

UCLA

UCLA Previously Published Works

Title

The changing microbial landscape of Western society: Diet, dwellings and discordance

Permalink

<https://escholarship.org/uc/item/89q015c9>

Journal

Molecular Metabolism, 5(9)

ISSN

2212-8778

Authors

Broussard, Josiane L

Devkota, Suzanne

Publication Date

2016-09-01

DOI

10.1016/j.molmet.2016.07.007

Peer reviewed

The changing microbial landscape of Western society: Diet, dwellings and discordance



Josiane L. Broussard¹, Suzanne Devkota^{2,*}

ABSTRACT

Background: The last 50–100 years has been marked by a sharp rise in so-called “Western-diseases” in those countries that have experienced major industrial advances and shifts towards urbanized living. These diseases include obesity, type 2 diabetes, inflammatory bowel diseases, and food allergies in which chronic dysregulation of metabolic and/or immune processes appear to be involved, and are likely a byproduct of new environmental influences on our ancient genome. What we now appreciate is that this genome consists of both human and co-evolved microbial genes of the trillions of microbes residing in our body. Together, host–microbe interactions may be determined by the changing diets and behaviors of the Western lifestyle, influencing the etiopathogenesis of “new-age” diseases.

Scope of review: This review takes an anthropological approach to the potential interplay of the host and its gut microbiome in the post-industrialization rise in chronic inflammatory and metabolic diseases. The discussion highlights both the changes in diet and the physical environment that have co-occurred with these diseases and the latest evidence demonstrating the role of host–microbe interactions in understanding biological responses to the changing environment.

Major conclusions: Technological advances that have led to changes in agriculture and engineering have altered our eating and living behaviors in ways never before possible in human history. These changes also have altered the bacterial communities within the human body in ways that are seemingly linked with the rise of many intestinal and systemic metabolic and inflammatory diseases. Insights into the mechanisms of this reciprocal exchange between the environment and the human gut microbiome may offer potential to attenuate the chronic health conditions that derail quality of life. This article is part of a special issue on microbiota.

© 2016 Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords Microbiome; Circadian; Inflammation; Western diet; Short-chain fatty acids

1. INTRODUCTION

The early 19th century marked the beginning of the Industrial Revolution in the United States, resulting in both cultural and economic shifts. Manufacturing and industry have changed how humans interact with and behave in the physical environment. Eating behavior and preferences have shifted toward convenience, packaging, and taste. Sleep can now be manipulated by artificial lighting, and labor and habitation have become primarily indoor activities. While industrialization and modern medicine have nearly eliminated deaths from acute infectious diseases and increased average lifespan, they have also created a new era of disease marked by sub-acute, chronic dysregulation of metabolic and immunological processes. Diabetes, obesity, food allergies, and inflammatory bowel diseases are among the negative health consequences whose increase in prevalence during industrialization has been linked to modern diets and our sterile, manufactured habitats [1,2].

Multiple factors are involved in the rise of these diseases. However, there is a growing appreciation for the contribution of an individual's native bacterial milieu to the complexity of these disorders. The bacteria in the human body and the genes they possess, the collective

microbiome, play important developmental roles in educating the intestinal immune system [3]. Specific species of bacteria are required for immune development, and, in the early stages of life, these bacteria are maternally and environmentally acquired [4]. It is therefore important to consider whether alterations in our physical environment in recent history have led to a shift in bacterial communities. The relative role of our microbiome in human health and disease and its adaptive evolution to “Westernization” will likely hold important, identifiable clues to the etiopathogenesis of modern diseases.

2. EVOLUTION OF THE WESTERN DIET AND MICROBIAL SELECTION

2.1. Western dietary trends

Evolution represents an ongoing interaction between an individual's genome and environment over the course of multiple generations. When the environment remains relatively constant, genetic traits that represent optimal survival for the population as a whole are maintained. As environmental conditions shift, directional selection moves the average population genome toward a new norm. Individuals possessing

¹Sleep and Chronobiology Laboratory, Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO, USA ²F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

*Corresponding author. F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA. E-mail: Suzanne.Devkota@cshs.org (S. Devkota).

Received June 8, 2016 • Revision received July 15, 2016 • Accepted July 15, 2016 • Available online 21 July 2016

<http://dx.doi.org/10.1016/j.molmet.2016.07.007>

the previously optimal genome experience evolutionary discordance between genome and environment, which manifests phenotypically as increased morbidity and mortality, and reduced reproductive fitness [5]. There is evidence that the significant dietary changes that occurred with the introduction of agriculture and animal husbandry occurred too recently on an evolutionary time scale for the human genome to successfully adapt [6]. The result of this discordance between our ancient, genetically determined biology and the dietary patterns of today's Western populations is the myriad of so-called "new age" diseases characterized by chronic states of metabolic derangement and misguided immune responses [7–9].

Before the development of agriculture and animal husbandry, early ancestral, humans' dietary choices were limited to minimally processed, wild plant and animal foods. However, with the initial domestication of plants and animals, the original nutrient characteristics of these formerly wild foods changed, subtly at first, but more rapidly with advancing technology after the Industrial Revolution [10]. Furthermore, the advent of agriculture introduced novel foods as staples for which the human genome had little evolutionary experience. Dairy foods, cereals, refined sugars, refined vegetable oils, alcohol, salt, and fatty domesticated meats were not present in the pre-agricultural diet. They now make up the primary constituents of the post-agricultural, typical Western diet and are consumed in caloric excess. The amounts of the three major macronutrients, carbohydrates, fats, and proteins, became skewed in the Western diet, and their composition has dramatically changed [11].

In the United States for example, the per capita consumption of all refined sugars in 2000 was 69 kg, whereas in 1970 it was 56 kg [12]. This 30-year trend for increased sugar consumption is representative of a much larger worldwide trend. The per capita refined sucrose consumption in England, for example, rose steadily from 6.8 kg in 1815 to 54.5 kg in 1970 [13]. Similar trends have been reported during the Industrial Era for other nations of northern Europe [14]. These changes in sugar consumption are not only reflected in quantity, but also in the increasingly processed nature of the sugars consumed. With the advent of chromatographic fructose enrichment technology in the late 1970s, it became economically feasible to manufacture high-fructose corn syrup (HFCS) in mass quantity [15]. In 1970 of the 56 kg sugar consumed per capita, 46.2% came from sucrose and 0.2% came from HFCS, while in the year 2000 of the 69.1 kg per capita, 29.8% came from sucrose and 28.9% came from HFCS [12]. With industrialization came not only the processing and refinement of sugars, but also of fats, and is most evidenced by the use of refined vegetable oils.

During the period from 1909 to 1999, a striking increase in the use of vegetable oils occurred. Per capita consumption of salad and cooking oils, shortening, and margarine increased 130%, 136%, and 410%, respectively [11]. These trends were made possible by the industrialization and mechanization of the oil-seed industry. The advent of mechanically driven steel expellers and hexane extraction processes allowed for greater world-wide vegetable oil productivity, whereas new purification procedures allowed for the use of nontraditionally consumed oils, such as cottonseed [16]. New manufacturing procedures allowed vegetable oils to take on atypical structural characteristics [17]. As a consequence, the large-scale addition of refined vegetable oils to the world's food supply after the Industrial Revolution profoundly altered many aspects of fat intake.

2.2. Gut microbiome responses to Western vs. non-Western diets

These technological advances of the food industry were likely unparalleled in any other point of our biological history, and, therefore, it is likely not a coincidence that metabolic and inflammatory diseases of Western

populations have rapidly increased. If discordance between genes and environment occurs in the host, the same is likely true of the microbiota in the gut environment. Indeed, evidence for discordance in the gut microbiome is supported by multiple studies exploring microbiomes from native populations on multiple continents with indigenous dietary practices. Yatsuneneko et al. demonstrated that the gut microbiota of individuals in the United States is far less diverse than the microbiota of native Amazonian and Malawian populations. Increased bacterial diversity in the gut is generally accepted as a marker of health. Not only is there less microbial diversity in the American gut, the composition of bacteria is different as well [18]. Strikingly, the microbial differences in richness and diversity emerge post-weaning upon adaptation to the native diet [18]. Similarly, a recent study compared the microbiomes of the BaAka pygmies of Central Africa, a native hunter–gatherer population, to their neighboring agriculturist Bantu community representing a "transitional" dietary pattern that is a combination of an ancient hunter–gatherer diet and the modern day diets of industrialized nations. While a relatively small study cohort of 29 individuals from each group, sequencing data revealed that the gut microbiota composition of the BaAka pygmies is more similar to the known composition of wild primates, whereas the Bantu composition is more similar to Western microbiomes [19]. The authors suggest that these populations may elucidate changes that occurred in the human gut microbiome in response to evolving agricultural and dietary practices and the resulting modern day Western diet.

One possible mechanistic underpinning for these potentially deleterious microbial changes may be decreased consumption of microbially accessible carbohydrates (MACs) in the form of fiber-rich foods. Sonnenburg et al. demonstrated that in rodents, decreased consumption of MACs over successive generations could result in complete loss of entire genera or species of microbiota, highlighting that "unhealthy" microbiomes can be permanently inherited if diets continue to lose their fiber component. Even more striking was the finding that the re-introduction of MACs into the diet was unable to recover the lost species to a greater and greater degree with each subsequent generation, suggesting extinction from the gut microbiota [20,21]. The long-term consequences of specific species extinction are not known, but a meaningful implication would be a decrease in bacterially-produced short-chain fatty acids (SCFA's) over time.

It has been well-described that the microbiota which can metabolize MAC's produce SCFAs of which acetate, butyrate, and propionate are the dominant forms [22]. To the microbiota, these are a necessary waste product to balance the redox equivalent product in the gut anaerobic environment [23], but to the intestinal colonocytes, SCFAs are the primary source of energy, comprising 60–70% of their energy supply [24]. In germ-free mice, colonocytes exhibit a deficiency in mitochondrial respiration and undergo autophagy. However, in a study monocolonizing germ-free mice with *Butyrivibrio fibrisolvens*, a butyrate-produced bacteria, the colonocytes were rescued from both the mitochondrial deficiency and autophagy [25]. Therefore the gradual loss of SCFA's over generations could result in serious defects in gut health. The clinical importance of these SCFAs to intestinal health and homeostasis has been demonstrated in several studies in which administration of SCFA's orally or via direct irrigation to patients with ulcerative colitis, Crohn's disease, and antibiotic-resistant diarrhea has shown amelioration of symptoms [26–28]. While more studies are needed, collectively, these data suggest that the shift away from the higher MAC diets of our ancestors may result in the loss of critical gut functions conferred by SCFA-producing bacteria.

Beyond the gut, SCFA's play a role in systemic metabolism, potentially as signaling molecules. Rodent studies have demonstrated increased

AMPK activity in liver and skeletal muscle with SCFA administration [29,30] as well as increased PGC1-alpha and UCP1 in brown adipose [29]. The resulting increase in thermogenesis and fatty acid oxidation suggests that diet-induced obesity may be prevented by SCFAs. However, an often perplexing paradox is that fermentation of MAC's in the cecum yield ~600 mmol SCFAs/day, resulting in SCFA production of 0.24–0.38 kg body weight, which contributes ~10% of human caloric requirements [31]. Therefore, it may seem that increased SCFAs could lead to increased available calories and weight gain. Indeed, rodent studies have shown that the obese microbiome may be more capable of producing SCFAs [32], and human studies have found fecal concentration of SCFAs to be higher in obese versus lean individuals [33]. However, more in-depth comparative studies are needed to examine the metabolic fate of SCFAs in and out of the gut in lean and obese individuals, and across Western and non-Western diets, in order to conclude whether these human SCFA effects are a cause or an effect of weight gain.

Additional insights, however, can be gained from the human studies looking at metabolic disease incidence in Western versus non-Western dietary traditions. A unifying theme among these native populations, irrespective of geographic location, is that diabetes and obesity is nearly unheard of. The cases where diabetes or insulin resistance emerges is in the subpopulations that have migrated closer to larger cities in Westernized regions or adopted Western dietary practices. For example, diabetes is rare in the Inuit of Greenland, who consume a nearly all meat and fat diet, whereas the Inuit of northern Canada have a prevalence approaching 2%, similar to that of Westernized Canadians [34]. This suggests the presence of a dietary determined force rather than the presence of a protective genetic trait. Similarly, there is no evidence of diabetes in the hunter–gatherer Aboriginal populations of remote regions of Northern Australia where the lifestyle is characterized by increased physical activity and a higher fiber diet consisting of lean wild meat and uncultivated vegetables. The average BMI is < 20, and fasting blood glucose, cholesterol, and blood pressure are all low [35]. In contrast, Westernized Aboriginal groups are three times as likely to develop diabetes than non-indigenous Australians upon transitioning to the Australian diet [36,37]. When Westernized diabetic Aborigines reverted temporarily to their traditional diet and lifestyle, there was an observed reduction in the metabolic abnormalities associated with diabetes [35]. Increased physical activity is a highly cited explanation for the decreased incidence of metabolic diseases in native populations. Interestingly, Pontzer et al. revealed that the total energy expenditure per day (TEE; kcal/g) among Hadza hunter–gatherers in northern Tanzania was not greater than their Western counterparts despite having significantly greater physical activity [38]. Hadza men and women walk several kilometers per day over varied terrain, forage for food, chop trees, and engage in other strenuous activities on a daily basis, while the Western lifestyle is characterized by long periods of sitting. Yet when correcting for lean mass and fat mass, TEE was indistinguishable from Westerners and others in market economies [39]. These data suggest that differences in obesity and diabetes between traditional and Western populations arise from differences in energy intake rather than expenditure. If this is indeed true, the gut microbiome's contribution to energy harvest may be a critical link in the rising incidence of metabolic disease in transitioning populations.

3. MICROBIAL SELECTION IN THE BUILT ENVIRONMENT

If changes in the gut microbiome contribute meaningfully to the rising incidence of modern disease, then all aspects of the Western lifestyle should be examined in this context. While diet is accepted as

one of the most potent driving forces shaping gut microbial communities [40,41], as highlighted above, other aspects of Westernization that contribute to disease need to be considered beyond changes in diet and physical activity. It is beginning to come to the fore that our physical environment is another important determinant of microbial communities. As individuals, we each possess our own personal bacterial clouds [42] that we carry with us throughout the day, and which can interact with, and be deposited in, the physical world. The microbes that survive in the built environment are resilient and adaptive and require attention as a unique feature of modern society.

Currently, 54% of the world's population lives in urban settings and this is expected to increase to 66% by 2050 [43]. The United Nations Department of Economic and Social Affairs believes that managing population growth in these urban areas will be one of the most important challenges of the 21st century [43]. To this end, understanding how our interactions with the urban environment may affect the etiopathogenesis of modern diseases is crucial.

Humans in Westernized cultures spend an average of 23 h per day indoors [43] and are, therefore, in regular contact with indoor dwelling microbes rather than with the external microbiomes found in air, water, and soil environments. Likewise, humans shed and expel microbes into confined spaces that may be shared with other individuals, increasing the likelihood of reciprocal exchange of microbiota between individuals [44]. Indeed, Song et al. compared 159 individuals and 36 dogs, comprising 60 families, and found that co-habitation created microbial homogeneity within families, as well as between individuals and their dogs, primarily in the skin microbiome, characterized by an abundance of Betaproteobacteria [45].

Furthermore, according to a separate longitudinal study of microbial colonization in a new home, microbial niches develop within days of occupancy from humans and pets, or on insects or food-borne bacteria [46]. Once in the home, they evolve the capability to resist eradication by dishwashers, washing machines, and sanitary cleaning solutions. For example, *Deinococcus radiodurans*, a UV-resistant microbe, has been shown to accumulate in building dust over time [47], and *Thermus aquaticus*, a native of hot springs, has been found in residential hot water heaters [48]. The ability of microbes to adapt to the extreme conditions of sterility that are typically enforced in the home and other environments such as hospitals may also favor pathogenicity in the microbiota by selecting for resilience. There is still relatively little known about the long-term impact of human interaction with indoor dwelling microbiota, but this must be taken into account when considering host–microbe interactions.

4. IRREGULAR SLEEP PATTERNS AND THE MICROBIOME

Findings from recent studies suggest that human interaction with the built environment can also impact the gut microbiome via alterations in host physiology. Modern inventions that manipulate electrical lighting have created great conveniences in day to day life, have also led to behaviors that did not exist in ancestral populations such as sleep curtailment, jet lag, and an increase in the prevalence of people engaging in shift-work. As a result, the field of human circadian clocks has lent insight into the health consequences of circadian misalignment. Circadian rhythms are near 24-hour biological oscillations found in all living things, including microbes. Normally, exposure to daylight synchronizes the circadian system, which regulates physiology and behaviors so that they occur at appropriate times of the day or night. In addition to the central circadian pacemaker, located in the suprachiasmatic nucleus of the brain [49], circadian clock machinery and

oscillations have been reported in multiple peripheral tissues, including adipose, pancreatic, skeletal, hepatic, and cardiac tissue [50–53]. During circadian misalignment, behaviors occur at inappropriate biological times. For example, during the circadian misalignment that typically accompanies jetlag and shiftwork, sleep is often attempted during the day, and wake/eating occurs at night. Findings from epidemiologic studies have shown that shift work is associated with multiple adverse health outcomes observed in modern society, including higher risks of diabetes, cardiovascular disease, and cancer [54–58]. Indeed, in studies of simulated circadian misalignment there is an association with alterations in energy balance that may predispose individuals to weight gain [59]. Experimental forced desynchrony protocols, in which behaviors occur and are assessed at inappropriate biological times, have shown that circadian misalignment is associated with reduced insulin sensitivity [60–62]. Furthermore, findings using experimentally-induced insufficient sleep have shown that worse circadian misalignment is associated with larger impairments in glucose tolerance [63].

Recently, Zarrinpar et al. reported that intestinal microbiota exhibits diurnal oscillations, driven primarily by the food intake rhythms of the host organism, leading to rhythmic composition and functional profiles of intestinal bacteria [64,65]. Closer examination of the gut microbiota suggests the existence of differential circadian variations in the microbial structure, depending on dietary composition of the host [66]. Specifically, Western diet-induced obesity can dampen the rhythmicity of feeding/fasting fluctuations in the gut microbiome [64].

In addition, experimental circadian misalignment alters the gut microbiome in a way that promotes increased energy absorption and positive energy balance due to changes in gut microbial community and structure [65]. In a study including mouse models as well as humans, jetlag induced intestinal dysbiosis due to altered feeding rhythmicity, promoting glucose intolerance, which was transferrable from humans to germ-free mice [65]. Taken together, an altered circadian rhythm on a background of a Western diet, as well as independently, has been linked to unfavorable changes in the gut microbiome.

Countermeasure strategies to these altered feeding patterns have been proposed in which an attempt is made to restrict feeding to the biological day, regardless of when sleep/wake occurs. This type of chrononutrition has been shown to partially restore normal gut microbiota [64] and protect against diet-induced obesity and metabolic disease [67]. In humans, restricting the timing of food intake from >14 h to between 10 and 11 h reduced body weight and improved sleep [68] and these findings persisted for over 1 year. However, whether it is the restriction of all nutrients or specific macronutrients that is most beneficial for weight loss during time-restricted feeding is unknown.

5. CONCLUSIONS

The technological developments of modern society have allowed advances in industry that have changed our diet, environment, and lifestyle in profound ways. Few would argue that these changes were not financially and socially beneficial. However, looking at the picture of human health over this period, it is clear that Western populations have achieved the benefit of increased longevity at the expense of experiencing an increase in chronic unhealthy states that are rarely present in native populations. The concept of chronic low-grade inflammation pervading everyday life is now a commonplace Western notion. Indeed, many of the diseases that have increased in prevalence over the past 100 years have a component of persistent, sub-acute insult. This

requires an understanding of the modern environmental exposures that may be contributors to these phenomena. The dietary changes that have occurred over this period have been the most widely studied culprit largely because the explosion of obesity has been the most visibly noticeable change directly linked to eating and lifestyle habits. However, delving into the myriad of compounded immunologic and metabolic complications that often lie below the surface requires a wider perspective that takes into account additional mechanisms. The commensal, co-evolved intestinal microbiome and its byproducts may not be the cause and the cure to every modern day disease, but what is now abundantly clear, is that these trillions of bacteria are not passive bystanders and may be playing a critical role in modern day diseases. While their absolute presence or absence may not kill us, several lines of evidence are revealing that their composition is related to optimal intestinal and metabolic health potentially via SCFA production, which is directly affected by diet and lifestyle habits. Unfurling the mechanistic underpinnings of host–microbe interactions will provide an opportunity to reciprocally shape our environment in ways that confer both health and longevity.

FUNDING

This work was supported by Society in Science, The Branco Weiss Fellowship, administered by the ETH Zürich and the Sleep Research Society Foundation.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest relevant to this article.

REFERENCES

- [1] Kostic, A.D., Gevers, D., Siljander, H., Vatanen, T., Hyötyläinen, T., Hämäläinen, A.-M., et al., 2015. The dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. *Cell Host & Microbe* 17(2):260–273. <http://dx.doi.org/10.1016/j.chom.2015.01.001>.
- [2] Okada, H., Kuhn, C., Feillet, H., Bach, J.F., 2010. The “hygiene hypothesis” for autoimmune and allergic diseases: an update. *Clinical and Experimental Immunology*, 1–9. <http://dx.doi.org/10.1111/j.1365-2249.2010.04139.x>.
- [3] Hepworth, M.R., Fung, T.C., Masur, S.H., Kelsen, J.R., McConnell, F.M., Dubrot, J., et al., 2015. Group 3 innate lymphoid cells mediate intestinal selection of commensal bacteria-specific CD4+ T cells. *Science* (New York, N.Y.) 348(6238):1031–1035. <http://dx.doi.org/10.1126/science.aaa4812>.
- [4] Palmer, C., Bik, E.M., DiGiulio, D.B., Relman, D.A., Brown, P.O., 2007. Development of the human infant intestinal microbiota. *PLoS Biology* 5(7): 1556–1573. <http://dx.doi.org/10.1371/journal.pbio.0050177>.
- [5] Gould, J.S., 2003. *The structure of evolutionary theory* vol. 94.
- [6] Cordain, L., Eaton, S.B., Sebastian, A., Mann, N., Lindeberg, S., Watkins, B.A., et al., 2005. Origins and evolution of the Western diet: health implications for the 21st century. *The American Journal of Clinical Nutrition* 81(2):341–354. [http://dx.doi.org/10.1016/s0920-5861\(96\)00158-7](http://dx.doi.org/10.1016/s0920-5861(96)00158-7).
- [7] Hanauer, S.B., 2006 January. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. *Inflammatory Bowel Diseases* 12(Suppl 1):S3–S9. <http://dx.doi.org/10.1097/O1.MIB.0000195385.19268.68>.
- [8] Ogden, C.L., Carroll, M.D., Kit, B.K., Flegal, K.M., 2012. Prevalence of obesity in the United States, 2009–2010. *NCHS Data Brief*(82):1–8.
- [9] Molodecky, N.A., Soon, I.S., Rabi, D.M., Ghali, W.A., Ferris, M., Chernoff, G., et al., 2012. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 142(1). <http://dx.doi.org/10.1053/j.gastro.2011.10.001>.

- [10] Wood, B., 2002. Hominid revelations from Chad. *Nature* 418(July):133–135. <http://dx.doi.org/10.1038/418133a>.
- [11] USDA, n.d. No Title. Continuing Survey of Food Intakes by Individuals.
- [12] USDA, 2002. No Title. Food Consumption (per Capita) Data System., <http://www.ers.usda.gov/Data/foodconsumption/datasystem.asp>. [accessed July 17, 2016].
- [13] Cleave, T.L., 1974. *The saccharine disease*. United Kingdom: John Wright & Sons Ltd.
- [14] Ziegler, E., 1967. Secular changes in the stature of adults and the secular trend of modern sugar consumption. *Kinderheilkd.*
- [15] Hanover, L.M., White, J.S., 1993. Manufacturing, composition, and applications of fructose. *American Journal of Clinical Nutrition* 58(5 Suppl.). <http://dx.doi.org/10.1007/s00299-006-0267-6>.
- [16] O'Keefe, S., 2000. *An overview of oils and fats with a special emphasis on olive oil*. The Cambridge World History of Food. Cambridge: Cambridge University Press.
- [17] E, E.A., 1984. Nutrition and biochemistry of trans and positional fatty acid isomers in hydrogenated oils. *Annual Review of Nutrition* 4:339–376.
- [18] Yatsunenko, T., Rey, F.E., Manary, M.J., Trehan, I., Dominguez-Bello, M.G., Contreras, M., et al., 2012. Human gut microbiome viewed across age and geography. *Nature* 486(7402):222–227. <http://dx.doi.org/10.1038/nature11053>.
- [19] Gomez, A., Petrzekova, K.J., Burns, M.B., Yeoman, C.J., Amato, K.R., Vlckova, K., et al., 2016. Gut microbiome of coexisting BaAka pygmies and Bantu reflects gradients of traditional subsistence patterns. *Cell Reports* 14(9): 2142–2153. <http://dx.doi.org/10.1016/j.celrep.2016.02.013>.
- [20] Sonnenburg, E.D., Smits, S.A., Tikhonov, M., Higginbottom, S.K., Wingreen, N.S., Sonnenburg, J.L., 2016. Diet-induced extinctions in the gut microbiota compound over generations. *Nature* 529(7585):212–215. <http://dx.doi.org/10.1038/nature16504>.
- [21] Sonnenburg, J.L., Xu, J., Leip, D.D., Chen, C.-H., Westover, B.P., Weatherford, J., et al., 2005. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. *Science* 307(5717):1955–1959. <http://dx.doi.org/10.1126/science.1109051>.
- [22] Cook, S.I., Sellin, J.H., 1998. Review article: short chain fatty acids in health and disease. *Alimentary Pharmacology & Therapeutics* 12(6):499–507. <http://dx.doi.org/10.1046/j.1365-2036.1998.00337.x>.
- [23] van Hoek, M.J.A., Merks, R.M.H., 2012. Redox balance is key to explaining full vs. partial switching to low-yield metabolism. *BMC Systems Biology* 6(1):22. <http://dx.doi.org/10.1186/1752-0509-6-22>.
- [24] Roediger, W.E., 1982. Utilization of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology* 83(2):424–429.
- [25] Donohoe, D.R., Garge, N., Zhang, X., Sun, W., O'Connell, T.M., Bunger, M.K., et al., 2011. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. *Cell Metabolism* 13(5):517–526. <http://dx.doi.org/10.1016/j.cmet.2011.02.018>.
- [26] Binder, H.J., 2010. Role of colonic short-chain fatty acid transport in diarrhea. *Annual Review of Physiology* 72:297–313. <http://dx.doi.org/10.1146/annurev-physiol-021909-135817>.
- [27] Hargit, J.M., Soergel, K.H., Komorowski, R.A., Wood, C.M., 1989. Treatment of diversion colitis with short-chain-fatty acid irrigation. *The New England Journal of Medicine* 320(1):23–28. <http://dx.doi.org/10.1056/NEJM198901053200105>.
- [28] Di Sabatino, A., Morera, R., Ciccocioppo, R., Cazzola, P., Gotti, S., Tinozzi, F.P., et al., 2005. Oral butyrate for mildly to moderately active Crohn's disease. *Alimentary Pharmacology and Therapeutics* 22(9):789–794. <http://dx.doi.org/10.1111/j.1365-2036.2005.02639.x>.
- [29] Gao, Z., Yin, J., Zhang, J., Ward, R.E., Martin, R.J., Lefevre, M., et al., 2009. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes* 58(7):1509–1517. <http://dx.doi.org/10.2337/db08-1637>.
- [30] Zydowo, M.M., Smoleński, R.T., Swierczyński, J., 1993. Acetate-induced changes of adenine nucleotide levels in rat liver. *Metabolism* 42(5):644–648. [http://dx.doi.org/10.1016/0026-0495\(93\)90225-D](http://dx.doi.org/10.1016/0026-0495(93)90225-D).
- [31] Bergman, E.N., 1990. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. *Physiological Reviews* 70(2):567–590.
- [32] Turnbaugh, P.J., Ley, R.E., Mahowald, M.A., Magrini, V., Mardis, E.R., Gordon, J.I., 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444(7122):1027–1031. <http://dx.doi.org/10.1038/nature05414>.
- [33] Schwierz, A., Taras, D., Schäfer, K., Beijer, S., Bos, N.A., Donus, C., et al., 2010. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity* (Silver Spring, Md.) 18(1):190–195. <http://dx.doi.org/10.1038/oby.2009.167>.
- [34] Egeland, G.M., Cao, Z., Young, T.K., 2011. Hypertriglyceridemic-waist phenotype and glucose intolerance among Canadian Inuit: the International Polar Year Inuit Health Survey for Adults 2007–2008. *Canadian Medical Association Journal* 183(9):E553–E558. <http://dx.doi.org/10.1503/cmaj.101801>.
- [35] O'Dea, K., 1991. Cardiovascular disease risk factors in Australian aborigines. *Clinical and Experimental Pharmacology & Physiology* 18(2):85–88.
- [36] NHMRC, 2000. *Nutrition in Aboriginal and Torres Strait Islander*.
- [37] Stewart, J.M., Sanson-Fisher, R.W., Eades, S., Fitzgerald, M., 2012. The risk status, screening history and health concerns of Aboriginal and Torres Strait Islander people attending an Aboriginal Community Controlled Health Service. *Drug and Alcohol Review* 31(5):617–624. <http://dx.doi.org/10.1111/j.1465-3362.2012.00455.x>.
- [38] Pontzer, H., Raichlen, D.A., Wood, B.M., Mabulla, A.Z.P., Racette, S.B., Marlowe, F.W., 2012. Hunter-gatherer energetics and human obesity. *PLoS One* 7(7). <http://dx.doi.org/10.1371/journal.pone.0040503>.
- [39] Pontzer, H., Raichlen, D.A., Wood, B.M., Emery Thompson, M., Racette, S.B., Mabulla, A.Z.P., et al., 2015. Energy expenditure and activity among Hadza hunter-gatherers. *American Journal of Human Biology* 27(5):628–637. <http://dx.doi.org/10.1002/ajhb.22711>.
- [40] David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., et al., 2014. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505(7484):559–563. <http://dx.doi.org/10.1038/nature12820>.
- [41] Muegge, B.D., Kuczynski, J., Knights, D., Clemente, J.C., González, A., Fontana, L., et al., 2011. Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science* (New York, N.Y.) 332(6032):970–974. <http://dx.doi.org/10.1126/science.1198719>.
- [42] Meadow, J.F., Altrichter, A.E., Bateman, A.C., Stenson, J., Brown, G.Z., Green, J.L., et al., 2015. Humans differ in their personal microbial cloud. *PeerJ* 3(1):e1258. <http://dx.doi.org/10.7717/peerj.1258>.
- [43] United Nations, 2014. *World urbanization prospects: the 2014 revision, highlights (ST/ESA/SER.A/352)*.
- [44] Dunn, R.R., Fierer, N., Henley, J.B., Leff, J.W., Menninger, H.L., 2013. Home life: factors structuring the bacterial diversity found within and between homes. *PLoS One* 8(5). <http://dx.doi.org/10.1371/journal.pone.0064133>.
- [45] Song, S.J., Lauber, C., Costello, E.K., Lozupone, C.A., Humphrey, G., Berg-Lyons, D., et al., 2013. Cohabiting family members share microbiota with one another and with their dogs. *eLife* 2013(2). <http://dx.doi.org/10.7554/eLife.00458>.
- [46] Lax, S., Smith, D.P., Hampton-Marcell, J., Owens, S.M., Handley, K.M., Scott, N.M., et al., 2014. Longitudinal analysis of microbial interaction between humans and the indoor environment. *Science* 345(6200):1048–1052. <http://dx.doi.org/10.1126/science.1254529>.
- [47] Martin, L.J., Adams, R.I., Bateman, A., Bik, H.M., Hawks, J., Hird, S.M., et al., 2015. Evolution of the indoor biome. *Trends in Ecology and Evolution*, 223–232. <http://dx.doi.org/10.1016/j.tree.2015.02.001>.
- [48] Brock, T.D., Boylen, K.L., 1973. Presence of thermophilic bacteria in laundry and domestic hot-water heaters. *Applied Microbiology* 25(1):72–76.
- [49] Lydic, R., Schoene, W.C., Czeisler, C.A., Moore-Ede, M.C., 1980. Suprachiasmatic region of the human hypothalamus: homolog to the primate circadian pacemaker? *Sleep* 2(3):355–361.

- [50] Gómez-Santos, C., Gómez-Abellán, P., Madrid, J.A., Hernández-Morante, J.J., Lujan, J.A., Ordovas, J.M., et al., 2009. Circadian rhythm of clock genes in human adipose explants. *Obesity (Silver Spring, Md.)* 17(8):1481–1485. <http://dx.doi.org/10.1038/oby.2009.164>.
- [51] Saini, C., Petrenko, V., Pulimeno, P., Giovannoni, L., Berney, T., Hebrok, M., et al., 2015. A functional circadian clock is required for proper insulin secretion by human pancreatic islet cells. *Diabetes, Obesity & Metabolism*, 355–365. <http://dx.doi.org/10.1111/dom.12616>.
- [52] Perrin, L., Loizides-Mangold, U., Skarupelova, S., Pulimeno, P., Chanon, S., Robert, M., et al., 2015. Human skeletal myotubes display a cell-autonomous circadian clock implicated in basal myokine secretion. *Molecular Metabolism* 4(11):834–845. <http://dx.doi.org/10.1016/j.molmet.2015.07.009>.
- [53] Davidson, A.J., Castañón-Cervantes, O., Stephan, F.K., 2004. Daily oscillations in liver function: diurnal vs circadian rhythmicity. *Liver International: Official Journal of the International Association for the Study of the Liver* 24(3):179–186. <http://dx.doi.org/10.1111/j.1478-3231.2004.0917.x>.
- [54] Vetter, C., Devore, E.E., Wegrzyn, L.R., Massa, J., Speizer, F.E., Kawachi, I., et al., 2016. Association between rotating night shift work and risk of coronary heart disease among women. *JAMA* 315(16):1726–1734. <http://dx.doi.org/10.1001/jama.2016.4454>.
- [55] Suwazono, Y., Sakata, K., Okubo, Y., Harada, H., Oishi, M., Kobayashi, E., et al., 2006. Long-term longitudinal study on the relationship between alternating shift work and the onset of diabetes mellitus in male Japanese workers. *Journal of Occupational and Environmental Medicine* 48(5):455–461. <http://dx.doi.org/10.1097/O1.jom.0000214355.69182.fa>.
- [56] Kivimäki, M., Batty, G.D., Hublin, C., 2011. Shift work as a risk factor for future type 2 diabetes: evidence, mechanisms, implications, and future research directions. *PLoS Medicine* 8(12). <http://dx.doi.org/10.1371/journal.pmed.1001138>.
- [57] Vyas, M.V., Garg, A.X., Iansavichus, A.V., Costella, J., Donner, A., Laugsand, L.E., et al., 2012. Shift work and vascular events: systematic review and meta-analysis. *BMJ* 345(jul26 1):e4800. <http://dx.doi.org/10.1136/bmj.e4800>.
- [58] Sigurdardottir, L.G., Valdimarsdottir, U.A., Fall, K., Rider, J.R., Lockley, S.W., Schernhammer, E., et al., 2012. Circadian disruption, sleep loss, and prostate cancer risk: a systematic review of epidemiologic studies. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 21(7):1002–1011. <http://dx.doi.org/10.1158/1055-9965.EPI-12-0116>.
- [59] McHill, A.W., Melanson, E.L., Higgins, J., Connick, E., Moehlman, T.M., Stothard, E.R., et al., 2014. Impact of circadian misalignment on energy metabolism during simulated nightshift work. *Proceedings of the National Academy of Sciences of the United States of America* 111(48):17302–17307. <http://dx.doi.org/10.1073/pnas.1412021111>.
- [60] Morris, C.J., Yang, J.N., Garcia, J.I., Myers, S., Bozzi, I., Wang, W., et al., 2015. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proceedings of the National Academy of Sciences of the United States of America* 112(17):E2225–E2234. <http://dx.doi.org/10.1073/pnas.1418955112>.
- [61] Scheer, F.A.J.L., Hilton, M.F., Mantzoros, C.S., Shea, S.A., 2009. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proceedings of the National Academy of Sciences of the United States of America* 106(11):4453–4458. <http://dx.doi.org/10.1073/pnas.0808180106>.
- [62] Buxton, O.M., Cain, S.W., O'Connor, S.P., Porter, J.H., Duffy, J.F., Wang, W., et al., 2012. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. *Science Translational Medicine* 4(129):129ra43. <http://dx.doi.org/10.1126/scitranslmed.3003200>.
- [63] Markwald, R.R., Melanson, E.L., Smith, M.R., Higgins, J., Perreault, L., Eckel, R.H., et al., 2013. Impact of insufficient sleep on total daily energy expenditure, food intake and weight gain. *Proceedings of the National Academy of Sciences of the United States of America* 110(14):5695–5700. <http://dx.doi.org/10.1073/pnas.1216951110>.
- [64] Zarrinpar, A., Chaix, A., Yooshef, S., Panda, S., 2014. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. *Cell Metabolism* 20(6):1006–1017. <http://dx.doi.org/10.1016/j.cmet.2014.11.008>.
- [65] Thaiss, C.A., Zeevi, D., Levy, M., Zilberman-Schapira, G., Suez, J., Tengeler, A.C., et al., 2014. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* 159(3):514–529. <http://dx.doi.org/10.1016/j.cell.2014.09.048>.
- [66] Leone, V., Gibbons, S.M., Martinez, K., Hutchison, A.L., Huang, E.Y., Cham, C.M., et al., 2015. Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host and Microbe* 17(5):681–689. <http://dx.doi.org/10.1016/j.chom.2015.03.006>.
- [67] Chaix, A., Zarrinpar, A., Miu, P., Panda, S., 2014. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. *Cell Metabolism* 20(6):991–1005. <http://dx.doi.org/10.1016/j.cmet.2014.11.001>.
- [68] Gill, S., Le, H.D., Melkani, G.C., Panda, S., 2015. Time-restricted feeding attenuates age-related cardiac decline in *Drosophila*. *Science* 347(6227):1265–1269. <http://dx.doi.org/10.1126/science.1256682>.