative symptoms in schizophrenia patients [119] (the depression-like social exclusion, as opposed to the agitated positive symptoms). The incidence of vitamin A deficiency is decreasing globally (Chapter 7, Fig. 7.1). Firmicutes of the Clostridiale order suppress intestinal vitamin A production in mice, possibly finishing up a weaning reaction that induces T regulatory cells (Treg); and fecal Clostridiale species correlated with plasma vitamin A level in adult humans [23,53,120,121]. In addition to the gut microbiome, plasma vitamin A level also negatively associated with *L. iners* in the cervicovaginal microbiome (more *L. crispatus* in women who had never given birth), another potential explanation for the ethnical differences in the vaginal microbiome [122], in addition to the vitamin D and hormone explanation for bacterial vaginosis [54,123], or some genetic factors.

Body temperature and the number of breath taken per minute appeared to associate with the microbiome in the peritoneal cavity in women of reproductive age [67]. From long-term records of the menstrual cycles, scientists were able to match disturbances to the menstrual cycles with luminance (or gravitational) differences in the lunar cycle [124,125], which affects sleeping together with the hormones [124,126]; Fertile women had menses at the full moon and ovulate in the darkest days [125]. In the cervical microbiome, menstrual irregularity correlated with *L. vaginalis* [54], which correlated with *L. crispatus* and so possibly decreases with older age and decreased hormones.

Air pollution, which is a strong risk factor for cardiovascular diseases [96], lung cancer, etc. [127], can at least be recorded on the city scale. For developing countries, the burning of biomass is still a major source of pollution, instead of from factories or cars [97,128,129], which means different chemicals and particles that the human microbiome is exposed to.

Lung capacity showed association with the fecal microbiome [90]. Besides physical exercises, do we know how much talking and singing a person does? Salivary IgA and cortisol have been used as biomarkers to show favorable effects of enjoying music and choral singing [130,131], and oxytocin would also be a key marker [132].

Wearable devices are constantly being developed, and body fluids other than blood could be more readily analyzed in the future. For example, sweat can be assayed for glucose, electrolytes, lactate, uric acid, metals, etc. [133,134]. Oxygen saturation and heart rate readings are commonly provided by smartwatches [135]. Such disease-relevant and easily accessible measurements could fit in with the microbiome record.

Single-cell sequencing for detailed immune cell populations and T-cell receptor (TCR), B-cell receptor (BCR) sequences are as yet too expensive to replace cell counts from routine blood tests, and ELISA (Enzyme-linked Immunosorbent Assay) for cytokines. Human leukocyte antigen (HLA) types (MHC-I, MHC-II) that represent a strong genetic factor for many diseases can be available from whole genome sequences, without additional experimental procedures. Less understood major histocompatibility complex (MHC)-like proteins such as CD1 genes and MR1 (MHC class I-related protein 1) are also important for interaction with molecules that are relevant for the human microbiome [2,136–141]. It has been shown in mice that the development of mucosal-associated invariant T cells (MAIT), the predominant innate-like lymphocytes important for mucosal and skin homeostasis, took place during a time window early in life (2–3 weeks old for mice) [3]. Commensal bacteria can produce the vitamin B2 (riboflavin) derivative 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) [2]. When such bacteria or metabolites were applied to the skin or gavaged orally, 5-OP-RU is presented by MR1 to the T cell receptor (TCR) of MAIT cells which induce MAIT development in the thymus [2,3]. The number of these cells varies considerably among individuals.

Microbiome information may help relieve the ethical controversy over risks for complex diseases reported by commercial tests of the human genome [142]. Family history, a strong epidemiological factor for many complex diseases (colorectal cancer, breast cancer, hypertension, autoimmune disorders, etc.), could mean both genetic and microbiome similarity. By adding such modifiable information which together explains a larger portion of the risk, disease risks can be received with a more scientific understanding. The key question would always be, shall we do something about it?

Clinical trials are already being performed on high-risk individuals for diseases such as rheumatoid arthritis (Fig. 8.2). Microbiome information (Chapter 4, Fig. 4.4; Chapter 7) would make an important complement to the immune parameters. Probiotics are also being tested for a number of diseases [143–145], and it would probably be better to start in preclinical individuals.

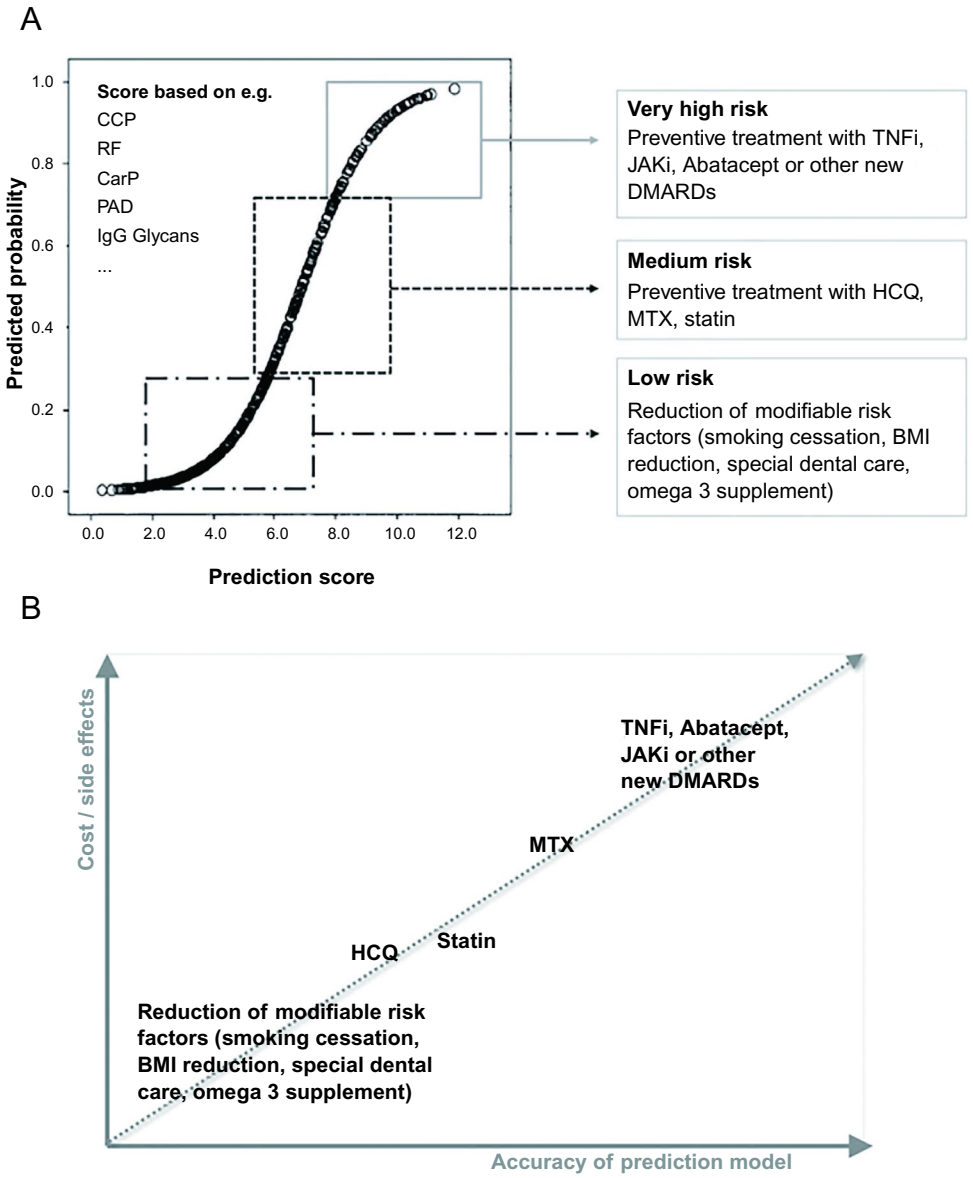


Fig. 8.2 Toward prevention of rheumatoid arthritis (RA). (A) Risk-based prevention model. (B) Linear relationship between cost/safety profile and required accuracy of the prediction model. More expensive and less safe treatment strategies will require higher accuracy of the prediction model to avoid unnecessary treatment of individuals that might not develop RA in the near future. *BMI*, body mass index; *DMARD*, disease modifying antirheumatic drug; *HCQ*, hydroxychloroquine; *MTX*, methotrexate; *TNFi*, tumor necrosis factor inhibitor. Credit: Fig. 2 of Mahler M, Martinez-Prat L, Sparks JA, Deane KD. Precision medicine in the care of rheumatoid arthritis: focus on prediction and prevention of future clinically-apparent disease. Autoimmun Rev 2020;19:102506. https://doi.org/10.1016/j.autrev.2020.102506.

8.3 Summary

From birth to old age, the microbiome in various body sites contains important information that could predict disease risks in the future (Fig. 8.1). Once-in-a-lifetime experiences and long-term exposures can all leave their mark in the human microbiome. The microbiome connects genetic and environmental factors, would greatly facilitate precision medicine and potentially allow many complex diseases to be prevented before the emergence of clinical symptoms. It will take engineers and scientists, and people from all walks of life to fill in a variety of information that is not currently recorded in microbiome studies. With demonstrated values for health, and as metagenomics become cheaper and bioinformatics becomes faster and more accessible, more people would be motivated to sample their microbiome. Facilities could be provided for educational purposes, and as part of a physical examination that are better aligned with occasional events, e.g., being locked down at home.

Worked sample 8.1

In your country or region, what do you think is the most needed microbiome test?

Where do you think the test should be offered?

How much do you think people are willing to pay for the test?

Worked sample 8.2

Prepare a shortlist of questions that you would like people to answer before, or after receiving results from the microbiome test you start to provide.

Are some people more willing to participate than others? What do they hope the microbiome test could do for them?

Do you see gaps in expectations? How would you like to improve, or refocus?

References

[1] Zegarra-Ruiz DF, Kim DV, Norwood K, Kim M, Wu W-JH, Saldana-Morales FB, et al. Thymic development of gut-microbiota-specific T cells. Nature 2021;1–5. https://doi.org/10.1038/s41586-021-03531-1.

[2] Legoux F, Bellet D, Daviaud C, El Morr Y, Darbois A, Niort K, et al. Microbial metabolites control the thymic development of mucosal-associated invariant T cells. Science 2019;366. https://doi.org/10.1126/science.aaw2719, eaaw2719.

[3] Constantinides MG, Link VM, Tamoutounour S, Wong AC, Perez-Chaparro PJ, Han S-J, et al. MAIT cells are imprinted by the microbiota in early life and promote tissue repair. Science 2019;366. https://doi.org/10.1126/science.aax6624, eaax6624.

[4] Zhang J, Branch DW, Ramirez MM, Laughon SK, Reddy U, Hoffman M, et al. Oxytocin regimen for labor augmentation, labor progression, and perinatal outcomes. Obstet Gynecol 2011;118:249–56. https://doi.org/10.1097/AOG.0b013e3182220192.
[5] Cho I, Yamanishi S, Cox L, Methé BA, Zavadil J, Li K, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature 2012;488:621–6. https://doi.org/10.1038/nature11400.
[6] Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell 2014;158:705–21. https://doi.org/10.1016/j.cell.2014.05.052.
[7] Lynn MA, Tumes DJ, Choo JM, Sribnaia A, Blake SJ, Leong LEX, et al. Early-life antibiotic-driven dysbiosis leads to dysregulated vaccine immune responses in mice. Cell Host Microbe 2018;23:653–660.e5. https://doi.org/10.1016/j.chom.2018.04.009.
[8] Peñagarikano O, Lázaro MT, Lu X-H, Gordon A, Dong H, Lam HA, et al. Exogenous and evoked oxytocin restores social behavior in the Cntnap2 mouse model of autism. Sci Transl Med 2015;7:271ra8. https://doi.org/10.1126/scitranslmed.3010257.
[9] Lawson EA. The effects of oxytocin on eating behaviour and metabolism in humans. Nat Rev Endocrinol 2017;13:700–9. https://doi.org/10.1038/nrendo.2017.115.
[10] Ben-Ari Y. Is birth a critical period in the pathogenesis of autism spectrum disorders? Nat Rev Neurosci 2015;16:498–505. https://doi.org/10.1038/nrn3956.
[11] Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. EMBO Rep 2012;13:440–7. https://doi.org/10.1038/embor.2012.32.
[12] Pattaroni C, Watzenboeck ML, Schneidegger S, Kieser S, Wong NC, Bernasconi E, et al. Early-life formation of the microbial and immunological environment of the human airways. Cell Host Microbe 2018;24:857–865.e4. https://doi.org/10.1016/j.chom.2018.10.019.
[13] Thorsen J, Rasmussen MA, Waage J, Mortensen M, Brejnrod A, Bønnelykke K, et al. Infant airway microbiota and topical immune perturbations in the origins of childhood asthma. Nat Commun 2019;10:5001. https://doi.org/10.1038/s41467-019-12989-7.
[14] Lynn DJ, Benson SC, Lynn MA, Pulendran B. Modulation of immune responses to vaccination by the microbiota: implications and potential mechanisms. Nat Rev Immunol 2021. https://doi.org/10.1038/s41577-021-00554-7.
[15] Mansbach JM, Luna PN, Shaw CA, Hasegawa K, Petrosino JF, Piedra PA, et al. Increased Moraxella and Streptococcus species abundance after severe bronchiolitis is associated with recurrent wheezing. J Allergy Clin Immunol 2020;145:518–527.e8. https://doi.org/10.1016/j.jaci.2019.10.034.
[16] Bunyavanich S, Shen N, Grishin A, Wood R, Burks W, Dawson P, et al. Early-life gut microbiome composition and milk allergy resolution. J Allergy Clin Immunol 2016;138:1122–30. https://doi.org/10.1016/j.jaci.2016.03.041.
[17] Stephen-Victor E, Crestani E, Chatila TA. Dietary and microbial determinants in food allergy. Immunity 2020;53:277–89. https://doi.org/10.1016/j.immuni.2020.07.025.
[18] Rachid R, Stephen-Victor E, Chatila TA. The microbial origins of food allergy. J Allergy Clin Immunol 2021;147:808–13. https://doi.org/10.1016/j.jaci.2020.12.624.
[19] Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe 2015;17:690–703. https://doi.org/10.1016/j.chom.2015.04.004.

[20] Verma R, Lee C, Jeun E-J, Yi J, Kim KS, Ghosh A, et al. Cell surface polysaccharides of *Bifidobacterium bifidum* induce the generation of Foxp3 + regulatory T cells. Sci Immunol 2018;3:eaat6975. https://doi.org/10.1126/sciimmunol.aat6975.

[21] Henrick BM, Rodriguez L, Lakshmikantz T, Pou C, Henckel E, Olin A, et al. Bifidobacteria-mediated immune system imprinting early in life. BioRxiv 2021. https://doi.org/10.1101/2020.10.24.353250.

[22] Vatanen T, Franzosa EA, Schwager R, Tripathi S, Arthur TD, Vehik K, et al. The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. Nature 2018;562:589–94. https://doi.org/10.1038/s41586-018-0620-2.

[23] Al Nabhani Z, Dulauroy S, Marques R, Cousu C, Al Bounny S, Déjardin F, et al. A weaning reaction to microbiota is required for resistance to immunopathologies in the adult. Immunity 2019;50:1276–1288.e5. https://doi.org/10.1016/j.immuni.2019.02.014.

[24] Knoop KA, Gustafsson JK, McDonald KG, Kulkarni DH, Coughlin PE, McCrate S, et al. Microbial antigen encounter during a preweaning interval is critical for tolerance to gut bacteria. Sci Immunol 2017;2. https://doi.org/10.1126/sciimmunol.aao1314, eaao1314.

[25] Lehtimäki J, Karkman A, Laatikainen T, Paalanen L, von Hertzen L, Haahtela T, et al. Patterns in the skin microbiota differ in children and teenagers between rural and urban environments. Sci Rep 2017;7:45651. https://doi.org/10.1038/srep45651.

[26] Ayeni FA, Biagi E, Rampelli S, Fiori J, Soverini M, Audu HJ, et al. Infant and adult gut microbiome and metabolome in rural Bassa and urban settlers from Nigeria. Cell Rep 2018;23:3056–67. https://doi.org/10.1016/j.celrep.2018.05.018.

[27] Depner M, Taft DH, Kirjavainen PV, Kalanetra KM, Karvonen AM, Peschel S, et al. Maturation of the gut microbiome during the first year of life contributes to the protective farm effect on childhood asthma. Nat Med 2020. https://doi.org/10.1038/s41591-020-1095-x.

[28] Stokholm J, Thorsen J, Blaser MJ, Rasmussen MA, Hjelmsø M, Shah S, et al. Delivery mode and gut microbial changes correlate with an increased risk of childhood asthma. Sci Transl Med 2020;12. https://doi.org/10.1126/scitranslmed.aax9929, eaax9929.

[29] Selma-Royo M, Calatayud Arroyo M, García-Mantrana I, Parra-Llorca A, Escuriet R, Martínez-Costa C, et al. Perinatal environment shapes microbiota colonization and infant growth: impact on host response and intestinal function. Microbiome 2020;8:167. https://doi.org/10.1186/s40168-020-00940-8.

[30] Kirjavainen PV, Karvonen AM, Adams RI, Täubel M, Roponen M, Tuoresmäki P, et al. Farm-like indoor microbiota in non-farm homes protects children from asthma development. Nat Med 2019;25:1089–95. https://doi.org/10.1038/s41591-019-0469-4.

[31] Barisic V, Abdelhadi A, Frank A, Riojas MA, Hazbón MH. Reclassification of the bifidobacterium and gardnerella genera. In: ATCC. ASM microbe 2019, San Francisco, California, United States; 2019.

[32] Ferretti P, Pasolli E, Tett A, Asnicar F, Gorfer V, Fedi S, et al. Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. Cell Host Microbe 2018;24:133–145.e5. https://doi.org/10.1016/j.chom.2018.06.005.

[33] Tun HM, Konya T, Takaro TK, Brook JR, Chari R, Field CJ, et al. Exposure to household furry pets influences the gut microbiota of infant at 3-4 months following various birth scenarios. Microbiome 2017;5:40. https://doi.org/10.1186/s40168-017-0254-x.

[34] Song SJ, Lauber C, Costello EK, Lozupone CA, Humphrey G, Berg-Lyons D, et al. Cohabiting family members share microbiota with one another and with their dogs. Elife 2013;2. https://doi.org/10.7554/eLife.00458, e00458.

[35] Ardura J, Gutierrez R, Andres J, Agapito T. Emergence and evolution of the circadian rhythm of melatonin in children. Horm Res 2003;59:66–72. doi:68571.
[36] Prakash M, Johnny J. Whats special in a child's larynx? J Pharm Bioallied Sci 2015;7:S55–8. https://doi.org/10.4103/0975-7406.155797.
[37] Geddes DT, Chadwick LM, Kent JC, Garbin CP, Hartmann PE. Ultrasound imaging of infant swallowing during breast-feeding. Dysphagia 2010;25:183–91. https://doi.org/10.1007/s00455-009-9241-0.
[38] Pou C, Nkulikiyimfura D, Henckel E, Olin A, Lakshmikanth T, Mikes J, et al. The repertoire of maternal anti-viral antibodies in human newborns. Nat Med 2019. https://doi.org/10.1038/s41591-019-0392-8.
[39] Msallam R, Balla J, Rathore APS, Kared H, Malleret B, Saron WAA, et al. Fetal mast cells mediate postnatal allergic responses dependent on maternal IgE. Science 2020;370:941–50. https://doi.org/10.1126/science.aba0864.
[40] Le Rouzic V, Corona J, Zhou H. Postnatal development of hepatic innate immune response. Inflammation 2011;34:576–84. https://doi.org/10.1007/s10753-010-9265-5.
[41] Nakagaki BN, Mafra K, de Carvalho É, Lopes ME, Carvalho-Gontijo R, de Castro-Oliveira HM, et al. Immune and metabolic shifts during neonatal development reprogram liver identity and function. J Hepatol 2018;69:1294–307. https://doi.org/10.1016/j.jhep.2018.08.018.
[42] Patnode ML, Beller ZW, Han ND, Cheng J, Peters SL, Terrapon N, et al. Interspecies competition impacts targeted manipulation of human gut bacteria by fiber-derived glycans. Cell 2019;179:59–73.e13. https://doi.org/10.1016/j.cell.2019.08.011.
[43] De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A 2010;107:14691–6. https://doi.org/10.1073/pnas.1005963107.
[44] Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature 2012;486:222–7. https://doi.org/10.1038/nature11053.
[45] Liu X, Tang S, Zhong H, Tong X, Jie Z, Ding Q, et al. A genome-wide association study for gut metagenome in Chinese adults illuminates complex diseases. Cell Discov 2021;7:9. https://doi.org/10.1038/s41421-020-00239-w.
[46] Liu X, Tong X, Zou Y, Lin X, Zhao H, Tian L, et al. Inter-determination of blood metabolite levels and gut microbiome supported by Mendelian randomization. BioRxiv 2020. https://doi.org/10.1101/2020.06.30.181438. 2020.06.30.
[47] Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, et al. Disordered microbial communities in asthmatic airways. PLoS One 2010;5. https://doi.org/10.1371/journal.pone.0008578, e8578.
[48] Schnorr SL, Candela M, Rampelli S, Centanni M, Consolandi C, Basaglia G, et al. Gut microbiome of the Hadza hunter-gatherers. Nat Commun 2014;5:3654. https://doi.org/10.1038/ncomms4654.
[49] Lane AA, McGuire MK, McGuire MA, Williams JE, Lackey KA, Hagen EH, et al. Household composition and the infant fecal microbiome: the INSPIRE study. Am J Phys Anthropol 2019;169:526–39. https://doi.org/10.1002/ajpa.23843.
[50] Denger K, Weiss M, Felux A-K, Schneider A, Mayer C, Spiteller D, et al. Sulphoglycolysis in *Escherichia coli* K-12 closes a gap in the biogeochemical Sulphur cycle. Nature 2014;507:114–7. https://doi.org/10.1038/nature12947.
[51] Roy AB, Hewlins MJE, Ellis AJ, Harwood JL, White GF. Glycolytic breakdown of sulfoquinovose in bacteria: a missing Link in the sulfur cycle. Appl Environ Microbiol 2003;69:6434–41. https://doi.org/10.1128/AEM.69.11.6434-6441.2003.
[52] Gashu D, Nalivata PC, Amede T, Ander EL, Bailey EH, Botoman L, et al. The nutritional quality of cereals varies geospatially in Ethiopia and Malawi. Nature 2021;594:71–6. https://doi.org/10.1038/s41586-021-03559-3.

[53] Jie Z, Liang S, Ding Q, Li F, Tang S, Wang D, et al. A transomic cohort as a reference point for promoting a healthy gut microbiome. Med Microecol 2021. https://doi.org/10.1016/j.medmic.2021.100039.

[54] Jie Z, Chen C, Hao L, Li F, Song L, Zhang X, et al. Life history recorded in the vagino-cervical microbiome along with multi-omics. Genomics Proteomics Bioinformatics 2021. https://doi.org/10.1016/j.gpb.2021.01.005.

[55] Mueller JT, Gasteyer S. The widespread and unjust drinking water and clean water crisis in the United States. Nat Commun 2021;12:3544. https://doi.org/10.1038/s41467-021-23898-z.

[56] dos Santos Santiago GL, Tency I, Verstraelen H, Verhelst R, Trog M, Temmerman M, et al. Longitudinal qPCR study of the dynamics of *L. crispatus*, *L. iners*, *A. vaginae*, (sialidase positive) *G. vaginalis*, and *P. bivia* in the vagina. PLoS One 2012;7. https://doi.org/10.1371/journal.pone.0045281, e45281.

[57] Gajer P, Brotman RM, Bai G, Sakamoto J, Schutte UME, Zhong X, et al. Temporal dynamics of the human vaginal microbiota. Sci Transl Med 2012;4:132ra52. https://doi.org/10.1126/scitranslmed.3003605.

[58] Fettweis JM, Serrano MG, Brooks JP, Edwards DJ, Girerd PH, Parikh HI, et al. The vaginal microbiome and preterm birth. Nat Med 2019;25:1012–21. https://doi.org/10.1038/s41591-019-0450-2.

[59] Koedooder R, Singer M, Schoenmakers S, Savelkoul PHM, Morré SA, de Jonge JD, et al. The vaginal microbiome as a predictor for outcome of in vitro fertilization with or without intracytoplasmic sperm injection: a prospective study. Hum Reprod 2019;34:1042–54. https://doi.org/10.1093/humrep/dez065.

[60] Schoenmakers S, Laven J. The vaginal microbiome as a tool to predict IVF success. Curr Opin Obstet Gynecol 2020;32:169–78. https://doi.org/10.1097/GCO.0000000000000626.

[61] Pelzer ES, Allan JA, Waterhouse MA, Ross T, Beagley KW, Knox CL. Microorganisms within human follicular fluid: effects on IVF. PLoS One 2013;8. https://doi.org/10.1371/journal.pone.0059062, e59062.

[62] Fardini Y, Chung P, Dumm R, Joshi N, Han YW. Transmission of diverse oral bacteria to murine placenta: evidence for the oral microbiome as a potential source of intrauterine infection. Infect Immun 2010;78:1789–96. https://doi.org/10.1128/IAI.01395-09.

[63] Urbaniak C, Gloor GB, Brackstone M, Scott L, Tangney M, Reid G. The microbiota of breast tissue and its association with breast cancer. Appl Environ Microbiol 2016;82:5039–48. https://doi.org/10.1128/AEM.01235-16.

[64] Chambers SA, Townsend SD. Like mother, like microbe: human milk oligosaccharide mediated microbiome symbiosis. Biochem Soc Trans 2020;48:1139–51. https://doi.org/10.1042/BST20191144.

[65] Pannaraj PS, Li F, Cerini C, Bender JM, Yang S, Rollie A, et al. Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. JAMA Pediatr 2017;171:647–54. https://doi.org/10.1001/jamapediatrics.2017.0378.

[66] Nayfach S, Rodriguez-Mueller B, Garud N, Pollard KS. An integrated metagenomics pipeline for strain profiling reveals novel patterns of bacterial transmission and biogeography. Genome Res 2016;26:1612–25. https://doi.org/10.1101/gr.201863.115.

[67] Chen C, Song X, Wei W, Zhong H, Dai J, Lan Z, et al. The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. Nat Commun 2017;8:875. https://doi.org/10.1038/s41467-017-00901-0.

[68] Chen C, Hao L, Wei W, Li F, Song L, Zhang X, et al. The female urinary microbiota in relation to the reproductive tract microbiota. Gigabyte 2020;2020:1–9. https://doi.org/10.46471/gigabyte.9.

[69] Wang J, Zheng J, Shi W, Du N, Xu X, Zhang Y, et al. Dysbiosis of maternal and neonatal microbiota associated with gestational diabetes mellitus. Gut 2018. https://doi.org/10.1136/gutjnl-2018-315988. gutjnl-2018-315988.
[70] Vuillermin PJ, O'Hely M, Collier F, Allen KJ, Tang MLK, Harrison LC, et al. Maternal carriage of Prevotella during pregnancy associates with protection against food allergy in the offspring. Nat Commun 2020;11:1452. https://doi.org/10.1038/s41467-020-14552-1.
[71] Cortés-Macías E, Selma-Royo M, Martínez-Costa C, Collado MC. Breastfeeding practices influence the breast milk microbiota depending on pre-gestational maternal BMI and weight gain over pregnancy. Nutrients 2021;13. https://doi.org/10.3390/nu13051518.
[72] Crusell MKW, Hansen TH, Nielsen T, Allin KH, Rühlemann MC, Damm P, et al. Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. Microbiome 2018;6:89. https://doi.org/10.1186/s40168-018-0472-x.
[73] Zhang Y, Xiao C-M, Zhang Y, Chen Q, Zhang X-Q, Li X-F, et al. Factors associated with gestational diabetes mellitus: a Meta-analysis. J Diabetes Res 2021;2021:6692695. https://doi.org/10.1155/2021/6692695.
[74] Hewage SS, Aw S, Chi C, Yoong J. Factors associated with intended postpartum OGTT uptake and willingness to receive preventive behavior support to reduce type 2 diabetes risk among women with gestational diabetes in Singapore: an exploratory study. Nutr Metab Insights 2021;14. https://doi.org/10.1177/11786388211016827. 11786388211016828.
[75] Wang Q, Sun Q, Li X, Wang Z, Zheng H, Ju Y, et al. Linking gut microbiome to bone mineral density: a shotgun metagenomic dataset from 361 elderly women. Gigabyte 2021;2021:1–7. https://doi.org/10.46471/gigabyte.12.
[76] Ohlsson C, Sjögren K. Effects of the gut microbiota on bone mass. Trends Endocrinol Metab 2015;26:69–74. https://doi.org/10.1016/j.tem.2014.11.004.
[77] Yan J, Herzog JW, Tsang K, Brennan CA, Bower MA, Garrett WS, et al. Gut microbiota induce IGF-1 and promote bone formation and growth. Proc Natl Acad Sci U S A 2016;113:E7554–63. https://doi.org/10.1073/pnas.1607235113.
[78] Zhao H, Chen J, Li X, Sun Q, Qin P, Wang Q. Compositional and functional features of the female premenopausal and postmenopausal gut microbiota. FEBS Lett 2019;593:2655–64. https://doi.org/10.1002/1873-3468.13527.
[79] Bouslimani A, Porto C, Rath CM, Wang M, Guo Y, Gonzalez A, et al. Molecular cartography of the human skin surface in 3D. Proc Natl Acad Sci U S A 2015;112:E2120–9. https://doi.org/10.1073/pnas.1424409112.
[80] Kindschuh WF, Baldini F, Liu MC, Gerson KD, Liao J, Lee HH, et al. Preterm birth is associated with xenobiotics and predicted by the vaginal metabolome. BioRxiv 2021. https://doi.org/10.1101/2021.06.14.448190. 2021.06.14.448190.
[81] Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. JAMA Netw Open 2019;2. https://doi.org/10.1001/jamanetworkopen.2018.5630, e185630.
[82] Zhu F, Ju Y, Wang W, Wang Q, Guo R, Ma Q, et al. Metagenome-wide association of gut microbiome features for schizophrenia. Nat Commun 2020;11:1612. https://doi.org/10.1038/s41467-020-15457-9.
[83] Jie Z, Liang S, Ding Q, Li F, Tang S, Sun X, et al. Disease trends in a young Chinese cohort according to fecal metagenome and plasma metabolites. Med Microecol 2021. https://doi.org/10.1016/j.medmic.2021.100037.
[84] Liu X, Tong X, Zhu J, Tian L, Jie Z, Zou Y, et al. Metagenome-genome-wide association studies reveal human genetic impact on the oral microbiome. bioRxiv 2021. https://doi.org/10.1101/2021.05.06.443017.

[85] Hou D, Zhou X, Zhong X, Settles ML, Herring J, Wang L, et al. Microbiota of the seminal fluid from healthy and infertile men. Fertil Steril 2013;100:1261–9. https://doi.org/10.1016/j.fertnstert.2013.07.1991.

[86] Lundy SD, Sangwan N, Parekh NV, Selvam MKP, Gupta S, McCaffrey P, et al. Functional and taxonomic dysbiosis of the gut, urine, and semen microbiomes in male infertility. Eur Urol 2021;79:826–36. https://doi.org/10.1016/j.eururo.2021.01.014.

[87] Chen H, Luo T, Chen T, Wang G. Seminal bacterial composition in patients with obstructive and non-obstructive azoospermia. Exp Ther Med 2018. https://doi.org/10.3892/etm.2018.5778.

[88] Cavarretta I, Ferrarese R, Cazzaniga W, Saita D, Lucianò R, Ceresola ER, et al. The microbiome of the prostate tumor microenvironment. Eur Urol 2017;72:625–31. https://doi.org/10.1016/j.eururo.2017.03.029.

[89] Javurek AB, Spollen WG, Ali AMM, Johnson SA, Lubahn DB, Bivens NJ, et al. Discovery of a novel seminal fluid microbiome and influence of estrogen receptor alpha genetic status. Sci Rep 2016;6:23027. https://doi.org/10.1038/srep23027.

[90] Jie Z, Liang S, Ding Q, Li F, Tang S, Wang D, et al. Dairy consumption and physical fitness tests associated with fecal microbiome in a Chinese cohort. Med Microecol 2021.

[91] Svensson T, Saito E, Svensson AK, Melander O, Orho-Melander M, Mimura M, et al. Association of sleep duration with all- and major-cause mortality among adults in Japan, China, Singapore, and Korea. JAMA Netw Open 2021;4(9):e2122837. https://doi.org/10.1001/jamanetworkopen.2021.22837.

[92] Valenzuela PL, Carrera-Bastos P, Gálvez BG, Ruiz-Hurtado G, Ordovas JM, Ruilope LM, et al. Lifestyle interventions for the prevention and treatment of hypertension. Nat Rev Cardiol 2021;18(4):251–75. https://doi.org/10.1038/s41569-020-00437-9.

[93] Kovatcheva-Datchary P, Nilsson A, Akrami R, Lee YS, De Vadder F, Arora T, et al. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of prevotella. Cell Metab 2015;22(6):971–82. https://doi.org/10.1016/j.cmet.2015.10.001.

[94] Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. Am J Gastroenterol 2013;108:718–27. https://doi.org/10.1038/ajg.2013.63.

[95] Jie Z, Yu X, Liu Y, Sun L, Chen P, Ding Q, et al. The baseline gut microbiota directs dieting-induced weight loss trajectories. Gastroenterology 2021. https://doi.org/10.1053/j.gastro.2021.01.029.

[96] Al-Kindi SG, Brook RD, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. Nat Rev Cardiol 2020;17:656–72. https://doi.org/10.1038/s41569-020-0371-2.

[97] Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu N, et al. The lancet commission on pollution and health. Lancet 2018;391:462–512. https://doi.org/10.1016/S0140-6736(17)32345-0.

[98] Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2004;19:245–51. https://doi.org/10.1111/j.0269-2813.2004.01862.x.

[99] Biesiekierski JR, Rosella O, Rose R, Liels K, Barrett JS, Shepherd SJ, et al. Quantification of fructans, galacto-oligosacharides and other short-chain carbohydrates in processed grains and cereals. J Hum Nutr Diet 2011;24:154–76. https://doi.org/10.1111/j.1365-277X.2010.01139.x.

[100] Hunt R, Fedorak R, Frohlich J, McLennan C, Pavilanis A. Therapeutic role of dietary fibre. Can Fam Physician 1993;39:897–900 [903–10].

[101] Elia M, Cummings JH. Physiological aspects of energy metabolism and gastrointestinal effects of carbohydrates. Eur J Clin Nutr 2007;61(Suppl 1):S40–74. https://doi.org/10.1038/sj.ejcn.1602938.
[102] Morgan RL, Preidis GA, Kashyap PC, Weizman AV, Sadeghirad B, Chang Y, et al. Probiotics reduce mortality and morbidity in preterm, low birth weight infants: a systematic review and network meta-analysis of randomized trials. Gastroenterology 2020. https://doi.org/10.1053/j.gastro.2020.05.096.
[103] Korpela K, Helve O, Kolho K, Saisto T, Skogberg K, Dikareva E, et al. Maternal fecal microbiota transplantation in cesarean-born infants rapidly restores normal gut microbial development: a proof-of-concept study. Cell 2020;1–11. https://doi.org/10.1016/j.cell.2020.08.047.
[104] Paun A, Yau C, Meshkibaf S, Daigneault MC, Marandi L, Mortin-Toth S, et al. Association of HLA-dependent islet autoimmunity with systemic antibody responses to intestinal commensal bacteria in children. Sci Immunol 2019;4. https://doi.org/10.1126/sciimmunol.aau8125, eaau8125.
[105] Vatanen T, Kostic AD, D'Hennezel E, Siljander H, Franzosa EA, Yassour M, et al. Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. Cell 2016;165:842–53. https://doi.org/10.1016/j.cell.2016.04.007.
[106] Akil AA-S, Yassin E, Al-Maraghi A, Aliyev E, Al-Malki K, Fakhro KA. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. J Transl Med 2021;19:137. https://doi.org/10.1186/s12967-021-02778-6.
[107] Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. Hum Mol Genet 2019;28:R133–42. https://doi.org/10.1093/hmg/ddz187.
[108] Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016;15:1257–72. https://doi.org/10.1016/S1474-4422(16)30230-7.
[109] Nedergaard M, Goldman SA. Glymphatic failure as a final common pathway to dementia. Science 2020;370:50–6. https://doi.org/10.1126/science.abb8739.
[110] Toledo JB, Arnold M, Kastenmüller G, Chang R, Baillie RA, Han X, et al. Metabolic network failures in Alzheimer's disease: a biochemical road map. Alzheimers Dement 2017;13(9):965–84. https://doi.org/10.1016/j.jalz.2017.01.020.
[111] Overmyer KA, Evans CR, Qi NR, Minogue CE, Carson JJ, Chermside-Scabbo CJ, et al. Maximal oxidative capacity during exercise is associated with skeletal muscle fuel selection and dynamic changes in mitochondrial protein acetylation. Cell Metab 2015;21(3):468–78. https://doi.org/10.1016/j.cmet.2015.02.007.
[112] Jang C, Hui S, Zeng X, Cowan AJ, Wang L, Chen L, et al. Metabolite exchange between mammalian organs quantified in pigs. Cell Metab 2019;30(3):594–606.e3. https://doi.org/10.1016/j.cmet.2019.06.002.
[113] Ruiz-Casado A, Martín-Ruiz A, Pérez LM, Provencio M, Fiuza-Luces C, Lucia A. Exercise and the hallmarks of cancer. Trends Cancer 2017;3:423–41. https://doi.org/10.1016/j.trecan.2017.04.007.
[114] Fiuza-Luces C, Santos-Lozano A, Joyner M, Carrera-Bastos P, Picazo O, Zugaza JL, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. Nat Rev Cardiol 2018;15:731–43. https://doi.org/10.1038/s41569-018-0065-1.
[115] Motiani KK, Collado MC, Eskelinen J-J, Virtanen KA, LÖyttyniemi E, Salminen S, et al. Exercise training modulates gut microbiota profile and improves endotoxemia. Med Sci Sports Exerc 2020;52:94–104. https://doi.org/10.1249/MSS.0000000000002112.
[116] Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11:649–62. https://doi.org/10.1038/nrrheum.2015.91.

[117] Hopfner F, Künstner A, Müller SH, Künzel S, Zeuner KE, Margraf NG, et al. Gut microbiota in Parkinson disease in a northern German cohort. Brain Res 2017;1667:41–5. https://doi.org/10.1016/j.brainres.2017.04.019.
[118] Bullich C, Keshavarzian A, Garssen J, Kraneveld A, Perez-Pardo P. Gut vibes in Parkinson's disease: the microbiota-gut-brain axis. Mov Disord Clin Pract 2019;6:639–51. https://doi.org/10.1002/mdc3.12840.
[119] Minichino A, Brondino N, Solmi M, Del Giovane C, Fusar-Poli P, Burnet P, et al. The gut-microbiome as a target for the treatment of schizophrenia: a systematic review and meta-analysis of randomised controlled trials of add-on strategies. Schizophr Res 2021;234:1–13. https://doi.org/10.1016/j.schres.2020.02.012.
[120] Grizotte-Lake M, Zhong G, Duncan K, Kirkwood J, Iyer N, Smolenski I, et al. Commensals suppress intestinal epithelial cell retinoic acid synthesis to regulate interleukin-22 activity and prevent microbial dysbiosis. Immunity 2018;49:1103–1115.e6. https://doi.org/10.1016/j.immuni.2018.11.018.
[121] Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature 2013;500:232–6. https://doi.org/10.1038/nature12331.
[122] Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SSK, McCulle SL, et al. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci U S A 2011;108(Suppl. 1):4680–7. https://doi.org/10.1073/pnas.1002611107.
[123] Jefferson KK, Parikh HI, Garcia EM, Edwards DJ, Serrano MG, Hewison M, et al. Relationship between vitamin D status and the vaginal microbiome during pregnancy. J Perinatol 2019;39:824–36. https://doi.org/10.1038/s41372-019-0343-8.
[124] Casiraghi L, Spiousas I, Dunster GP, McGlothlen K, Fernández-Duque E, Valeggia C, et al. Moonstruck sleep: synchronization of human sleep with the moon cycle under field conditions. Sci Adv 2021;7. https://doi.org/10.1126/sciadv.abe0465, eabe0465.
[125] Helfrich-Förster C, Monecke S, Spiousas I, Hovestadt T, Mitesser O, Wehr TA. Women temporarily synchronize their menstrual cycles with the luminance and gravimetric cycles of the moon. Sci Adv 2021;7. https://doi.org/10.1126/sciadv.abe1358, eabe1358.
[126] Taxier LR, Gross KS, Frick KM. Oestradiol as a neuromodulator of learning and memory. Nat Rev Neurosci 2020;21:535–50. https://doi.org/10.1038/s41583-020-0362-7.
[127] Liu Y, Ding H, Ting CS, Lu R, Zhong H, Zhao N, et al. Exposure to air pollution and scarlet fever resurgence in China: a six-year surveillance study. Nat Commun 2020;11:1–13. https://doi.org/10.1038/s41467-020-17987-8.
[128] Daellenbach KR, Uzu G, Jiang J, Cassagnes L, Leni Z, Vlachou A, et al. Sources of particulate-matter air pollution and its oxidative potential in Europe. Nature 2020;587. https://doi.org/10.1038/s41586-020-2902-8.
[129] Alotaibi R, Bechle M, Marshall JD, Ramani T, Zietsman J, Nieuwenhuijsen MJ, et al. Traffic related air pollution and the burden of childhood asthma in the contiguous United States in 2000 and 2010. Environ Int 2019;127:858–67. https://doi.org/10.1016/j.envint.2019.03.041.
[130] Mccraty R, Atkinson M, Rein G, Watkins AD. Music enhances the effect of positive emotional states on salivary IgA. Stress Med 1996;12:167–75. https://doi.org/10.1002/(SICI)1099-1700(199607)12:3<167::AID-SMI697>3.0.CO;2-2.
[131] Kreutz G, Bongard S, Rohrmann S, Hodapp V, Grebe D. Effects of choir singing or listening on secretory immunoglobulin A, cortisol, and emotional state. J Behav Med 2004;27:623–35. https://doi.org/10.1007/s10865-004-0006-9.
[132] Greenberg DM, Decety J, Gordon I. The social neuroscience of music: understanding the social brain through human song. Am Psychol 2021. https://doi.org/10.1037/amp0000819.

[133] Nyein HYY, Bariya M, Kivimäki L, Uusitalo S, Liaw TS, Jansson E, et al. Regional and correlative sweat analysis using high-throughput microfluidic sensing patches toward decoding sweat. Sci Adv 2019;5. https://doi.org/10.1126/sciadv.aaw9906, eaaw9906.
[134] Yang Y, Song Y, Bo X, Min J, Pak OS, Zhu L, et al. A laser-engraved wearable sensor for sensitive detection of uric acid and tyrosine in sweat. Nat Biotechnol 2019. https://doi.org/10.1038/s41587-019-0321-x.
[135] Bayoumy K, Gaber M, Elshafeey A, Mhaimeed O, Dineen EH, Marvel FA, et al. Smart wearable devices in cardiovascular care: where we are and how to move forward. Nat Rev Cardiol 2021;18(8):581–99. https://doi.org/10.1038/s41569-021-00522-7.
[136] Van Rhijn I, Godfrey DI, Rossjohn J, Moody DB. Lipid and small-molecule display by CD1 and MR1. Nat Rev Immunol 2015;15:643–54. https://doi.org/10.1038/nri3889.
[137] Donia MS, Fischbach MA. Small molecules from the human microbiota. Science 2015;349:1254766. https://doi.org/10.1126/science.1254766.
[138] Ma C, Han M, Heinrich B, Fu Q, Zhang Q, Sandhu M, et al. Gut microbiome—mediated bile acid metabolism regulates liver cancer via NKT cells. Science 2018;876. https://doi.org/10.1126/science.aan5931.
[139] Nicolai S, Wegrecki M, Cheng T-Y, Bourgeois EA, Cotton RN, Mayfield JA, et al. Human T cell response to CD1a and contact dermatitis allergens in botanical extracts and commercial skin care products. Sci Immunol 2020;5. https://doi.org/10.1126/sciimmunol.aax5430, eaax5430.
[140] An D, Oh SF, Olszak T, Neves JF, Avci FY, Erturk-Hasdemir D, et al. Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells. Cell 2014;156:123–33. https://doi.org/10.1016/j.cell.2013.11.042.
[141] Linehan JL, Harrison OJ, Han S-J, Byrd AL, Vujkovic-Cvijin I, Villarino AV, et al. Non-classical immunity controls microbiota impact on skin immunity and tissue repair. Cell 2018;172:784–796.e18. https://doi.org/10.1016/j.cell.2017.12.033.
[142] Becker J, Burik CAP, Goldman G, Wang N, Jayashankar H, Bennett M, et al. Resource profile and user guide of the polygenic index repository. Nat Hum Behav 2021. https://doi.org/10.1038/s41562-021-01119-3.
[143] Pan H, Guo R, Ju Y, Wang Q, Zhu J, Xie Y, et al. A single bacterium resurrects the microbiome-immune balance to protect bones from destruction in a rat model of rheumatoid arthritis. Microbiome 2019;7:107. https://doi.org/10.1186/s40168-019-0719-1.
[144] Pan H, Li R, Li T, Wang J, Liu L. Whether probiotic supplementation benefits rheumatoid arthritis patients: a systematic review and meta-analysis. Engineering 2017;3:115–21. https://doi.org/10.1016/J.ENG.2017.01.006.
[145] O'Toole PW, Marchesi JR, Hill C, Na YC, Kim HS. Next-generation probiotics: the spectrum from probiotics to live biotherapeutics. Nat Microbiol 2017;2:17057. https://doi.org/10.1038/nmicrobiol.2017.57.