

Epidemiology  
Review Article

\*Both authors contributed equally to this manuscript.

**Cite this article:** Torp Austvoll C, Gallo V, Montag D (2020). Health impact of the Anthropocene: the complex relationship between gut microbiota, epigenetics, and human health, using obesity as an example. *Global Health, Epidemiology and Genomics* 5, e2, 1–10. <https://doi.org/10.1017/ghg.2020.2>

Received: 13 May 2018  
Revised: 13 December 2019  
Accepted: 17 February 2020



**Key words:**

Anthropocene; biodiversity loss; epigenetics; global health; microbiota; obesity

**Author for correspondence:**

Doreen Montag, E-mail: [d.montag@qmul.ac.uk](mailto:d.montag@qmul.ac.uk)

# Health impact of the Anthropocene: the complex relationship between gut microbiota, epigenetics, and human health, using obesity as an example

Cecilie Torp Austvoll<sup>1,\*</sup> , Valentina Gallo<sup>1,2,3,\*</sup> and Doreen Montag<sup>1</sup> 

<sup>1</sup>Centre for Primary Care and Public Health, Queen Mary University of London, London, UK; <sup>2</sup>London School of Hygiene and Tropical Medicine, London, UK and <sup>3</sup>School of Public Health, Imperial College London, London, UK

## Abstract

The growing prevalence of obesity worldwide poses a public health challenge in the current geological epoch, the Anthropocene. Global changes caused by urbanisation, loss of biodiversity, industrialisation, and land-use are happening alongside microbiota dysbiosis and increasing obesity prevalence. How alterations of the gut microbiota are associated with obesity and the epigenetic mechanism mediating this and other health outcome associations are in the process of being unveiled. Epigenetics is emerging as a key mechanism mediating the interaction between human body and the environment in producing disease. Evidence suggests that the gut microbiota plays a role in obesity as it contributes to different mechanisms, such as metabolism, body weight and composition, inflammatory responses, insulin signalling, and energy extraction from food. Consistently, obese people tend to have a different epigenetic profile compared to non-obese. However, evidence is usually scattered and there is a growing need for a structured framework to conceptualise this complexity and to help shaping complex solutions. In this paper, we propose a framework to analyse the observed associations between the alterations of microbiota and health outcomes and the role of epigenetic mechanisms underlying them using obesity as an example, in the current context of global changes within the Anthropocene.

## Introduction

In this paper, we will analyse the Anthropocene as the context in which human actions are continuously leading to global change that is resulting in mass-extinction and biodiversity loss. The anthropogenic planetary context is defining humans' experiences of health and well-being, their relationships with the environment, risks to and experiences of ill-health and diseases [1]. Biodiversity loss has a direct impact on human health [2]. One of the pathways of impact is related to the microbiota. Biodiversity loss is directly impacting the microbiota diversity of humans, soil and other species, which are interrelated [3]. Decreased diversity of the human gut microbiota during the development phase and during later life course can have several impacts on health outcomes [4,5]. One of the pathways of interaction between the human gut microbiota and health outcomes is through epigenetics. This can be exemplified through the current obesity epidemic. A framework capturing the complex interaction between the anthropogenic activities and their impact on health through the reduction of biodiversity and epigenetic changes has been constructed (Fig. 1).

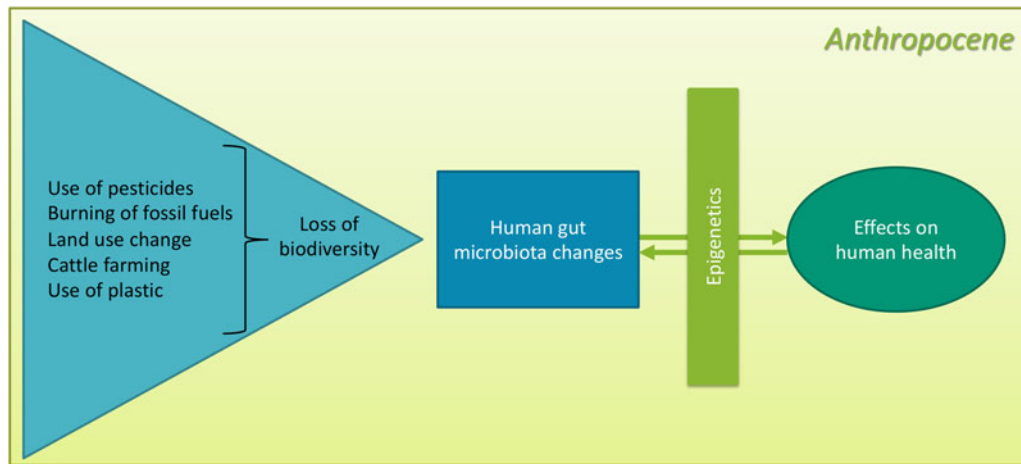
In this paper, the existing scientific evidence will be reviewed and analysed within this proposed framework, using obesity as an example. This paper addresses the growing interest in microbiota in relation to health that seems to be (partly) mediated via epigenetics. The paper gives an overview over existing data, providing advice for future research and public health directions on this topic.

## Anthropocene

The Anthropocene is the new geological epoch where anthropogenic activities, such as the burning of fossil fuels (technology and infrastructure) and land use change (agriculture and urbanisation), are shaping and have led to a dysbiosis in planetary processes [6, 7]. Anthropogenic activities led to a global change, including increased use of pesticides, use of plastics (a derivative of oil) and other contaminants that are polluting oceans, air and soil, leading to changes at the planetary scale [8].

Planetary changes include climate change and biodiversity loss [8]. Climate change has a direct impact on biodiversity, which, in turn, is impacting climate change through its central role in ecosystem health, regulating local and regional climate [9–13]. Deteriorated local,

© The Author(s) 2020. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Fig. 1.** Framework analysing the health effects of loss of biodiversity in the Anthropocene.

regional and planetary ecosystems play a central role in influencing population health, putting people at higher risk for a range of infectious and non-communicable diseases, such as obesity, which have gained more momentum in research since the WHO Ecosystem Millennium Assessment in 2005 [14], the WHO/CBD State of Knowledge Review on Biodiversity and Human Health [15] and particularly since Whitmee *et al.* [1] defining work on Planetary Health.

Biodiversity and genetic (intraspecies) and species loss are direct consequences of the global change in characterising the Anthropocene [13, 16]. It is impacting food security, microbial ecology and functionality, and, above all, human health [15]. Microbial ecology and functionality play a central role in the human microbiota gut, through interaction with environmental microbial diversity in soil and food over a life-span [7, 17–22]. Humans have evolved within the planetary system and are dependent upon its functioning local, regional and planetary ecosystems. Human gut microbiota and immune system have co-evolved due to exposure to various microbes in the surrounding environment [23], such as helminths; or, as Rook [24] defines them, as ‘immunoregulatory old friends’ which have been lost through global changes, biodiversity loss in the soil environment [25–27].

The impact of global change and biodiversity loss in the context of the Anthropocene on the human gut microbiota has not been directly analysed yet. While the Anthropocene can be defined as a dysbiosis of the planetary system, a dysbiosis of the human gut microbiota could be seen as a resemblance of this on an ecosystem level, indicating a systemic dysbiosis on the micro and macro levels of the planetary system.

### The human gut microbiota

The terms microbiota and microbiome are often used interchangeably. In this paper, the term microbiota is used to refer to all microorganisms that reside within the human body, and the term microbiome to their genomes and genetic information [28]. The average ratio of bacteria cells to human cells has been estimated to be 1:1 [29–31]. Most of the bacteria are located in the large intestine and on the human skin, with *Bacteroidetes* and *Firmicutes*, as main phyla accounting for >90% of the total gut microbiota [29].

The human microbiota gut is formed of phyla, bacterial species and strains, yeasts and other microbes [32]. It is important for maintaining human health, playing a role in proper digestion, synthesis of vitamins, production of neurotransmitters, absorption of minerals, regulating the immune system and inflammatory response while preserving the integrity of the gut epithelial barrier [33–37].

The development of the human gut microbiota composition in the first 2 years of life defines the immune system among other functions, central for child development and growth [28]. Several studies have found an association with lower diversity in the gut and chronic inflammation, thereby influencing obesity and other non-communicable diseases (NCDs), such as allergies, diabetes, cancer and some psychiatric disorders [16, 24–27, 38–47].

### The effects of the Anthropocene on the human gut microbiota

A recent review of geographical differences in gut microbiota with diet showed that people eating an omnivorous diet had a higher diversity of bacteria compared to vegetarians [48]. Moreover, gut microbiota composition differs widely according to a geographical area and between different ethnic groups within the same area, with the highest diversity of bacteria species encountered in the African population [48]. A comparative study of gut microbiota among Colombians, Europeans and Asians found that in Colombians, there is a tendency in *Firmicutes* diminishing with increasing body mass index (BMI), whereas no association was observed for *Bacteroidetes* [49]. Escobar *et al.* [49] pointed out that geography contributed to determining bacteria composition more than BMI or gender.

Research by McDade *et al.* [50] in a rural Ecuadorian Amazonian context found no existing chronic background inflammation among residents. Blackwell *et al.* [51] reported similar results among Bolivian Amazonian foraging horticulturalists with higher inflammatory indicators in younger age which are depleted in later years of life. Further research has shown that babies that have been exposed to unharmed infections (old friends) in early childhood have a stronger immune system and low chronic inflammation in later life [52, 53]. Similar results have been reported from other Ecuadorian Amazonian and Peruvian Amazonian contexts [54, 55]. Chronic background inflammation is directly related to metabolic disorders, of which obesity is one.

Recent studies on the diverse human gut microbial functional-ity have looked at the impact of ‘westernisation’ and industrialisation; how ‘cultural change’ have impacted human gut microbiota by looking at hunter-gather groups, people living in rural and urban contexts [56, 57]. Clemente *et al.* [56] analysed faeces, skin and oral samples among rural Yanomami people in the Venezuelan Amazon region. They demonstrated an even more diverse composition and with the lowest variability of human microbiota than those of ‘semitranscultured’ Guahibo Amerindians and Malawians. The microbiome was similar across Yanomami people than across other study participants. Clemente *et al.* [56] concluded that the way of living, having been isolated in the Amazon in contrast to a ‘semi-westernised’ lifestyle had an essential impact on the microbiota composition. Yatsunenko *et al.* [57] conducted a cohort study among Venezuelan Amazonian, rural Malawian and urban US people on the impact of microbiota between age and geography. They found a difference in ‘bacterial assemblage and functional gene repertoires’ (p. 222) between the first two more rural Venezuelan and Malawian and the urban US populations with similarities across age [57]. They concluded that a difference in the diet has contributed to the distinct adult microbiota. Diet then is associated with lifestyle and social structure [57]. In another study on seasonality and food consumption and impact on human gut microbiota among Hadza hunter-gatherers in Tanzania, Smits *et al.* [58] have demonstrated that seasonality and availability of food and food quality plays a role in the human gut microbiota among people with a very biodiverse and a highly functional human gut microbiota. Smits *et al.* [58] presented that while Firmicutes composition was the same during different seasons, Bacteroidetes operational taxonomic units changed. In comparison with 18 different populations from 16 distinct countries, they conclude that those from more agricultural and rural hunter-gatherer areas where higher in Prevotellaceae than those from urbanised and industrialised contexts. Commonalities were also found with the existence of Spirochaetaceae and Succinivibrionaceae among agricultural and rural areas, and the seasonal disappearance of Bacteroidetes taxa was shown similar to those generally encountered among people living in industrialised contexts [58]. They concluded that there is a substantial ‘cultural’ difference between human gut microbiota [58]. This evidence suggests that the analysis of the association between gut microbiota and obesity must be geographical location dependent, and the comparison between distant geographical locations would be invaluable in unveiling underlying mechanisms.

### Epigenetics and epigenetic pathways

Epigenetics is the study of heritable changes which affect gene functioning without modifying the DNA sequence [59, 60]. Epigenetic patterns are shaped dynamically throughout the life-course, and vary from cell types, in contrast to the genetic sequence. The ways epigenetic changes regulate DNA expression and cell maintenance are mainly attributed to the covalent modification of DNA by methylation [61].

Epigenetic mechanisms have been associated with the microbiota in their modulation of weight, metabolism, appetite control, insulin signalling and inflammation through metabolite production [62–67]. These mechanisms are gaining progressively more attention as potentially explaining the growing prevalence of obesity worldwide [34, 68].

There is evidence to show that epigenetics plays a vital role in transmitting obesity and type-2 diabetes risk to the offspring [69]. Current research has also shown that obese people tend to have different epigenetic patterns compared to non-obese, reinforcing the relative importance of epigenetics in the study of obesity [70–73].

### The role of the gut microbiota in human health using obesity as an example

The development of the early human gut microbiota and immune system and future influences through food intake are essential when approaching obesity. The modulation of host energy balance (intake and type of food, food behaviour, intestinal absorption, energy recovery from the diet and the anabolic/catabolic balance) and others have concluded that obesity can be viewed as a condition of persistent low-grade inflammation and inflammatory disease [74–78].

The obesity epidemic has become a primary global public health concern as the prevalence of obesity has been growing fast and steady since the 1970s, but at different rates across nations [39]. According to the most comprehensive analysis, by 2025, the global obesity prevalence will reach 18% in men and 21% in women, while severe obesity will reach 6% in men and 9% in women [79]. Within the global burden of obesity, global childhood obesity has risen dramatically over the last few decades: children are increasingly becoming heavier worldwide [80] and obese children are at higher risk of becoming obese and overweight adults [68].

Obesity is defined by an excessive accumulation of fat mass within the body [81]. According to the thrifty genotype hypothesis [82], the current human predisposition to fat accumulation is the result of an evolutionary selection of people with specific genetic combinations which have made them more resistant to the hunger/feast diet. This same genetic predisposition, in a modern obesogenic environment with constant access to food alongside urbanisation and sedentary lifestyles, has generated a higher prevalence of obesity and overweight [83]. There is also a link between mitochondrial abnormalities and metabolic disorders, such as obesity, diabetes and insulin resistance, suggesting that excessive energy stores have adverse effects on lipid and glucose metabolism, as it may decrease insulin sensitivity within muscle, liver and adipose tissue and thereby disrupting the balance between energy storage and expenditure [84–86]. Obesity has increased alongside the establishment of modern developed states, social welfare systems and economic structures [39, 87–89]. Current projections estimate a shifting burden of obesity towards the poorer and lower-income nations, as many of them are dramatically changing their diets towards high energy-dense foods often lacking essential nutrients [83].

Some genetic determinants play a role in the development of obesity; monogenic forms of severe early onset obesity in children have been described, such as Biedl syndrome or Prader–Willi syndrome [90]. The primary mechanism which has been suggested to explain – at least partially – these associations is an epigenetic modification of DNA expression [91]. The ways epigenetic changes regulate DNA expression and cell maintenance are mainly attributed to the covalent modification of DNA by methylation [91]. Current research has also shown that obese people tend to have different epigenetic patterns compared to non-obese, reinforcing the relative importance of epigenetics in the study of obesity [70–73, 92].

In humans, the microbiota composition is usually different in lean and obese people with obese having showed a reduction in Bacteroidetes accompanied by a rise in Firmicutes [34, 36, 62, 63, 66, 68, 93, 94]. Evidence shows that some bacteria, particular in the Firmicutes phyla, are better at harvesting energy from the food than other phyla and bacterial species thereby contributing to weight gain [34, 65, 68, 93]. Remely *et al.* [94] also found a significantly higher ratio of Firmicutes and Bacteroidetes in type-2 diabetics compared to lean controls and obese. Others have shown no difference between the two phyla in obese and lean controls [29, 34, 93], hence illustrating how a rise in phyla may indicate different results in different people or might be a consequence of status rather than a cause. Also, in the phyla of Firmicutes, there are both so-called beneficial bacteria and Gram negatives; hence, more research is needed to see what types of bacteria, strains and species within the phyla that are in particular linked to excess body weight or linked to changes in how bacteria extract energy from the diet.

A lack of diversity in the microbiota has been associated with dysbiosis in the gut and low-grade chronic inflammation that promotes metabolic disorders, such as obesity and type-2 diabetes in both humans and animals [34, 64, 94–96]. Importantly, the ecosystem of the microbiota continues to change throughout a life course and is likely to be affected by epigenetics [97]. Following, the microbiota is becoming increasingly more recognised as an influencer in epigenetic modifications that takes place throughout a life course [68]. With this, more research needs to be done in order to fully comprehend the relationship between epigenetics and obesity, in terms of what is the first modulator.

Epigenetic mechanisms have been associated with the microbiota in their modulation of weight, metabolism, appetite control, insulin signalling and inflammation through metabolite production [62–67]. These mechanisms are gaining progressively more attention as potentially explaining the growing prevalence of obesity worldwide [34, 68].

The combination of potential genetic/epigenetic, social and environmental risk factors for obesity, has prompted research to focus on the variation of individual risk within obesogenic environments; e.g. epigenetic processes that take place in early life, energy-rich environments such as infant over-nutrition, and maternal obesity, which can significantly increase the risk of obesity later in life [91]. This has contributed to a shift towards epigenetic mechanisms, and to how genes are regulated and expressed throughout a life course [98]. Nevertheless, epigenetic changes and obesity outcomes should be considered into a broader approach accounting for the complexity of the issue, new developments of understanding of the gut microbiota concerning biodiversity in surrounding environments and the importance of the gut microbiota in the context of the Anthropocene [25, 27, 73, 99].

### Early life factors

Some research has emphasised the importance of preserving the microbial ecology of the gastrointestinal tract during early development, i.e. pre-natal, in pregnant women and fetuses after birth. The microbiota development is expected to begin at birth when babies pass through the vaginal canal where they are exposed to the mother's bacteria and also through breastfeeding [68]. New research has also indicated that the colonisation of microbes may begin even before birth, as some live bacteria get

transferred across the placenta hence indicating the importance of nurturing the gut during pre-natal and during pregnancy [100].

It is estimated that humans establish their full microbiota within the first 2–3 years of life [28, 36, 66]. Increasing importance has been given to 'windows of opportunity' for preventing obesity and other metabolic disorders in early life. This might include proper nutrition during pregnancy and breastfeeding and avoiding antibiotics and caesarean section (C-section) whenever possible [28, 101–103]. Caesarean delivery has been associated with increased body mass in childhood and adolescence [104] and with an increased risk of both overweight and obesity in preschool children [105]. Exposure to antibiotics before 6 months of age or during infancy has been associated with increased body mass in healthy children [106]; and evidence suggests that antibiotics may permanently dysregulate foetal metabolic patterns as they can alter epigenetic pathways or maternal microbiota [106, 107]. The offspring of malnourished parents (either over- or under-nourished) have an increased risk of developing both diabetes 1 and 2 and obesity as a result of the changes in the gut microbiota and epigenetic markers [66, 108].

### Exposure to antibiotics *in utero* or very early life and risk of obesity

Prenatal exposure to antibiotics was found to be associated with childhood obesity [109, 110]. The association between antibiotic use and obesity was stronger in babies born with a higher birth weight (>3500 g), while the association with overweight was stronger among babies born smaller ( $\leq$ 3500 g) [109]. The association was maintained during all pregnancy period, without meaningful differences [110].

Early infancy exposure to antibiotics was consistently found to be associated with an increased risk of obesity later in life [106, 111, 112]. Cumulative exposure to broad-spectrum antibiotics in early life was found to be associated with an increased risk of obesity [112]. The effect was maintained in exposure at both very early ages (0–5 months) and later (5–11 months). Interestingly, narrow-spectrum antibiotics were not associated with an increased risk of obesity in any of the age groups considered, suggesting that they could not reach or alter the gut microbiota [112]. Consistently, macrolides, a type of broad-spectrum antibiotics were found to be more strongly associated with obesity compared to other molecules [106]. The association between antibiotic use within the first 24 months and obesity was found to be stronger in boys than girls, and with similar cumulative effects [106].

Antibiotics were found to modify the association between maternal and child body weight. In an analysis of the Danish National Birth Cohort, a strong association between maternal the BMI and child BMI at age 7 was found [111]. This could be explained through a different mechanism including genetic/epigenetic factors, social and behavioural, or through the transmission of gut microbiota at the time of delivery. Antibiotic use before age 6 months interacts with this association, increasing the risk of obesity in children born by normal weight mother, but decreasing it in children born by overweight one [111]. These results suggest that gut microbiota transmission might have a predominant role in explaining mother–child concordance for body weight.

### Caesarean section and risk of obesity

Delivery by C-section reduces the ability of the new born to come into contact with the vaginal and faecal microbiota of the mother

during birth. Therefore, they miss this physiological source of bacterial colonisation.

Delivery via C-section was consistently associated with an increased risk of obesity later in life [104, 105, 110, 113]. In meta-analysis, children born by C-section were more likely to be obese by the time they reach 5 years [113]. In one of the studies, by age 11, caesarean-delivered children had almost doubled risk of being overweight or obese. This association was stronger and longer lasting among children born from overweight/obese mothers than from normal-weight mothers [104]. This partially contradicts the interaction maternal-child weight with antibiotic use [111]. Risk estimate was similar for delivery by planned or emergency C-section [110]. To what extent C-section has also linked to alterations in the microbiota needs further examination.

### Mode of infant feeding and impact on gut microbiota and obesity

Breastfeeding contributes to the protection against obesity in children [114]. Breastfeeding at 1 month of age and for more than 6 months was associated with the maximum inverse associations, in one study [115]. Gut microbiota and its dysbiosis in very early ages were shown to play a vital role in this association, as infant exclusively breastfed or formula fed had radically different microbes profiles, with partially breastfed infants having an intermediate profile [116]. Interestingly, among partially breastfed infants, formula supplementation was associated with a profile similar to that of non-breastfed infants, whereas the introduction of complementary foods without formula was associated with a profile more similar to that of exclusively breastfed infants [116].

### Factors associated with obesity later in life

Through the life course, many factors have shown to have an impact on the microbiota, such as diet, nutrition, antibiotics, disease, genetics and exposure to medications [29]. Growing evidence also supports the association between human microbiota and obesity and several studies have demonstrated how the 'indigenous' gut microbiota plays a crucial role as an epigenetic regulator via epigenetic modifications that impact gene expression at different life stages [68].

There have been studies suggesting that an increase of members of the Firmicutes phylum leads to elevated short-chain fatty acids (SCFAs), such as butyrate, and increased energy extraction from the diet in addition to promoting the maintenance of the intestinal epithelium [68]. The SCFAs have been found to influence the epigenetic regulations of genes in obese subjects and how an epigenetic mechanism in the gut microbiota may be altered due to nutrition [108].

SCFAs are also believed to engage the epigenetic regulation of inflammatory reactions via a free fatty acid receptor (FFAR) and other short-chain fatty acid receptors [94]. They have also been linked to different levels of the satiety hormone, which could lead to an increase in food intake [36]. Besides, these may shape epigenetic mechanisms, and for example, butyrate is known as a potent histone deacetylase inhibitor thereby playing a role in metabolic processes [68]. There is also an association between the microbiota and T-cell differentiation linking gut dysbiosis to changes affecting the Th17/Treg balance under inflammatory digestive conditions and are also relevant in the early stages of obesity and insulin resistance [64].

Another way of modifying the gut microbiota is through diet. As our gut microbiota is very dynamic, it can easily be profoundly affected by external exposures, such as diet, lifestyle, epigenetics, genetics age, nutrition, medication and other environmental factors influencing the diversity of the gut microbiota [117, 118]. In mice, switching from low fat, plant-based diet rich in fibre, to a 'Western diet' high in fat and sugar altered the bacteria composition within a single day [45]. In humans, 'Western' high-fat diets have resulted in a reduction in Bacteroidetes and an increase in Firmicutes and foods high in fibre have shown to increase the phylum of Bacteroidetes and to a more diverse microbiota [34]. Others have shown that gut dysbiosis can be altered by a diet rich in non-digestible but fermentable carbohydrates, which were found to promote significant weight loss [90].

Several studies have stated that epigenetic processes in relation to the gut microbiota play a crucial position in the development of obesity and other metabolic disorders, as bacteria can cause changes in the DNA methylation patterns of host cells by providing epigenetically active metabolites and substances, and these metabolites are essential for DNA methylation so vital for humans [34, 35, 63–66, 68, 93, 94].

### Effects of diet and/or probiotic supplementation on the alteration in body composition and microbiota

The role of gut microbiota in diet-related obesity and some genetic forms of obesity has been investigated in a clinical trial including children with Prader–Willi syndrome and diet-related obesity [90]. A diet rich in non-digestible carbohydrates induced significant weight loss and concomitant structural changes of the gut microbiota in both groups, together with the alleviation of inflammation. This change was also accompanied by a relative increase of functional genome groups for acetate production from carbohydrates fermentation in the gut. These findings suggest a role of gut dysbiosis in obesity which is independent of the aetiology of the condition [90].

However, not all probiotics impact dysbiosis in the same way. Supplementation with galactooligosaccharides among overweight and obese men and women selectively increased the abundance of *Bifidobacterium* species in faeces by five-fold ( $p = 0.009$ ) [119]. However, this did not contribute to significant changes in insulin sensitivity, as no significant alterations in peripheral and adipose tissue, insulin sensitivity, body composition, energy and substrate metabolism were found [119].

A complex double-blind, randomised cross-over clinical trial was conducted to examine the exposure to probiotics on psychological state, eating behaviour and body composition among women [120]. Study subjects were classified as (1) metabolically obese/normal-weight [121]; (2) metabolically healthy/obese [122]; (3) metabolically unhealthy/obese or 'at risk' obese [120] and (4) normal weight obese syndrome [123]. An insufficient, but significant, reduction in BMI, body resistance, fat mass (kg and %) and a substantial increase in free fatty mass (kg and %) were observed in all normal-weight/obese and pre-obese/obese subjects after probiotic intake. In the same groups, a reduction of bacterial overgrowth syndrome and lower psychopathological scores were observed after the intervention [120].

### The role of the gut microbiota composition

A relative abundance of *Akkermansia muciniphila* was shown to be negatively associated with BMI in the animal models of

obese mice [124], in pregnant women [125, 126] and overweight children [127]. Interestingly, however, the same alteration was also observed in adults within the normal range of BMI: a stool sample of Korean twins who were either obese or diabetic but included a broad spectrum of phenotypes was analysed to explore the distribution of gut microbiota in relation to body weight [128]. For both clinical and microbial phenotypes, longitudinal samples (samples of the same individual taken over time) were more similar than those of twins; however, the twins were more similar than unrelated individuals. The abundance of *A. muciniphila* was negatively associated with BMI, fasting blood sugar and insulin levels [128].

Some changes in microbiota were shown to be causally related to obesity rather than the other way around, through clinical trials. A randomised, double-blind, placebo-controlled study to evaluate the efficacy of transglucosidase (TGD) in modulating blood glucose levels and body weight gain in patients with type-2 diabetes showed that the *Bacteroidetes-to-Firmicutes* ratio in the TGD groups significantly increased compared to the placebo group after 12 weeks. This, in turn, was associated with decreased blood glucose levels and prevention of body weight gain [129].

### The role of epigenetics in explaining the association between gut microbiota and obesity

The abundance of specific phyla and bacteria in the microbiome in association with epigenetic changes was studied in a pilot study on pregnant women [63]. The association between relative abundances of the predominant phyla in the gut microbiota and whole-genome methylation analysis was studied. DNA methylation patterns in white blood cells were associated with gut microbiota profiles, in particular comparing mothers with higher levels of *Firmicutes* with mothers with higher levels of *Bacteroidetes* and *Proteobacteria*. Pathway analysis revealed potential associations between gut microbiota relative abundance and cardiovascular diseases, inflammatory response, metabolic pathways and cancer.

Data from a Norwegian birth cohort of 552 children were used to sequence 16S rRNA genes on gut microbiota among 169 women, 4 days after delivery and 844 samples of their infants at six-time points during the first 2 years of life [130]. These data were used to measure how pre-pregnancy weight and gestational weight gain influence the gut microbiota of mothers during delivery and of their infants in early life. While maternal gut microbiota was found to vary according to pre-gestational weight and gestational weight change, these were only weakly associated with compositional differences in the gut microbiota of their infants [130].

Similarly, differences between 16S rRNA gene sequencing data across normal BMI, overweight and obese groups were found with diversity decreasing in the obese when compared with the normal group, with or without diet confounding factors, in a cross-sectional study in a Korean population [131].

Finally, a placebo-controlled intervention study to evaluate the effect of supplementation with GLP-1 agonists (glucagon-like peptide-1 agonists) on the bacteria composition in insulin-dependent type-2 diabetic individuals, obese and lean non-diabetic individuals using a methylation analysis was evaluated. In comparison with lean individuals, the abundance of *Faecalibacterium prausnitzii* and microbiota diversity was remarkably lower in obese and type-2 diabetic subjects. The analysis of five CpGs in the promoter region of FFAR3 showed significant lower methylation in obese and type-2 diabetics. It increased in obese patients throughout the period. These results

unveiled a substantial correlation between a higher BMI and lower methylation of FFAR3. Conversely, LINE-1, a marker of global methylation, indicated no significant differences between the three groups or the time points, although the methylation of type-2 diabetics tended to increase over time.

### Interactions of the gut microbiota, obesity and epigenetic mechanisms in the Anthropocene

More research has pointed out how our microbiota has geographical characteristics, thereby indicating that the geographic origin and environment also play a role concerning human ecosystems [56–58, 132] and that geography and ethnicity play a role in microbial composition in humans [117]. People living in industrialised societies have shown to have a different bacteria composition and often to be less diverse than non-urbanised and indigenous populations [55, 58]. Moreover, De Filippo *et al.* [133] analysed children from rural places in South-Saharan Africa eating a diet very high in fibre which showed a very different microbiota composition compared to European children, in which the children in Europe were more likely to have a dominance of *Firmicutes* compared to *Bacteroidetes*, which is similar to [58]. What this literature had in common was describing the differences based on the so-called ‘culture’ concerning lifestyle, such as ‘westernisation’ and geography, in terms of industrialised, urban, rural and isolated contexts.

Geography in this sense could be seen as an indicator for a functioning ecosystem, disturbed and destructed ecosystem if one looks at isolated Amazonian contexts, rural contexts in Amazonia and Malawi and urban contexts in the USA respectively. Anthropogenic actions altering planetary processes characterise the Anthropocene. Indigenous anthropogenic impact on the Amazon overall biodiversity and soil biodiversity has been demonstrated as increasing biodiversity for 4500 years [134, 135]. Deforestation is decreasing soil biodiversity [136]. None of soil diversity changes has been analysed in any of the studies. However, the consistency of the gut microbiota in humans have been developed and nurtured as a result of human interaction with nature, as in the form of early human settlement during the geographical epoch of the Holocene, with the development of agricultural practices and changes in dietary habits [25, 27]. Rook’s research [24–27, 38, 40–43] has been essential to our understanding of the co-evolution of the human gut microbiota with its environment. The importance of the soil diversity, particularly the existence of specific species ‘old friends’ as Rook points out and their loss during the Anthropocene need to be taken into account when analysing the development of human gut microbiota and geographical differences. Lifestyle seems to be a too simplistic explanation for a more systemic change with planetary consequences.

Moreover, research by Robinson *et al.* [137] is advocating for landscape architecture from a microbiome-ecosystem perspective, which is also supported by a meta-analysis on the positive aspects of gardening on human health [138]. These could then also be analysed from a One Health [139] perspective, including microbiota changes in different species and contexts, with a particular focus on obese cats and dogs [140–143]. Under this circumstance, obesity needs to be analysed in context, and we suggest as a consequence of a global change in the Anthropocene, summing events such as urbanisation, deforestation, transportation, land-use change, changes in agricultural practices, use of pesticides and loss of soil biodiversity [8, 144, 145].

## Conclusion

The role of the gut microbiota, obesity and epigenetic mechanisms is increasingly recognised. Obesity should be understood with environmental variables which are in turn embedded in the current context of global change and particularly biodiversity loss within the Anthropocene. Further research should take into account biodiversity, microbiota and epigenetic changes when developing new obesity research streams. These population-based approaches based on a systemic response should complement incentives to combat the growing obesity prevalence at the individual level. All interventions, including systemic, public health response to obesity will need to focus on building intersectional and interdisciplinary strategies that seek to understand the complexity of obesity in the Anthropocene.

**Conflict of interest.** The authors declare no conflict of interest.

**Ethical standards.** Not applicable.

## References

- Whitmee S, Haines A, Beyrer C, Boltz F, Capon AG, de Souza Dias BF, Ezeh A, Frumkin H, Gong P, Head P and Horton R (2015) Safeguarding human health in the Anthropocene epoch: report of the Rockefeller Foundation – Lancet Commission on Planetary Health. *The Lancet* **386**(10007), 1973–2028.
- Marselle MR, Stadler J, Korn H, Irvine KN and Bonn A (2019) *Biodiversity and Health in the Face of Climate Change*. Cham: Springer.
- Trevelline BK, Fontaine SS, Hartup BK and Kohl KD (2019) Conservation biology needs a microbial renaissance: a call for the consideration of host-associated microbiota in wildlife management practices. *Proceedings of the Royal Society B* **286**, 20182448.
- Haahtela T (2019) A biodiversity hypothesis. *Allergy* **74**(8), 1445–1456.
- Lindley SJ, Cook PA, Dennis M and Gilchrist A (2019) Biodiversity, physical health and climate change: a synthesis of recent evidence. *Biodiversity and Health in the Face of Climate Change*. Cham: Springer, pp. 17–46.
- Crutzen PJ (2016) Geology of mankind. In Crutzen PJ, Brauch HG (eds), *Paul J Crutzen: A Pioneer on Atmospheric Chemistry and Climate Change in the Anthropocene*. Springer, pp. 211–215.
- Gillings MR and Paulsen IT (2014) Microbiology of the Anthropocene. *Anthropocene* **5**, 1–8.
- Rockström J, Steffen W, Noone K, Persson Å, Chapin FSI, Lambin E, Lenton TM, Scheffer M, Folke C, Schellnhuber H, Joachim, Nykvist B, De Wit CA, Hughes T, Van der Leeuw S, Rodhe H, Sörlin S, Snyder PK, Costanza R, Svedin U, Falkenmark M, Karlberg L, Corell RW, Fabry VJ, Hansen J, Walker B, Liverman D, Richardson K, Crutzen P and Foley J (2009) Planetary boundaries: exploring the safe operating space for humanity. *Ecology and Society* **14**, 32.
- Cardinale BJ, Duffy JE, Gonzalez A, Hooper DU, Perrings C, Venail P, Narwani A, Mace GM, Tilman D, Wardle DA, Kinzig AP, Daily GC, Loreau M and Grace JB (2012) Biodiversity loss and its impact on humanity. *Nature* **486**, 59–67.
- Loreau M, Naeem S, Inchausti P, Bengtsson J, Grime JP, Hector A, Hooper DU, Huston Ma, Raffaelli D, Schmid B, Tilman D and Wardle Da (2001) Biodiversity and ecosystem functioning: current knowledge and future challenges. *Science (New York, NY)* **294**, 804–808.
- Naeem S, Bunker DE, Hector A, Loreau M and Perrings C (2009) *Biodiversity, Ecosystem Functioning, & Human Wellbeing*. Oxford, UK: Oxford University Press.
- Naeem S, Chazdon R, Duffy JE, Prager C, Worm B (2016) Biodiversity and human well-being: an essential link for sustainable development. *Proceedings of the Royal Society* **283**, 20162091.
- Seddou N, Mace GM, Naeem S, Tobias JA, Pigot AL, Cavanagh R, Mouillot D, Vause J and Walpole M (2016) Biodiversity in the Anthropocene: prospects and policy. *Proceedings of the Royal Society* **283**, 20162094.
- WHO (2005) *Ecosystems and Human Well-Being. Health Synthesis. A Report of the Millennium Ecosystem Assessment*. Geneva: World Health Organization.
- WHO/CBD (2015) *Connecting Global Priorities: Biodiversity and Human Health. A State of Knowledge Review: World Health Organization and Secretariat of the Convention on Biological Diversity*.
- Johnson CN, Balmford A, Brook BW, Buettel JC, Galetti M, Guangchun L and Wilmshurst JM (2017) Biodiversity losses and conservation responses in the Anthropocene. *Science (New York, N.Y.)* **356**(6335), 270–275.
- Bell T, Gessner MO, Griffiths RI, McLaren JR, Morin PJvan der Heijden M and van der Putten W (2009) Microbial biodiversity and ecosystem functioning under controlled conditions and in the wild. In Naeem S, Bunker DE, Hector A, Loreau M and Perrings C (eds), *Biodiversity, Ecosystem Functioning, and Human Wellbeing: An Ecological and Economic Perspective Oxford*. Oxford (UK): Oxford University Press, pp. 121–133.
- Clavel T, Lagkouvardos I, Blaut M and Stecher B (2016) The mouse gut microbiome revisited: from complex diversity to model ecosystems. *International Journal of Medical Microbiology* **306**, 316–327.
- Gordo I (2019) Evolutionary change in the human gut microbiome: from a static to a dynamic view. *PLoS Biology* **17**, e3000126.
- Heiman ML and Greenway FL (2016) A healthy gastrointestinal microbiome is dependent on dietary diversity. *Molecular Metabolism* **5**, 317–320.
- Lozupone CA, Stombaugh J, Gonzalez A, Ackermann G, Wendel D, Vázquez-Baeza Y, Jansson JK, Gordon JI and Knight R (2013) Meta-analyses of studies of the human microbiota. *Genome Research* **23**, 1704–1714.
- Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK and Knight R (2012) Diversity, stability and resilience of the human gut microbiota. *Nature* **489**, 220–230.
- Davenport ER, Sanders JG, Song SJ, Amato KR, Clark AG and Knight R (2017) The human microbiome in evolution. *BMC Biology* **15**, 127.
- Rook GA and Brunet LR (2005) Old friends for breakfast. *Clinical and Experimental Allergy* **35**, 841–842.
- Rook GA (2013) Regulation of the immune system by biodiversity from the natural environment: an ecosystem service essential to health. *Proceedings of the National Academy of Sciences* **110**, 18360–7.
- Rook GA, Raison CL and Lowry CA (2014) Microbiota, immunoregulatory old friends and psychiatric disorders. In Lyte M and Cryan JF (eds), *Microbial Endocrinology: The Microbiota-Gut-Brain Axis in Health and Disease*. Switzerland: Springer, pp. 319–356.
- Rook GA and Knight R (2015) Environmental microbial diversity and noncommunicable diseases. In WHO/CBD, editor. *Connecting Global Priorities: Biodiversity and Human Health A State of Knowledge Review*. World Health Organization and Secretariat of the Convention on Biological Diversity, pp. 151–164.
- Robertson RC, Manges AR, Finlay BB and Prendergast AJ (2018) The human microbiome and child growth – first 1000 days and beyond. *Trends in Microbiology* **27**, 131–147.
- Baothman OA, Zamzami MA, Taher I, Abubaker J and Abu-Farha M (2016) The role of gut microbiota in the development of obesity and diabetes. *Lipids in Health and Disease* **15**, 108.
- Sender R, Fuchs S and Milo R (2016) Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology* **14**, e1002533.
- Whiteside SA, Razvi H, Dave S, Reid G and Burton JP (2015) The microbiome of the urinary tract – a role beyond infection. *Nature Reviews Urology* **12**, 81.
- Ley RE, Peterson DA and Gordon JI (2006) Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell* **124**, 837–848.
- Brandtzaeg P (2010) Homeostatic impact of indigenous microbiota and secretory immunity. *Beneficial Microbes* **1**, 211–227.
- Harakeh SM, Khan I, Kumosani T, Barbour E, Almasaudi SB, Bahijri SM, Alfadul SM, Ajabnoor G and Azhar EI (2016) Gut microbiota: a contributing factor to obesity. *Frontiers in Cellular and Infection Microbiology* **6**, 95.
- Kasubuchi M, Hasegawa S, Hiramatsu T, Ichimura A and Kimura I (2015) Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. *Nutrients* **7**, 2839–2849.

36. Soderborg TK, Borengasser SJ, Barbour LA and Friedman JE (2016) Microbial transmission from mothers with obesity or diabetes to infants: an innovative opportunity to interrupt a vicious cycle. *Diabetologia* **59**, 895–906.
37. Soderborg TK, Clark SE, Mulligan CE, Janssen RC, Babcock L, Ir D, Lemas DJ, Johnson LK, Weir T and Lenz LL (2018) The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD. *Nature Communications* **9**, 4462.
38. Bloomfield SF, Rook GA, Scott EA, Shanahan F, Stanwell-Smith R and Turner P (2016) Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. *Perspectives in Public Health* **136**, 213–224.
39. Offer A, Pechey R and Ulijaszek S (2010) Obesity under affluence varies by welfare regimes: the effect of fast food, insecurity, and inequality. *Economics and Human Biology* **8**, 297–230.
40. Rook G and Brunet L (2005) Microbes, immunoregulation, and the gut. *Gut* **54**, 317–320.
41. Rook GA (2007) The hygiene hypothesis and the increasing prevalence of chronic inflammatory disorders. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **101**, 1072–1074.
42. Rook GA (2009) Review series on helminths, immune modulation and the hygiene hypothesis: the broader implications of the hygiene hypothesis. *Immunology* **126**, 3–11.
43. Rook G (2010) 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: Darwinian medicine and the ‘hygiene’ or ‘old friends’ hypothesis. *Clinical and Experimental Immunology* **160**, 70–79.
44. Turnbaugh PJ (2017) Microbes and diet-induced obesity: fast, cheap, and out of control. *Cell Host & Microbe* **21**, 278–281.
45. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA and Affourtit JP (2009) A core gut microbiome in obese and lean twins. *Nature* **457**, 480.
46. Walters WA, Xu Z and Knight R (2014) Meta-analyses of human gut microbes associated with obesity and IBD. *FEBS Letters* **588**, 4223–4233.
47. Cornejo-Pareja I, Muñoz-Garach A, Clemente-Postigo M and Tinahones FJ (2019) Importance of gut microbiota in obesity. *European Journal of Clinical Nutrition* **72**, 26–37.
48. Senghor B, Sokhna C, Ruimy R and Lagier J-C (2018) Gut microbiota diversity according to dietary habits and geographical provenance. *Human Microbiome Journal* **7**, 1–9.
49. Escobar JS, Klotz B, Valdes BE and Agudelo GM (2014) The gut microbiota of Colombians differs from that of Americans, Europeans and Asians. *BMC Microbiology* **14**, 311.
50. McDade TW, Tallman PS, Madimenos FC, Liebert MA, Cepon TJ, Sugiyama LS and Snodgrass JJ (2012) Analysis of variability of high sensitivity C-reactive protein in lowland Ecuador reveals no evidence of chronic low-grade inflammation. *American Journal of Human Biology* **24**, 675–681.
51. Blackwell AD, Trumble BC, Maldonado Suarez I, Stieglitz J, Beheim B, Snodgrass JJ, Kaplan H and Gurven M (2016) Immune function in Amazonian horticulturalists. *Annals of Human Biology* **43**, 382–396.
52. McDade TW, Georgiev AV and Kuzawa CW (2016) Trade-offs between acquired and innate immune defenses in humans. *Evolution, Medicine and Public Health* **2016**, 1–16.
53. McDade TW, Ryan C, Jones MJ, MacIsaac JL, Morin AM, Meyer JM, Borja JB, Miller GE, Kobor MS and Kuzawa CW (2017) Social and physical environments early in development predict DNA methylation of inflammatory genes in young adulthood. *Proceedings of the National Academy of Sciences* **114**, 7611–7616.
54. Tallman P (2018) “Now we live for the money”: shifting markers of status, stress, and immune function in the Peruvian Amazon. *Ethos (Berkeley, California)* **46**, 134–157.
55. Urlacher SS, Ellison PT, Sugiyama LS, Pontzer H, Eick G, Liebert MA, Cepon-Robins TJ, Gildner TE and Snodgrass JJ (2018) Tradeoffs between immune function and childhood growth among Amazonian forager-horticulturalists. *Proceedings of the National Academy of Sciences* **115**, E3914–E3921.
56. Clemente JC, Pehrsson EC, Blaser MJ, Sandhu K, Gao Z, Wang B, Magris M, Hidalgo G, Contreras M and Noya-Alarcón Ó (2015) The microbiome of uncontacted Amerindians. *Science Advances* **1**, e1500183.
57. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN and Anokhin AP (2012) Human gut microbiome viewed across age and geography. *Nature* **486**(7402), 222.
58. Smits SA, Leach J, Sonnenburg ED, Gonzalez CG, Lichtman JS, Reid G, Knight R, Manjurano A, Changalucha J and Elias JE (2017) Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania. *Science (New York, N.Y.)* **357**(6353), 802–806.
59. Bird A (2007) Perceptions of epigenetics. *Nature* **447**(7143), 396.
60. Lock M, Burke W, Dupré J, Landecker H, Livingston J, Martin P, Meloni M, Pálsson G, Rapp R and Weiss K (2015) Comprehending the body in the era of the epigenome. *Current Anthropology* **56**, 163–164.
61. Gluckman P and Hanson M (2009) Developmental and epigenetic pathways to obesity: an evolutionary-developmental perspective. *International Journal of Obesity* **32**(S7), S62.
62. Dhurandhar EJ and Keith SW (2014) The aetiology of obesity beyond eating more and exercising less. *Best Practice & Research Clinical Gastroenterology* **28**, 533–544.
63. Kumar H, Lund R, Laiho A, Lundelin K, Ley RE, Isolauri E and Salminen S (2014) Gut microbiota as an epigenetic regulator: pilot study based on whole-genome methylation analysis. *MBio* **5**, e02113–14.
64. Luo A, Leach ST, Barres R, Hesson LB, Grimm MC and Simar D (2017) The microbiota and epigenetic regulation of T helper 17/regulatory T cells: in search of a balanced immune system. *Frontiers in Immunology* **8**, 417.
65. Paul B, Barnes S, Demark-Wahnefried W, Morrow C, Salvador C, Skibola C and Tollefsbol TO (2015) Influences of diet and the gut microbiome on epigenetic modulation in cancer and other diseases. *Clinical Epigenetics* **7**, 112.
66. Nielsen JH, Haase TN, Jaksch C, Nalla A, Sostrup B, Nalla AA, Larsen L, Rasmussen M, Dalgaard LT and Gaarn LW (2014) Impact of fetal and neonatal environment on beta cell function and development of diabetes. *Acta Obstetrica et Gynecologica Scandinavica* **93**, 1109–1122.
67. Youngson NA and Morris MJ (2013) What obesity research tells us about epigenetic mechanisms. *Philosophical Transactions of the Royal Society B: Biological Sciences* **368**, 20110337.
68. Chang L and Neu J (2015) Early factors leading to later obesity: interactions of the microbiome, epigenome, and nutrition. *Current Problems in Pediatric and Adolescent Health Care* **45**, 134–142.
69. Baskaran C and Kandemir N (2018) Update on endocrine aspects of childhood obesity. *Current Opinion in Endocrinology, Diabetes and Obesity* **25**, 55–60.
70. Dalgaard K, Landgraf K, Heyne S, Lempradl A, Longinotto J, Gossens K, Ruf M, Orthofer M, Strogantsev R and Selvaraj M (2016) Trim28 haploinsufficiency triggers bi-stable epigenetic obesity. *Cell* **164**, 353–364.
71. Stenvinkel P (2014) Obesity – a disease with many aetiologies disguised in the same oversized phenotype: has the overeating theory failed? *Nephrology Dialysis Transplantation* **30**, 1656–1664.
72. Herrera BM, Keildson S and Lindgren CM (2011) Genetics and epigenetics of obesity. *Maturitas* **69**, 41–49.
73. Prescott S and Logan A (2017) Down to earth: planetary health and biophilosophy in the symbiocene epoch. *Challenges* **8**, 19.
74. Cox AJ, West NP and Cripps AW (2015) Obesity, inflammation, and the gut microbiota. *The Lancet Diabetes & Endocrinology* **3**, 207–215.
75. Boulangé CL, Neves AL, Chilloux J, Nicholson JK and Dumas M-E (2016) Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Medicine* **8**, 42.
76. Divella R, De Luca R, Abbate I, Naglieri E and Daniele A (2016) Obesity and cancer: the role of adipose tissue and adipo-cytokines-induced chronic inflammation. *Journal of Cancer* **7**, 2346.
77. Saltiel AR and Olefsky JM (2017) Inflammatory mechanisms linking obesity and metabolic disease. *The Journal of Clinical Investigation* **127**, 1–4.



78. Wensveen FM, Valentić S, Šestan M, Turk Wensveen T and Polić B (2015) The “big bang” in obese fat: events initiating obesity-induced adipose tissue inflammation. *European Journal of Immunology* **45**, 2446–2456.
79. Collaboration NRF (2016) Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *The Lancet* **387**, 1377–1396.
80. Baker JL, Olsen LW and Sørensen TI (2007) Childhood body-mass index and the risk of coronary heart disease in adulthood. *New England Journal of Medicine* **357**, 2329–2337.
81. WHO (2016) Obesity and Overweight Factsheet. Geneva: World Health Organisation; 2016 [updated 23.07.2017]. Available at <http://www.who.int/mediacentre/factsheets/fs311/en/>.
82. Neel JV (1962) Diabetes mellitus: a “thrifty” genotype rendered detrimental by “progress”? *American Journal of Human Genetics* **14**, 353.
83. Popkin BM and Gordon-Larsen P (2004) The nutrition transition: worldwide obesity dynamics and their determinants. *International Journal of Obesity* **28**, S2.
84. Bournat JC and Brown CW (2010) Mitochondrial dysfunction in obesity. *Current Opinion in Endocrinology, Diabetes, and Obesity* **17**, 446.
85. Lahera V, de las Heras N, López-Farré A, Manucha W and Ferder L (2017) Role of mitochondrial dysfunction in hypertension and obesity. *Current Hypertension Reports* **19**, 11.
86. Sivitz WI and Yorek MA (2010) Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. *Antioxidants & Redox Signaling* **12**, 537–577.
87. Ulijaszek SJ (2017) *Models of Obesity: From Ecology to Complexity in Science and Policy*. Cambridge: Cambridge University Press.
88. Ulijaszek SJ and Lofink H (2006) Obesity in biocultural perspective. *Annual Review of Anthropology* **35**, 337–360.
89. Ulijaszek S, McLennan A and Graff H (2016) Conceptualizing ecobio-social interactions: Lessons from obesity. In Singer M (ed.), *A Companion to the Anthropology of Environmental Health*. UK: John Wiley & Sons, pp. 83–100.
90. Zhang Y-J, Li S, Gan R-Y, Zhou T, Xu D-P and Li H-B (2015) Impacts of gut bacteria on human health and diseases. *International Journal of Molecular Sciences* **16**, 7493–7519.
91. Gluckman P and Hanson M (2009) Developmental and epigenetic pathways to obesity: an evolutionary-developmental perspective. *International Journal of Obesity* **32**, S62.
92. Warin M, Moore V, Davies M and Ulijaszek S (2016) Epigenetics and obesity: the reproduction of habitus through intracellular and social environments. *Body & Society* **22**, 53–78.
93. Goni L, Cuervo M, Milagro FI and Martínez JA (2015) Future perspectives of personalized weight loss interventions based on nutrigenetic, epigenetic, and metagenomic data. *The Journal of Nutrition* **146**, 905S–912S.
94. Remely M, Aumueller E, Merold C, Dworzak S, Hippe B, Zanner J, Pointner A, Brath H and Haslberger AG (2014) Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity. *Gene* **537**, 85–92.
95. Lakhan SE and Kirchgessner A (2011) Gut microbiota and sirtuins in obesity-related inflammation and bowel dysfunction. *Journal of Translational Medicine* **9**, 202.
96. Larsen N, Vogensen FK, Van Den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH and Jakobsen M (2010) Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS ONE* **5**, e9085.
97. Cureau N, AlJahdali N, Vo N and Carbonero F (2016) Epigenetic mechanisms in microbial members of the human microbiota: current knowledge and perspectives. *Epigenomics* **8**, 1259–1273.
98. Palou A and Bonet ML (2013) Challenges in obesity research. *Nutricion Hospitalaria* **28**, 144–153.
99. von Hertzen L, Beutler B, Bienenstock J, Blaser M, Cani PD, Eriksson J, Farkkila M, Haahela T, Hanski I, Jenmalm MC, Kere J, Knip M, Kontula K, Koskenvuo M, Ling C, Mandrup-Poulsen T, von Mutius E, Makela MJ, Paunio T, Pershagen G, Renz H, Rook G, Saarela M, Vaarala O, Veldhoen M and de Vos WM (2015) Helsinki alert of biodiversity and health. *Annals of Medicine* **47**, 218–225.
100. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J and Versalovic J (2014) The placenta harbors a unique microbiome. *Science Translational Medicine* **6**, 237–265.
101. Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV and Knight R (2018) Current understanding of the human microbiome. *Nature Medicine* **24**, 392.
102. Mischke M and Plösch T (2013) More than just a gut instinct – the potential interplay between a baby’s nutrition, its gut microbiome, and the epigenome. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* **304**, R1065–R1099.
103. Nauta AJ, Ben Amor K, Knol J, Garsen J and Van der Beek E (2013) Relevance of pre- and postnatal nutrition to development and interplay between the microbiota and metabolic and immune systems. *The American Journal of Clinical Nutrition* **98**, 586S–593S.
104. Blustein J, Attina T, Liu M, Ryan AM, Cox LM, Blaser MJ and Trasande L (2013) Association of caesarean delivery with child adiposity from age 6 weeks to 15 years. *International Journal of Obesity* **37**, 900.
105. Rutayisire E, Wu X, Huang K, Tao S, Chen Y and Tao F (2016) Cesarean section may increase the risk of both overweight and obesity in preschool children. *BMC Pregnancy and Childbirth* **16**, 338.
106. Saari A, Virta LJ, Sankilampi U, Dunkel L and Saxen H (2015) Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. *Pediatrics* **135**, 617–626.
107. Azad MB, Moossavi S, Owora A and Sepehri S (2017) Early-life antibiotic exposure, gut microbiota development, and predisposition to obesity. *Intestinal Microbiome: Functional Aspects in Health and Disease*. 88th Nestlé Nutrition Institute Workshop. Basel: Karger Publishers, pp. 67–80.
108. Canani RB, Di Costanzo M, Leone L, Bedogni G, Brambilla P, Cianfarani S, Nobili V, Pietrobelli A and Agostoni C (2011) Epigenetic mechanisms elicited by nutrition in early life. *Nutrition Research Reviews* **24**, 198–205.
109. Mor A, Antonsen S, Kahlert J, Holsteen V, Jørgensen S, Holm-Pedersen J, Sørensen H, Pedersen O and Ehrenstein V (2015) Prenatal exposure to systemic antibacterials and overweight and obesity in Danish schoolchildren: a prevalence study. *International Journal of Obesity* **39**, 1450.
110. Mueller NT, Whyatt R, Hoepner L, Oberfield S, Dominguez-Bello MG, Widén E, Hassoun A, Perera F and Rundle A (2015) Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. *International Journal of Obesity* **39**, 665.
111. Ajslev T, Andersen C, Gamborg M, Sørensen T and Jess T (2011) Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *International Journal of Obesity* **35**, 522.
112. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A and DeRusso PA (2014) Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatrics* **168**, 1063–1069.
113. Keag OE, Norman JE and Stock SJ (2018) Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: systematic review and meta-analysis. *PLoS Medicine* **15**, e1002494.
114. Yan J, Liu L, Zhu Y, Huang G and Wang PP (2014) The association between breastfeeding and childhood obesity: a meta-analysis. *BMC Public Health* **14**, 1267.
115. Wang L, Collins C, Ratliff M, Xie B and Wang Y (2017) Breastfeeding reduces childhood obesity risks. *Childhood Obesity* **13**, 197–204.
116. Forbes JD, Azad MB, Vehling L, Tun HM, Konya TB, Guttman DS, Field CJ, Lefebvre D, Sears MR and Becker AB (2018) Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life. *JAMA Pediatrics* **172**, e181161.
117. Gupta VK, Paul S and Dutta C (2017) Geography, ethnicity or subsistence-specific variations in human microbiome composition and diversity. *Frontiers in Microbiology* **8**, 1162.
118. Ley RE, Turnbaugh PJ, Klein S and Gordon JI (2006) Microbial ecology: human gut microbes associated with obesity. *Nature* **444**, 1022.
119. Canfora EE, van der Beek CM, Hermes GD, Goossens GH, Jocken JW, Holst JJ, van Eijk HM, Venema K, Smidt H and Zoetendal EG (2017)

- Supplementation of diet with galacto-oligosaccharides increases Bifidobacteria, but not insulin sensitivity, in obese pediatric individuals. *Gastroenterology* **153**, 87–97, e3.
120. **De Lorenzo A, Costacurta M, Merra G, Gualtieri P, Cioccoloni G, Marchetti M, Varvaras D, Docimo R and Di Renzo L** (2017) Can psychobiotics intake modulate psychological profile and body composition of women affected by normal weight obese syndrome and obesity? A double blind randomized clinical trial. *Journal of Translational Medicine* **15**, 135.
  121. **Seo MH and Rhee E-J** (2014) Metabolic and cardiovascular implications of a metabolically healthy obesity phenotype. *Endocrinology and Metabolism* **29**, 427–434.
  122. **O'Connell J, Lynch L, Cawood TJ, Kwasnik A, Nolan N, Geoghegan J, McCormick A, O'Farrelly C and O'Shea D** (2010) The relationship of omental and subcutaneous adipocyte size to metabolic disease in severe obesity. *PLoS ONE* **5**, e9997.
  123. **Di Renzo L, Sarlo F, Petramala L, Iacopino L, Monteleone G, Colica C and De Lorenzo A** (2013) Association between  $-308$  G/A TNF- $\alpha$  polymorphism and appendicular skeletal muscle mass Index as a marker of sarcopenia in normal weight obese syndrome. *Disease Markers* **35**, 615–623.
  124. **Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG and Delzenne NM** (2013) Crosstalk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proceedings of the National Academy of Sciences* **110**, 9066–9071.
  125. **Collado MC, Isolauri E, Laitinen K and Salminen S** (2008) Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. *The American Journal of Clinical Nutrition* **88**, 894–899.
  126. **Santacruz A, Collado MC, Garcia-Valdes L, Segura M, Martin-Lagos J, Anjos T, et al.** (2010) Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *British Journal of Nutrition* **104**, 83–92.
  127. **Karlsson F, Tremaroli V, Nielsen J and Bäckhed F** (2013) Assessing the human gut microbiota in metabolic diseases. *Diabetes* **62**, 3341–3349.
  128. **Yassour M, Lim MY, Yun HS, Tickle TL, Sung J, Song Y-M, Lee K, Franzosa EA, Morgan XC and Gevers D** (2016) Sub-clinical detection of gut microbial biomarkers of obesity and type 2 diabetes. *Genome Medicine* **8**, 17.
  129. **Sasaki M, Ogasawara N, Funaki Y, Mizuno M, Iida A, Goto C, Koikeda S, Kasugai K and Joh T** (2013) Transglucosidase improves the gut microbiota profile of type 2 diabetes Mellitus patients: a randomized double-blind, placebo-controlled study. *BMC Gastroenterology* **13**, 81.
  130. **Stanislawski MA, Dabelea D, Wagner BD, Sontag MK, Lozupone CA and Eggesbø M** (2017) Pre-pregnancy weight, gestational weight gain, and the gut microbiota of mothers and their infants. *Microbiome* **5**, 113.
  131. **Yun Y, Kim H-N, Kim SE, Heo SG, Chang Y, Ryu S, Shin H and Kim H-L** (2017) Comparative analysis of gut microbiota associated with body mass index in a large Korean cohort. *BMC Microbiology* **17**, 151.
  132. **Blackwell AD, Pryor G, Pozo J, Tiwia W and Sugiyama LS** (2009) Growth and market integration in Amazonia: a comparison of growth indicators between Shuar, Shiwar, and nonindigenous school children. *American Journal of Human Biology* **21**, 161–171.
  133. **De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G and Lionetti P** (2010) Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proceedings of the National Academy of Sciences* **107**, 14691–6.
  134. **Demetrio WC, Conrado AC, Acioli A, Ferreira AC, Bartz ML, James SW, da Silva E, Maia LS, Martins GC and Macedo RS** (2019) Anthropogenic soils promote biodiversity in Amazonian rainforests. *BioRxiv*, 552364.
  135. **Maezumi SY, Alves D, Robinson M, de Souza JG, Levis C, Barnett RL, de Oliveira EA, Urrego D, Schaan D and Iriarte J** (2018) The legacy of 4,500 years of polyculture agroforestry in the Eastern Amazon. *Nature Plants* **4**, 540.
  136. **Franco AL, Sobral BW, Silva AL and Wall DH** (2018) Amazonian deforestation and soil biodiversity. *Conservation Biology* **33**, 590–600.
  137. **Robinson J, Mills J and Breed M** (2018) Walking ecosystems in microbiome-inspired green infrastructure: an ecological perspective on enhancing personal and planetary health. *Challenges* **9**, 40.
  138. **Soga M, Gaston KJ and Yamaura Y** (2017) Gardening is beneficial for health: a meta-analysis. *Preventive Medicine Reports* **5**, 92–99.
  139. **Zinsstag J, Schelling E, Waltner-Toews D, Whittaker M and Tanner M** (2015) *One Health: The Theory and Practice of Integrated Health Approaches*. Oxfordshire and Boston: CABI, 447 p.
  140. **Salas-Mani A, Jeusette I, Castillo I, Manuelian CL, Lionnet C, Iraculis N, Sanchez N, Fernández S, Vilaseca L and Torre C** (2018) Fecal microbiota composition changes after a BW loss diet in beagle dogs. *Journal of Animal Science* **96**, 3102–3111.
  141. **Forster GM, Stockman J, Noyes N, Heuberger AL, Broeckling CD, Bantle CM and Ryan EP** (2018) A comparative study of serum biochemistry, metabolome and microbiome parameters of clinically healthy, normal weight, overweight, and obese companion dogs. *Topics in Companion Animal Medicine* **33**, 126–135.
  142. **Omatsu T, Omura M, Katayama Y, Kimura T, Okumura M, Okumura A, Murata Y and Mizutani T** (2018) Molecular diversity of the faecal microbiota of toy poodles in Japan. *Journal of Veterinary Medical Science* **80**, 749–754.
  143. **Pallotto MR, De Godoy MR, Holscher HD, Buff PR and Swanson KS** (2018) Effects of weight loss with a moderate-protein, high-fiber diet on body composition, voluntary physical activity, and fecal microbiota of obese cats. *American Journal of Veterinary Research* **79**, 181–190.
  144. **Montag D, Kuch U, Rodriguez L and Müller R** (2017) Overview of the Panel on Biodiversity and Health under Climate Change In: Diversity CoB, editor. *The Lima Declaration on Biodiversity. Climate Change: Contributions from Science to Policy for Sustainable Development. CBD Technical Series: Convention of Biological Diversity*, pp. 91–108.
  145. **Tasnim N, Abulizi N, Pither J, Hart MM and Gibson DL** (2017) Linking the gut microbial ecosystem with the environment: does gut health depend on where we live? *Frontiers in Microbiology* **8**, 1935.