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Meeting Report

Seventh Annual Conference of *in*VIVO Planetary Health on Transforming Life: Unify Personal, Public, and Planetary Health

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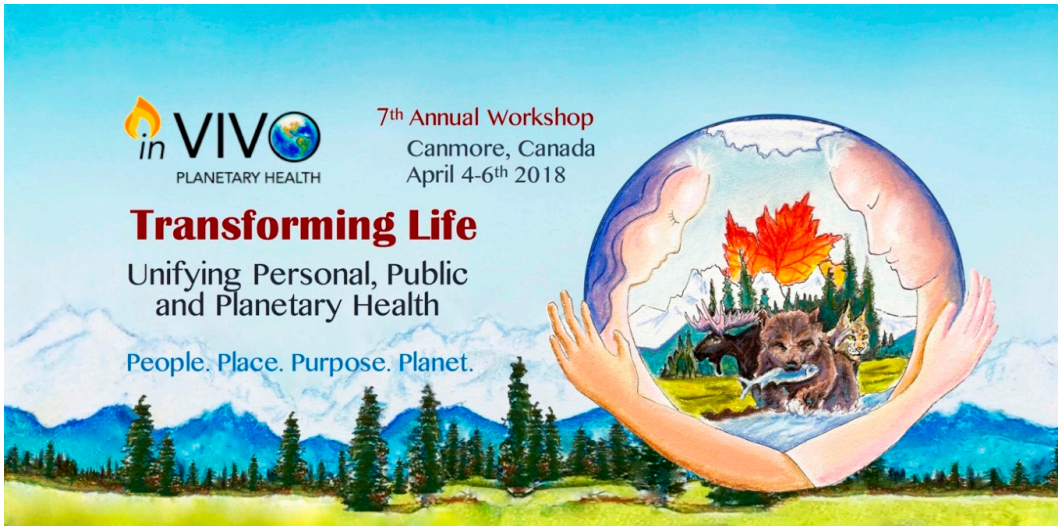
Abstract: *in*VIVO Planetary Health is a progressive, humanist scientific movement promoting both evidence and advocacy around concepts of planetary health which denote the interdependence between human health and place at all scales. Our seventh annual conference was held in Canmore, Alberta 4-6th April 2018, themed "*Transforming Life: Unify Personal, Public, and Planetary Health*" included diverse topics and perspectives to emphasise the interdependent vitality of all natural and anthropogenic ecosystems—social, political and otherwise. A key outcome of this meeting was the *The Canmore Declaration: Statement of Principles for Planetary Health* (published separately) which underscores that improving the health of all systems depends on: mutualistic values; planetary consciousness; advocacy; unity of purpose; recognition of biopsychosocial interdependence; emotional bonds between people and the land; efforts to counter elitism, social dominance and marginalization; meaningful cross-sectoral and cross-cultural narrative; self-awareness; and a personal commitment to shaping new normative attitudes and behaviors. Here we present the collection of abstracts of invited lectures and oral communications presented during the meeting. These formed the foundations and direction for discussions that became the basis of *The Canmore Declaration*.

Keywords: planetary health; biodiversity; microbiome; mental health; greenspace; nature relatedness; food systems; birth cohorts; social justice; inflammation; NCDs; personalized medicine; stress; ONE health; allergy; obesity; health equity; cultural competency; indigenous health; environmental health; ecology; microbiome; DOHaD; health promotion

1. Introduction

The seventh annual conference of *in*VIVO Planetary Health held in Canmore, Alberta was themed "*Transforming Life: Unify Personal, Public, and Planetary Health*" and explored and encouraged novel, integrative ways to approach global health challenges.



The global challenges facing humanity include climate change, biodiversity losses, population growth, grotesque socioeconomic inequalities, environmental degradation, health disparities, the dominance of ultra-processed foods, and the pandemic crisis of non-communicable diseases (NCDs)—now the leading burden of human disease, responsible for 38 million deaths annually [1]. In addition, there is ongoing political polarization and conflict, and growing 'dis-ease', which compromises quality of life and sets individuals on a path to NCDs. Health at all levels—person, place, and planet—is interdependent, and will depend on solutions that recognize that the future of human health is enmeshed with politics, economics, public policies (or lack, thereof), and social values [2]. This is an era where specialists are needed not only in *particular professions or research areas, "but in integrating information from different disciplines"* [3].

The emerging concept of planetary health emphasizes that human health is intricately connected to the health of natural systems within the Earth's biosphere—and that the health of all species depends on the health, biodiversity, and stability of whole systems. Planetary health is a product of human social, political, and economic 'ecosystems'.

Our meeting addressed the critical need to remove the lines of distinction between disciplines and between personal, public, and planetary health [2]. We recognize the unprecedented necessity for ambitious integrative approaches that not only define these interconnections, but capitalize on them to create novel, collaborative, and mutualistic solutions. We discussed the need for large, bold initiatives that generate a dynamic platform to integrate diverse expertise and technologies; that recognize the wider social and cultural determinants of planetary health; that serve as a voice for advocacy; and that will capture the imagination and engage the global community at large.

The agenda focused on understanding and improving the complex relationships between human health and planetary health, including how the ecobiological interactions in our living environments (including food systems, climate change and biodiversity, and microbial ecology) impact well-being, together with the wider societal factors that govern these. This included the need for a greater understanding of our psychological relationships with the Earth and its natural systems. It also recognized that a lack of experience in nature and emotional disconnection from the natural environment, especially in children, may undermine the goals of planetary health.

A central dimension of our meeting in Canmore was the opportunity to discuss the relationships between climate change, mental health, and ecological grief, using case studies from First Nations communities. This extended our established interest in how human health challenges are the culmination of a 'dual burden'—*increasing adverse exposure* (e.g., fast food, toxins, and stress) *coupled with the loss* of much that was protective in ancestral environments. The facets of 'loss' extend from the physical (loss of biodiversity, species, local foods, and produce) to the loss of community (loss of language, tradition, and stories), and the far less tangible aspects of loss (such as loss of value systems,

purpose, peace, respect, spirituality, compassion, hope, and wonder). This underscores that the solutions must also focus on restoring protective and buffering factors, minimizing adversity and inequality, and addressing the underlying systemic causes. Canmore provided an ideal backdrop to explore the impact of disconnection from natural environments and the loss of appreciation for traditional cultures—which extends from effects on individual mental and physical health to unsustainable social, economic, and environmental consequences.

Discussions around the microbiome provided a useful way to illustrate symbiotic relationships and the ways in which societal exposures—its policies and systems—might promote or detract from health. Microbiome science is a topic that has united researchers from virtually every branch of science and medicine. The ways in which the microbiome extends into health discussions (ranging from the future of agriculture, city planning, climate change, biodiversity, nature relatedness, and mental health) have forced difficult questions upon society as a whole. All life—including the unseen—is interconnected; the 'ecosystems' in our social structures, governments, corporations, and others can influence the ecosystems that sustain us, or act as barriers to health.

Collectively, these discussions paved the way for the development of the *Canmore Declaration on Planetary Health*, which defined planetary health as the interdependent *vitality* of all natural and anthropogenic ecosystems, inseparably bonded to human health [4]. This underscored that improving the health of all systems depends on: mutualistic values; planetary consciousness; advocacy; unity of purpose; recognition of biopsychosocial interdependence; emotional bonds between people and the land; efforts to counter elitism, social dominance and marginalization; meaningful cross-sectoral and cross-cultural narrative; self-awareness; and a personal commitment to shaping new normative attitudes and behaviors [4].

In summary, the unifying concept of 'Planetary Health' provides a collective vision for science, medicine, and all of society. While achieving the goals of human health is predicated on ecological justice and the stability of fragile planetary ecosystems that sustain all life [5], it also depends on the social, cultural, and spiritual values systems of societies. Here, we present the abstracts from the meeting—covering diverse but interrelated topics interconnected by our core agenda.

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2. Prescott, S.L.; Logan, A.C. Down to Earth: Planetary Health and Biophilosophy in the Symbiocene Epoch. *Challenges* **2017**, *8*, 19.
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2. Speakers' Abstracts

2.1. Session 1: Setting the Scene—From Personal to Planetary Health

2.1.1. Setting the Scene: A Unifying Approach to Personal, Public, and Planetary Health

Susan L. Prescott

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The *in*VIVO Planetary Health initiative recognizes that the health of humanity (in every sense) is interdependent on the health of the environment. We see the need to have a more expansive (broad and long ranging) vision in addressing human, environmental, and planetary health. It draws on the overarching premise that 'it is time to shape a better future'—emphasizing the imperative for change on all levels. Paradoxically, in a culture where 'there is a never enough', we are 'losing' everything that once gave us deeper value, and our sense of purpose, place, and identity. It may be argued that our shifting values and loss of deeper purpose are a root cause of social and economic instability and underlie the more superficial drivers of environmental and societal degradation. This erosion is gradual and associated with a shift in the 'normative' position to one of greed and self-interest. To some extend this has 'radicalized' empathy, kindness, and compassion. At the same time, we are carrying the increasing burden of technology and a culture of unhealthy 'excess': ultra-processed food, sedentary indoor behavior, air and water contamination, excessive noise and light pollution, stress, electromagnetic radiation, screen time, sleep disruption, and many other adverse exposures that were not present in traditional environments. Of great concern, the burden and consequences of these adverse exposures is greatest in the socially disadvantaged, amplifying the disparities in health and opportunity, and further widening social inequity. Together with the 'missing' elements (e.g., absence of green space, traditional foods, and community) the many adversities associated with urbanicity are eroding health in built environments with the higher burden of NCDs shouldered by disadvantaged populations. Viewed through the lens of 'connectedness' (i.e., that we are all interconnected), this inequity can (and should be) viewed as a fundamental imbalance in our 'social ecosystem', which has systemic consequences for all of us and beyond to our 'environmental ecosystems'. There is already enormous hope for change, with numerous efforts at the macro, meso, and microscales to promote human and environmental health. Networks such as this provide a vital framework for connecting experts across diverse domains to contribute to the global narrative through both evidence and advocacy.

2.1.2. KEYNOTE: Psychoterratic Health in the Symbiocene

Glenn Albrecht

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No Abstract available: Biophilosopher Dr. Albrecht spoke about the vision of Symbiocene Health "*In the era after the Anthropocene, the Symbiocene, the physical and mental health of humans will be vitally connected to health in symbiotically structured biomes at micro, meso, and macroscales*". He proposed that Symbiocene 'development' principles will provide a motive for young people to re-integrate their bodies, lives, and lifestyles to a grounded view of health. Moreover, since 'health' is a shared property between trillions of organisms within biomes at all levels, the Symbiocene offers the prospect of human sharing and collaboration in the maintenance and optimization of life and health for 'all'. Since human Earth emotions are also affected by the state of the body microbiome, the somaterratic and the psychoterratic need to be in vital positive integration at sub-bioregional levels. "*The Symbiocene is my revolutionary meme for a future for humanity that will be hugely creative, healthy, and beautiful*."

2.1.3. Redefining the Modern Health Crisis—Infectious and Socially Communicable Disease

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While infectious disease as a cause of death has declined overall, the youngest and the oldest, especially in low resource settings, remain highly vulnerable. Adding to this severe existing burden for populations living in low resource settings is an increase in non-communicable (originally defined as non-infectious) diseases (NCD). NCD had been recognized in high and middle-income countries

to be on the rise over the last few decades, but in recent times, they have begun to decline in high and upper-middle income countries, yet are rapidly rising in low-income countries. The early life (likely even prenatal and possibly preconception) is a key period determining susceptibility to NCD in later life, highlighting that a focus on early life (e.g., the first 1000 days from conception to two years of age) for interventions is paramount not only for infectious but also NCD diseases. This early life window of opportunity is highly relevant for interventions targeting not only infections, but as NCD have recently been redefined as socially communicable, associated with social connections between individuals. As the precise underlying mechanisms that drive this increased susceptibility in early life for infections and socially communicable diseases are beginning to be delineated, this early life period may change from a window of susceptibility to a window of opportunity, redirecting the developmental trajectory to one of health and well-being for life.

2.1.4. Health Impacts from Climate Change: Global Challenge with Local Impacts—Projected Local Change in Precipitation and Its Impacts on Waterborne Diseases in Canada, 2020–2080

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Background: The impact of climate change on water quantity and quality has been well described. These impacts can have profound and interrelated public health and geo-political effects [1,2]. The role of persistent drought in unrest—leading to the current Syrian crisis, which has been linked to climate change [3]—and extreme rain events that are increasing with the rising amplitude of hydrologic cycles in many parts of the world add to the burden of climate-related illness [4].

This paper focuses on changes in water availability and quality linked to climate change in British Columbia, Canada. Northern parts of the province have already seen an increase of over two degrees in average temperatures since 1900 with dramatic loss of crucial water storage capacity in melting snowpack and glaciers. Regions of the province have experienced up to 21% increased precipitation in this time period. We examined the relationship between extreme rain events and dry periods related to waterborne illness in three watersheds serving a large metropolitan area [5].

Methods: Reported cases of cryptosporidiosis and giardiasis from 1997 to 2009 in a population served by a municipal surface drinking water system were analyzed using distributed lag non-linear models. Cases were linked to drinking water source. Weekly lags in precipitation of up to six weeks were assessed and adjusted for seasonality, the preceding dry/wet period, secular trends, and holiday effects. The mean annual case counts were predicted for 2060–2069 using downscaled daily precipitation projections from 10 global climate models under a moderate emissions growth scenario.

Results: Including 7422 cases, a significant increase in cryptosporidiosis and giardiasis five to six weeks after extreme precipitation (>90th percentile) was found during the study period. A lag of five weeks was associated with the highest rate ratio (1.17; 1.07–1.24). The risk was further increased if there had been a preceding dry period, which appears to be driven by turbidity. Temperature did not contribute significantly to this risk. Climate models indicate decreases in the average weekly and extreme precipitation during dry seasons in the 2060s, but increases in rainy seasons compared with 2000–2009. The overall annual disease burden increased by 6.3–14.2% (ensemble mean 12.1%) using these estimates.

Discussion: We found a significant risk of waterborne illness associated with extreme precipitation events in a large and well-protected municipal drinking water system. The effects were most pronounced following a dry period. To try and reduce these future risks, the additional filtration of finished water is being deployed for these sources. There is a clear need to increase resilience in water systems in order to address the impacts due to climate change; however, resilience costs money, and such resources are not equally distributed. Marginalized communities are less likely to be able to afford modern filtration. In addition to addressing this inequity, British Columbia (BC) will also need to reduce greenhouse gases in order to adequately address both the local and global

challenges of climate change. The struggle by the province, First Nations, and other citizens to stop the construction of another large pipeline from the Alberta tar sands is an important and timely effort in this regard.

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2.1.5. Personal Data Clouds to Understand Wellness and Predict Disease

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Chronic diseases are the leading cause of illness globally. The number of children and adults who suffer from chronic diseases has skyrocketed over the last few decades, as urbanization and the adoption of western diets and lifestyles has increased our exposure to environmental factors that are detrimental to our health, and decreased our exposure to factors that are associated with protection. The cost of new medications is also rising, placing an increased financial burden on families and healthcare systems. P4 medicine is a radically new approach that has a strong potential to reverse this trend. The underlying concept is based on a paradigm shift from a primary emphasis on *Disease* to that of *Wellness*. Instead of focusing on the reversal of established disease, P4 medicine harnesses omics-based big data science to identify and quantify objective molecular markers related to the physiological processes that underpin wellness in healthy individuals. The approach entails following a cohort of "healthy" individuals over time, and generating personal, multi-omic data clouds for each subject at multiple time points. The data clouds are interrogated to reveal deviations from wellness, which can be thought of as early warning signals that predict disease transitions before any overt clinical symptoms manifest (e.g., elevated blood sugar levels indicate prediabetes). The personal data clouds are also utilized to identify actionable changes to diet/lifestyle, and/or other pharmacological-based interventions that are known to diminish the early signs of disease. The efficacy of interventions to restore and/or optimize wellness can be objectively assessed employing a multi-omic approach. Large international efforts are currently underway to roll out this promising approach to adults, but there are no programs in place to bring the benefits of P4 medicine to children. Notably, in utero and early infancy represents a crucial period of heightened plasticity, where gene-by-environmental interactions can lead to developmental changes that determine disease risk throughout the life course. Therefore, the potential for P4 medicine to reduce the burden of chronic diseases is maximal in the first few years of life. Blending P4 medicine with longitudinal birth cohort studies represents a promising and radically new approach to predict and prevent the development of chronic diseases.

2.1.6. The ORIGINS Project: A Local Community Project with a Global Vision

Desiree Silva [1,2,3] and Susan L. Prescott [1,2,3]

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Chronic inflammatory non-communicable diseases (NCDs) pose the greatest threat to human health globally. All of these conditions have their 'origins' in early life, and there is a pressing need to understand how the modern environment is contributing to this unsustainable health burden. There are mounting concerns that this new generation will have a shorter life expectancy than their parents. Early interventions will be the only way of curtailing this. The staggering increase in the burden of early onset NCDs—including childhood obesity, the allergy epidemic, and an increasing burden of mental ill health in children and youth—further underscore the need for early intervention. The philosophy of the ORIGINS project is that planetary health begins in every local community—that birth cohorts can be a multidimensional therapeutic strategy for the community they serve, as well as an agent of global change.

The ORIGINS Project is building a research platform to enable world-class investigations into when and why NCDs develop through the study of early environments, maternal and paternal physical health, the microbiome, and genetics. As well as facilitating strategic long-term research capacity, ORIGINS will be a pipeline for short-term productivity through a series of clinical trials, mechanistic studies, and targeted research questions—all with the ultimate goal of reducing the rising epidemic of inflammatory NCDs through 'a healthy start for a better future'.

ORIGINS is a collaboration between the Telethon Kids Institute and Joondalup Health Campus (JHC), with core funding of $26 million over the next 10 years (from the Paul Ramsay Foundation and the Australian Federal Government).

Our Plan: Over five years, we aim to recruit 10,000 women and their partners early in pregnancy and collect biological samples, routine data, and web-based questionnaires on their physical and mental health, diet, physical activity patterns, and a range of factors in their environment, creating a large biobank and databank. Initially, we will intensively follow up these families until the children are five years of age. We will then assess how these early life exposures have influenced their child's growth, development, and health. Nested within the main observational cohort will be a series of intervention studies and randomized control trials to improve modifiable aspects of the early life environment (e.g., nutrition, nature play, positive emotional assets, physical activity, microbial diversity, weight gain, and language development). ORIGINS is embedded in clinical care at JHC, and positive findings will be **promptly translated** into routine care for all families.

Our aims: The early environment in pregnancy and early childhood determine physiological, structural, immune, metabolic, and behavioral development, and influence susceptibility to both early and later onset diseases. Strategies to improve early life conditions and exposures in early life are critical in reducing the rising global burden of chronic disease.

Aim 1: To improve the health of the next generation through a better understanding of how to optimize the early environment.
Aim 2: To generate a new birth cohort at JHC with a substantial databank and biobank to enable world-class research.
Aim 3: To fully **integrate** the ORIGINS Project within the **clinical framework** of JHC.
Aim 4: To initiate and integrate harmonized **nested clinical trials** and community-based interventions within this framework.
Aim 5: To understand the interaction of newly recognized exposures, such as the gut microbiome (which has not been well studied in previous cohorts) of the mother and child as a key

determinant of health and the risk of common NCDs (because of recognized immune, metabolic, and neurodevelopment effects).

Aim 6: To utilize new P4 (personalized medicine) technology platforms (such as epigenetics, metagenomics, metabolomics, and proteomics) to understand the underlying inflammatory mechanisms and other pathways that lead to the current NCD burden.

Aim 7: To harmonize with other major birth cohort studies, nationally and internationally, to enable more collaborative work in the future; potentially allowing for the identification of risk factors in more rare health outcomes requiring large sample sizes.

ORIGINS is already a significant asset for the community with ongoing potential to improve child and adolescent health; maternal, paternal, child, and adolescent health research capacity; research productivity; research collaboration; and translational impact. ORIGINS will also generate many opportunities to explore the underlying mechanisms of environmental influences and how these vary with genetic predisposition. It will generate a significant biorepository (DNA, breast milk, urine, plasma, and mononuclear cells), building substantial additional future capacity to address critical questions (including genetic, epigenetic, metagenomic, and metabolomic studies) as technologies and new avenues of investigation evolve. We encourage community-driven research. Consumer and community representation and participation has been incorporated into the ORIGINS governance structure to ensure that the community is fully engaged and informed. We also have strong links with other birth cohorts locally, nationally, and internationally, and we are working toward developing a global cohort network to harmonize and mutually enhance research capacity.

How this is different from other cohort initiatives: ORIGINS is fully integrated into clinical care and community services, with real-time feedback and intervention. It is grounded in making meaningful changes in policy and practice that will reduce the burden of common health conditions through early interventions. In addition to observational data, this will provide a framework for a series of smaller intervention studies that will be nested within the main observational cohort (each to be funded separately). Interventions will be focused on improving the modifiable aspects of the early life environment (such as nutrition, physical activity, time spent indoors and outdoors, smoking and pollutants, microbial diversity, and water, air, and food quality). These are the most logical, large-scale and effective long-term strategies to improve *all aspects* of physical and psychological well-being, both in childhood and in later life. These interventions will be strategically coordinated, optimizing on harmonized recruitment processes and harmonized 'outcomes' and 'exposures' data measures. This more integrated approach will ensure more strategic interdisciplinary collaboration, coordinated follow-up with greater economies of scale, and a more holistic multisystem approach to achieving a healthier start to life for the long-term health of the community.

2.2. Session 2: Natural Environments, Immune Health, and Well-Being

2.2.1. Natural Environments, Microbiota, and Immunoregulation in Mental Health: Implications for Public Health

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Over a decade ago, the then-director of the National Institute of Mental Health, Thomas Insel, proposed that, "In contrast to researchers in cancer and heart disease who have sought cures and preventions, biological psychiatrists in both academia and industry have set their sights on incremental and marketable advances, such as drugs with fewer adverse effects," and furthermore, that, "Psychiatry will need to develop strategies for [the] prevention for each of these disorders" [1]. One approach to the prevention of psychiatric disorders is to identify risk factors and design interventions that target these risk factors and mitigate risk. Increasing evidence suggests that chronic low-grade inflammation and exaggerated immune (re)activity, which may reflect impaired

immunoregulation, is a risk factor for trauma and stressor-related disorders, as well as affective disorders [2]. For example, those with a diagnosis of post-traumatic stress disorder (PTSD) have ana increased risk of autoimmune disease relative to other psychiatric disorders and those with no psychiatric disorder [3], while increased biomarkers of inflammation prior to trauma exposure are predictive of PTSD symptoms following trauma exposure [4]. Overall, inflammation-related disorders are increasing in modern urban societies. One hypothesis that has been proposed to explain these increases is the hygiene hypothesis, biodiversity hypothesis, or "old friends" hypothesis. According to the "old friends" hypothesis, inflammation-related disorders are increasing in modern urban settings due to impaired immunoregulation subsequent to reduced exposure to diverse microorganisms with which humans co-evolved. Immunoregulation, which is indicated by a balanced expansion of effector T cell populations (i.e., Type 1 T helper (Th1), Th2, and Th17 cells) and regulatory T cells (Treg, which induce immunoregulatory and anti-inflammatory responses), is known to be driven by microbial signals, mainly by organisms with which mammals co-evolved, including: (i) the commensal microbiota, which have been altered by the Western lifestyle, including a diet that is commonly low in microbiota-accessible carbohydrates; (ii) pathogens associated with the "old infections" that were present throughout life in evolving human hunter–gatherer populations; and (iii) organisms from the natural environment with which humans were inevitably in daily contact (and so had to be tolerated by the immune system). Immunoregulation is thought to be compromised in modern high-income settings due to reduced contact with these three categories of organisms. In support of this hypothesis, we recently demonstrated that immunization with a heat-killed preparation of the soil-derived bacterium, *Mycobacterium vaccae* NCTC 11,659, prevents the development of a PTSD-like syndrome in a murine model, the chronic subordinate colony housing (CSC) model of chronic psychosocial stress [5]. Immunization with *M. vaccae* induced a more proactive behavioral coping strategy during psychosocial stress, attenuated stress-induced changes in the alpha and beta diversity of the gut microbiome, and prevented stress-induced spontaneous colitis and the stress-induced exaggeration of chemically induced colitis in a model of inflammatory bowel disease (IBD). The latter effects were associated with reduced anti-CD3-stimulated release of pro-inflammatory cytokines, interferon gamma and interleukin 6, from freshly isolated mesenteric lymph node cells stimulated in vitro, and increases in the anti-CD3-stimulated release of the anti-inflammatory cytokine, interleukin 10. Finally, immunization with *M. vaccae* prevented stress-induced increases in anxiety-like behaviors. Together, these findings are consistent with the "old friends" hypothesis, and suggest that restoring exposures to immunoregulatory environmental microorganisms or their component parts may have benefits for prevention or treatment of inflammation-related outcomes, including the risk of trauma and stressor-related disorders.

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2.2.2. Urban Landscapes, Mobility, and Environmental Exposure: A Prospective Nationally Representative Study of Children Aged 10/11 Years, Scotland, UK

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The environment where we live, work, travel, and socialize has a profound influence on health. Those who are born just five miles apart in Glasgow have a difference in life expectancy of 13.9 years for males and 8.5 years for females. Existing literature typically uses 'neighborhood' as the unit of analysis, assuming often (either explicitly or implicitly) that people live in, and their health is influenced by, a spatially defined unit. The aim of this study is to describe urban mobility and environmental exposure across the entire urban landscape.

Using the 'Studying Physical Activity in Children's Environments across Scotland' (SPACES) study, we developed a novel concept to construct a model of the entire urban landscape within the Central Belt of Scotland. The model used a 25 m^2 grid system (~3 million grid squares) in which each grid cell captured detailed built-environment information such as: the road network, retail outlets, leisure centres, and greenspace, together with other contextual information such as walkability measures and SES (Socioeconomic status). SPACES used GPS to collect individual-level mobility information for over 800 10-year-old children over the course of one week. Each child's location was recorded every 15 s during waking hours. GPS tracks were joined to the urban landscape model. This created a comprehensive land-use description with an understanding of whether and when each child visited each grid cell, and what the environment there is like.

Using negative binomial regression, we explored which features of the built environment were associated with the child visiting that space at all, and with the time spent there. The study found features of the built environment which, regardless of distance from home, children were more or less likely to spend time in contact with. The findings highlighted interactions between mobility across the landscape and both individual (gender) and household characteristics (parent education attainment).

2.2.3. Nature Relatedness and Mental Health

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For most of humanity's existence, the natural environment has been an important physical context in which we developed and lived. However, modern life diverges considerably from this ancestral history, and allows many to live largely disconnected from nature in their day-to-day lives. Nevertheless, some individuals still manage to maintain a connection to nature. Differences in how people relate to the natural world have implications for the health of the planet, as those with a stronger connection to nature are more likely to hold pro-environmental attitudes and engage in sustainable behaviors [1,2]. However, is a connection to nature also associated with the health of individuals, in particular their mental health? An answer to this question emerges from two of my research projects on this topic. The first is a meta-analysis examining the link between nature relatedness and subjective well-being [3]. Quantitatively summarizing data from 30 samples with over 8500 individuals in total, my co-authors and I found that those who are more connected to nature report higher life satisfaction, more positive emotions, and a greater sense of vitality. Noticing that the majority of the research in this area had been conducted in a limited number of countries, the second research project examined the cross-cultural generalizability of nature relatedness' positive association with mental health [4]. Recruiting almost 1400 individuals from Canada, Japan, and Russia, my co-authors and I found that being connected to nature is related to emotional, psychological, and social well-being in all three cultures. These findings suggest that one's relationship with nature may play an important role in

promoting a variety of aspects of mental health. To further understand the links between nature relatedness and human health, more research is needed involving indicators of physical health.

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2.2.4. A Dose of Nature: An Interdisciplinary Study into the Co-Benefits of Green Prescriptions, and a Proposal of the GRx-Loop Hypothesis

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Context: It is becoming widely recognized that natural environments play a positive role in the health and well-being of humans [1,2]. Maintaining this relationship and understanding the mechanisms behind the health benefits that we derive from nature is important for public and planetary health. The need to understand and promote the benefits is amplified by our recent (evolutionarily speaking) urban-centric trajectory, which has led to changing biological and social interactions, and to a rise in non-communicable diseases (NCDs) [3,4].

Green Prescriptions (GRx) are broadly recognized as 'nature-based interventions' that have the potential to provide significant benefits to the management and prevention of chronic health conditions i.e., NCDs. GRx are prescribed physical, social, and/or conservation-based activities, or simple contact (multisensory) with natural environments. GRx may also lead to important 'co-benefits' for biodiversity conservation, and positive cascading impacts upon community stewardship/development, social integration, and environmental sustainability.

Aims: It is acknowledged that GRx are underutilized, and some of the reasons limiting widespread adoption will be investigated as part of this interdisciplinary PhD, which combines social science and ecology-based science (macro and micro). Developing an understanding of factors affecting the design, implementation, and impacts of GRx on human health and biodiversity conservation is a key aim.

Systems Thinking: *The GRx-Loop Hypothesis*—a six-phase model to:

- Understand the mechanisms behind GRx (referral system);
- Investigate the impacts of conservation activities upon the health of GRx users and on biodiversity, including the diversity of the environmental microbiome in the areas of GRx implementation; and
- Determine whether there is a virtuous/positive feedback effect, whereby GRx appointments eventually increase and non-medical GP appointments decrease, with reinforcing impacts on urban biodiversity.

Methods: This project will include a range of methods from social sciences (action research, walking interviews), and biosciences (innovative ecological methods including remote-sensing, bioacoustics analysis using programmed detectors, ground-based surveys, and sampling/analysis of the environmental microbiome.

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2.2.5. High-Throughput Modeling of Neonicotinoid-Induced Pathogen Susceptibility in *Drosophila melanogaster* Identifies a Beneficial Role of Lactobacilli Supplementation

Brendan A. Daisley [1,2], Mark Trinder [1,2], Tim W. McDowell [3], Hylke Welle [1,2,4], Josh S. Dube [2], Sohrab N. Ali [2,5], Hon S. Leong [2,6], Mark W. Sumarah [3] and Gregor Reid [1,2,6]

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Pesticides are used extensively in food production to maximize crop yields. However, neonicotinoid insecticides exert unintentional toxicity to honey bees (*Apis mellifera*) that may partially be associated with massive population declines referred to as colony collapse disorder. We hypothesized that imidacloprid (a common neonicotinoid; IMI) exposure would make *Drosophila melanogaster* (an insect model for the honey bee) more susceptible to bacterial pathogens, heat stress, and intestinal dysbiosis. Our results suggested that the immune deficiency (Imd) pathway is necessary for *D. melanogaster* survival in response to IMI toxicity. IMI exposure induced alterations in the host microbiota, as noted by increased indigenous *Acetobacter* and *Lactobacillus* spp. Furthermore, sub-lethal exposure to IMI resulted in decreased *D. melanogaster* survival when simultaneously exposed to bacterial infection and heat stress (37 °C). This coincided with exacerbated increases in *TotA* and *Dpt* (Imd downstream pro-survival and antimicrobial genes, respectively) expression compared to controls. The supplementation of IMI-exposed *D. melanogaster* with *Lactobacillus plantarum* ATCC 14,917 mitigated survival deficits following *Serratia marcescens* (bacterial pathogen) septic infection. These findings support the insidious toxicity of neonicotinoid pesticides and the potential for probiotic lactobacilli to reduce IMI-induced susceptibility to infection.

2.2.6. Impact of Environmental Pollutants on Child Health from a Geographic Perspective

Alvaro Orsonio-Vargas (Canada)

No abstract available: Dr. Orsonio-Vargas discussed approaches to understanding the relationship between hazardous air pollutants and adverse birth outcomes (ABO), and the unknown relationship with pollutants released by industry. This knowledge gap is even greater when considering mixtures of pollutants. The findings of these analyses are now published elsewhere in the *Challenges* journal as part of the special issue on planetary health.

1. Ngwezi, D.P.; Hornberger, L.K.; Cabeza-Gonzalez, J.L.; Chandra, S.; Fruitman, D.; Osornio-Vargas, A. Tracking Trends in Emissions of Developmental Toxicants and Potential Associations with Congenital Heart Disease in Alberta, Canada. *Challenges* **2018**, *9*, 28.
2. Ngwezi, D.P.; Hornberger, L.K.; Serrano-Lomelin, J.; Nielsen, C.C.; Fruitman, D.; Osornio-Vargas, A. Industrial Developmental Toxicants and Congenital Heart Disease in Urban and Rural Alberta, Canada. *Challenges* **2018**, *9*, 26.

2.2.7. Governance and Empowerment for Health in Indigenous Communities

Jamie Snook

Executive Director, Torngat Wildlife, Plants and Fisheries Secretariat. PhD Student, University of Guelph, Guelph, ON N1G 2W1, Canada

No abstract available: Indigenous researcher and community leader Jamie Snook discussed the vision of the Torngat Wildlife, Plants, and Fisheries Secretariat, which encompassed healthy ecosystems and healthy communities with shared stewardship of wildlife, plants, and fisheries. This needs to recognize the complex social determinants of health at the proximal level (land and ecosystems, food systems security, livelihood of local peoples), intermediate level (community capacities, indigenous knowledge systems and cultures), and the distal level (the importance of self-determination, and the influence of colonialism, law policy racism, and gender issues). The goal is Inuit co-management: governance by, for, and with Inuit.

2.2.8. Spatial Relationships of Neighborhood Vegetation Greenness and Infant Gut Microbiota

Charlene Nielsen

Earth and Atmospheric Sciences and Pediatrics, University of Alberta, Edmonton, Edmonton, AB T6G 2R3, Canada

No abstract available: Charlene Nielsen explored the use of spatial data and methods to determine the relationship between residential greenness and infant gut microbiota. Preliminary results were presented. The final results are not available at this stage, and will be published in the near future.

2.2.9. The Effects of Aeroallergens on Asthma and Allergy in Canada: Another Impact of Climate Change?

Cecilia Sierra-Heredia [1], Ryan Allen [1], Sarah B. Henderson [2], Jordan Brubacher [1] and Tim Takaro [1]

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Over the past 50 years, there has been a steep increase in the incidence and prevalence of childhood asthma and allergies worldwide. This trend has occurred over such a short period that it cannot be entirely explained by genetic modifications within the human population. Given that environmental factors also play a role in the development of atopic disorders, it has been hypothesized that climate change may be partially responsible for the observed increase.

Pollen is an important allergen in ambient air, and is thus important to explore as an environmental factor in the development of asthma and allergy. Pollen grains contain non-infectious proteins that can induce an immune response in some people. For those who are sensitive to the proteins, pollen can trigger adverse allergic reactions.

Climate change has the potential to affect pollen exposures via four different mechanisms: (1) increasing the length of the pollen season; (2) altering the number of pollen grains produced; (3) increasing the allergenicity of each grain; and (4) changing the geographic ranges of plant species. These changes may result in further increases in the incidence and prevalence of asthma and allergies

and related healthcare expenses. As such, better understanding of pollen seasons, counts, properties, and distributions is needed for public health planning. We are currently undertaking a study that will be the first to describe temporal patterns in pollen concentrations using 16 years of measurements in the Canadian cities of Vancouver, Edmonton, Winnipeg, and Toronto.

2.2.10. The Associations between Natural Environments and Health Outcomes Are Complex and Understudied

Andrew S. Bossick [1,2] and Ganesa Wegienka [1]

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[2] PhD Student, University of Washington, Seattle, WA 98105, USA

Background: The associations between natural environments and health outcomes are complex and understudied.

Objective: As the Nature Relatedness Scale (NRS) has not been previously used by clinical researchers at our institution, we sought to understand study participant receptivity to the NRS.

Methods: Patients enrolled in the Patient Advisor (PA) program at Henry Ford Health System (HFHS) in Detroit, Michigan, USA and its metropolitan area were asked to read the Nature Relatedness questionnaire, complete up to five brief questions, and provide written comments on their thoughts about the questionnaire. PAs are patient volunteers recruited to provide their opinions on various topics related to clinical care and research at HFHS. No additional instructions for reviewing the questionnaire were offered. The review process was conducted entirely electronically.

Results: Of the 54 responders, 85.2% stated that they would complete the survey if asked, 85.2% found the survey to be "easy" to "extremely easy to complete", and 77.8% were "comfortable" to "extremely comfortable" with answering the questions on the survey. However, 14.8% said they would not complete the NRS. Some of the cited reasons were because it: was "frivolous"; had "bad" questions; made "no sense"; and, appeared to be related to "mental health issues" (versus "general" health). One respondent reported: "It seems to have political undertones." Additional concerns were about researcher motives for administering this survey, the broadness of questions, or that it was too long and the scale should be changed. Some respondents reported that the survey was "interesting and thought provoking", "good", and had an "interesting premise".

Conclusions: Overall, a great majority of respondents would answer the NRS if asked. In our location, it may be beneficial to introduce the NRS with a brief description of what the NRS is meant to measure and why it has been included in data collection.

2.2.11. Geospatial Measurement of the Outdoor Natural Environment: Preliminary Results from a Review and Future Recommendations

Suzanne Mavoa

School of Population and Global Health, University of Melbourne, Parkville, VIC 3010, Australia

Research investigating the health benefits of outdoor nature has established that exposure to green space and urban vegetation is associated with positive mental and emotional effects. However, the relationship between urban nature and physical health is less well understood. The mechanisms by which this occurs, and the specific aspects of green space that are important for health are unknown. Furthermore, nature encompasses more than just green space. While researchers are beginning to investigate broader aspects of nature, such as blue space and biodiversity, the relationship between these other natural features of the environment and health also represents an important knowledge gap. A fundamental limitation that makes it difficult to overcome these knowledge gaps is the lack of data and methods with which to more comprehensively and specifically measure outdoor nature. To address this gap, this study aims first to review and evaluate existing geospatial methods of objectively measuring the natural environment in health research. The second aim is to draw on

research from other fields to propose new methods that better capture the specific aspects of nature that are of relevance to health. Preliminary results of the review and recommendations for future measurement of the outdoor natural environment were presented.

2.2.12. Disconnect from Nature Is Apparent in High-Rise Apartment Dwellers—Results from Comprehensive Lifestyle Surveys

Danica-Lea Larcombe [1], Susan Prescott [2], Alan Logan [3], Eddie van Etten [1] and Pierre Horwitz [1]

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Introduction/Aim: Biodiversity (which includes trees and all other species) is continuing to decline worldwide in many urban areas. A reasonable case can be that people living in high-rise apartment buildings built in place of greater biodiversity have a reduced exposure to soil, plants, and animals, but do residents make an effort to visit green spaces to compensate for it, or do they choose to ignore nature altogether, and what might be the consequences?

Methods: This study investigates the relationships between high-rise apartments, environmental biodiversity, and the biodiversity of the human skin microbiota. Forty-three eligible participants to date have randomly received either three real or artificial indoor plants, and are being tested for stress (SF36 Health Survey), lifestyle factors (Lifestyle Survey), and communities of skin bacteria (16S DNA Sequencing) over a 12-month period, both before and after receiving plants. In addition, lifestyle surveys are invited from all high-rise apartment dwellers in the city of Perth, Western Australia.

Results: Lifestyle factors from 85 surveys indicate that many high-rise apartment dwellers have poor nature relatedness and do not like (43%) or are unsure about (20%) getting their hands dirty in soil. Dwellers do not often (30%) or are unsure (15%) about going out in nature. Visits to local parks were less than once per month, if at all, for 44% of respondents, whilst many never visited natural bushland areas (38%), forested national parks (46%), or farms with animals (80%). It was found that 81% of respondents do not have access to a community garden, and of those who do, 81% do not garden in it. Overall, 80% of residents do not participate in gardening at all.

Conclusion: Disconnect with nature is apparent in high-rise apartment dwellers. The consequences may be higher stress levels and a reduction in the diversity of human microbiota, which leads to inflammation and the development of chronic disease. The lack of exposure to environmental microbiota due to disconnect from nature in high-rise apartment environments may lead to an 'immune adaption syndrome', which is the term for the inability to adapt to microbe-poor environments.

2.2.13. Measuring Connectedness to Nature in Preschool Children in an Urban Setting and Its Relation with Psychological Functioning and Quality of Life

Tanja Sobko [1], Zhenzhen Jia [1] and Gavin Brown [2]

[1] School of Biological Sciences, Faculty of Science, The University of Hong Kong, Hong Kong, China
[2] Faculty of Education & Social Work, The University of Auckland, Auckland 1010, New Zealand

Background: Urban residents are less connected with nature [1,2]. The natural outdoor environment is beneficial for health [3], and many intervention programs aim to promote healthy lifestyle by reconnecting children with nature [4]. Since no valid tools to measure Connectedness to Nature (CN) in young children are available today, it is difficult to evaluate the effect of relevant interventions. The objective of this study was to develop such a tool.

Methods: A new CN index for parents of preschoolers (CNI-PPC) was developed based on the previously existing original CNI for school children [5]. The CNI-PPC was tested in urban population for its external validity and internal consistency (n = 493). The internal structure of the CNI-PPC was

tested by confirmatory factor analysis. The Strength and Difficulties Questionnaire (SDQ), a valid tool for assessing children's quality of life and mental functioning, assessed CNI-PPC external validity.

Results: The 16-item scale adequately captured four major factors: enjoyment of nature (Cronbach's α = 0.86), empathy for nature (0.87), sense of responsibility (0.75), and awareness of nature (0.80). Three CNI-PPC were highly related to the outcomes of SDQ: (1) the more enjoyment of nature the children displayed, the less overall impairment and distress they had; (2) the higher sense of responsibility the children had, the less hyperactivity, fewer behavioral/peer difficulties, and better prosocial behavior they exhibited; (3) the more they were aware of nature, the less emotional difficulties they experienced. Variance explained was large (range R^2 = 0.42 to 0.80). Overall, the CNI-PPC factors had strong relationships with the mental functioning and life quality that parents perceived in their children.

Conclusions: The results indicated that the CNI-PPC is a valid and meaningful tool to measure the CN of preschoolers by parents. This simple parent-proxy scale may help practitioners and researchers to quantify preschoolers' CN and investigate how it influences their lifestyle-related habits and physical/psychological functioning.

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2. Louv, R. *Last Child in the Woods: Saving Our Children from Nature-Deficit*; Algonquin Books: New York, NY, USA, 2008.
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2.2.14. Improved Eating Habits and Active Playtime through Connecting Preschool Children to Nature: Preliminary Results of a Randomized Controlled Trial

Tanja Sobko [1], Zhenzhen Jia [1], Linna Ma [1], Chiahuei Tseng [2] and Matthew Kaplan [3]

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[3] College of Agricultural Sciences, Pennsylvania State University, University Park, PA 16802, USA

Background: Preschoolers in Hong Kong live an unhealthy lifestyle, as they spend much time in sedentary activities and have poor eating habits [1,2]. Since the outdoor activities improve physical and mental health [2–4], this randomized controlled trail aimed to test whether connecting families with nature could positively influence the dietary and physical activity habits of urban preschoolers.

Methods: The studied outcomes were compared before and after the Play&Grow program in the intervention arm (n = 102, aged 36 $\pm$ 3.8 months, boys n = 53). The families attended the Play&Grow sessions weekly for 10 weeks. Play&Grow is a locally developed, healthy lifestyle intervention program that included a novel element: connectedness to nature. Each session contained: outdoor play time, a short discussion on health/environmental topics, food activities (play with and taste vegetables), and nature discovering (touch, listen, smell, see, and feel the nature) [5]. Dietary and activity habits were assessed by validated questionnaires and activity trackers. Repeated measures t-test was used to analyze the outcomes.

Results: After the intervention, the children: (a) were more connected to nature ($p = 0.002$), especially in their sense of responsibilities ($p = 0.001$); (b) spent more time on light intensity activities (weekday: $p = 0.008$; weekend: $p < 0.001$) and moderate intensity activities (weekend: $p < 0.001$); (c) had improved eating habits, reflected in food responsiveness ($p = 0.001$), food fussiness ($p = 0.003$), slowness in eating ($p = 0.002$), emotional undereating ($p < 0.001$), and vegetable consumption ($p < 0.001$); and (d) improved quality of life, reflected in physical functioning ($p = 0.009$). The parents improved in instrumental feeding ($p < 0.001$), emotional feeding ($p < 0.001$), and encouragement to eat ($p = 0.011$).

Conclusions: These results provide preliminary evidence that the novel healthy lifestyle promotion program Play&Grow has significant positive health-related influences on preschool children. We therefore suggest, based on our results, to expose younger children to outdoor and indoor nature-related activities, and offer our short and simple Play&Grow program protocol for a wider audience.

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2. Thompson Coon, J.; Boddy, K.; Stein, K.; Whear, R.; Barton, J.; Depledge, M.H. Does participating in physical activity in outdoor natural environments have a greater effect on physical and mental wellbeing than physical activity indoors? A systematic review. *Environ. Sci. Technol.* **2011**, *45*, 1761–1772.
3. Ling, J.; Robbins, L.B.; Wen, F. Interventions to prevent and manage overweight or obesity in preschool children: A systematic review. *Int. J. Nurs. Stud.* **2016**, *53*, 270–289.
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2.3. Session 3: Planting the SEEDS: Establishing Healthy Microbial Habitats in Early Life

2.3.1. Gut Bacteria, Host, and Dietary Metabolic Interplay during Colonization in Early Life

Niels van Best [1,2], John Penders [2], Ulrike Rolle-Kampczyk [3], Martin von Bergen [3,4], Frank Schaap [5], Steven Olde Damink [5], Paul Savelkoul [2] and Mathias Hornef [1]

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The adult intestine harbors a dense and relatively stable microbial community. In contrast, neonates are born essentially sterile, with the establishment of the microbiota starting upon rupture of the amniotic membranes. Since most dramatic changes in bacterial density and composition are observed during early life, this phase might critically influence the ultimate microbial composition and the lifelong maintenance of host–microbial homeostasis. Given the importance of the gut microbiota in the development of various non-communicable diseases, it is pivotal to have a comprehensive understanding of the dynamics in the gastrointestinal microbial ecosystem in early life. We aimed

to examine the interplay of microbiota functional development and host metabolism depending on the diet.

Therefore, the combination of transcriptomics, metabolomics, and microbial profiling was used to characterize the site-specific colonization dynamics of the murine intestine during the postnatal period. Next to 16S rRNA gene sequencing, transcriptomic analysis was performed, as well as the high-throughput mass spectrometry-based metabolite profiling of digestive and systemic organs to examine changes in the quantity and composition of metabolites.

The microbiota composition appeared highly individual directly after birth, but changed into a more homogenous pattern within one week. Moreover, the gastrointestinal tract harbored a comparable microbiota composition during the pre-weaning period, but shifted toward its site-specific pattern thereafter. The bacterial alterations coincided with changes in hepatic and gastric metabolites.

Suggested Reading

1. Van Best, N.; Hornef, M.W.; Savelkoul, P.H.M.; Penders, J. On the origin of species: Factors shaping the establishment of infant's gut microbiota. *Birth Defects Res. Part C Embryo Today Rev.* **2015**, *105*, 240–251.
2. Van Best, N.; Jansen, P.L.; Rensen, S.S. The gut microbiota of nonalcoholic fatty liver disease: Current methods and their interpretation. *Hepatol. Int.* **2015**, *9*, 406–415.

2.3.2. The Indoor Environmental Microbiome and Atopy Development in Childhood

Kei Fujimura and Susan Lynch

Division of Gasteroenterology, Department of Medicine, University of California—San Francisco, San Francisco, CA 94143, USA

No abstract available: Dr. Fujimura discussed the parallel development the human gut microbiome and infant immune maturation in early life, and explored the hypothesis that there may be distinct patterns of early-life gut microbiota that are related to the risk of disease (childhood atopy and asthma), and whether these may be influenced by early life house dust microbiota. She presented findings from the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) cohort, which suggest that the neonatal gut microbiota state is associated with the risk of childhood atopy and asthma. Specifically, products associated with a high-risk neonatal gut microbiota profile appear to induce pro-allergic inflammation and suppress T regulatory cells. She concluded:

- Early life gut microbiome is perturbed and metabolically reprogrammed in those at high-risk for childhood atopy and/or asthma
- The associated products of the high-risk neonatal gut microbiota promote allergic inflammation from previously healthy human T cells in vitro
- Infants with a high-risk microbiome profile are exposed to less bacterial diversity in early life and share fewer taxa from with their environment.

Suggested Reading

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2.3.3. Maturation of the Gut Microbiome: Early Complexity Protects against Asthma Risk

Jakob Stokholm

COPSAC Study, University of Copenhagen, and Departments of Medicine and Microbiology, and the Human Microbiome Program, New York University, New York, NY 10003, USA

No abstract available: Dr. Stokholm presented the findings of his team's recent Nature Communications paper [1], which found that one-year-old children with an immature microbial composition have an increased risk of asthma at age five years. He concluded that: fecal microbial diversity scores increased over the first year of life with changes in the dominant taxa and that, using clustering methods (partitioning around medoids), two distinct cluster patterns could be identified with age. Asthma risk is associated with composition at one year of age (beta diversity, specific bacterial genera, and delayed microbial maturation). This microbial effect was modulated by maternal asthma status.

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2.3.4. Interactions between Systemic Immunity and Gut Microbiome in Four Infant Populations

Nelly Amenyogbe [1], Pedro Dimitriu [2], Kinga Smolen [1], Eric Brown [3], Brett Finlay [3], Tobias Kollmann [4] and William W. Mohn [2]

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Systemic immune responses in early life differ between geographically distinct populations, often manifesting as critical differences in susceptibility to both infectious and inflammatory disease and response to vaccinations. While genetics certainly play a role, the microbiome also guides immune development, starting at birth. However, to what extent innate immune phenotypes vary between populations, and whether this is in part driven by unique microbial exposures, is largely unknown. To address this gap in knowledge, we compared innate immune cytokine responses to bacterial products, Toll-like receptor (TLR) agonists, among two-year-old infants from Belgium, Canada, Ecuador, and South Africa. Additionally, the fecal microbiome was measured using 16S amplicon sequencing. By integrating immune and microbiota datasets, we were able to detect microbial taxa that correlated to cytokine production within each population in a pattern reflecting the type of TLR agonist used, including associations between pro-inflammatory cytokines and bacterial taxa that were consistently detected across multiple cohorts. Strikingly, we found that South African infants profoundly underresponded to TLR agonists compared to infants from any other cohort. To test a possible cause-and-effect relationship between their gut microbiomes and immune response, we gavaged germ-free mice with stools from either South African (SAF) or Canadian (CAD) infants, as these populations harbored the most distinct microbiomes and immune phenotypes. Splenocytes from SAF-gavaged mice mounted weaker cytokine responses to TLR agonists compared to CAD-gavaged mice, which was consistent with the corresponding infant immune phenotypes. Accordingly, the SAF mice also exhibited small intestine villous blunting and decreased gut barrier integrity. Our findings suggest that variable systemic immunity between populations is in part driven by different microbial exposures, and with that, the magnitude of inflammatory response in healthy individuals may vary according to the host's microbial environment.

2.3.5. Developmental Trajectories of the Child Microbiome: New Lessons from Scandinavia and Beyond

Karsten Kristiansen

Laboratory of Genomics and Molecular Biomedicine, Department of Biology, University of Copenhagen and Institute of Metagenomics, BGI-Research, Shenzhen 518803, China

No abstract available: Dr. Kristiansen presented results from his recent collaborations that investigated the microbiota of the female reproductive tract and why it may matter [1]. The findings indicate that the entire female reproductive tract is extensively inhabited by bacteria, with large variation between individuals. The bacterial communities represent a continuum along the entire reproductive tract, raising the question of whether there is colonization of the fetus already in the uterus. He also presented data showing that maternal fecal microbiota is the dominant contributor to the gut microbiota at birth, with an apparently minor contribution from the vagina. The effects of caesarian versus vaginal delivery may still be seen even at five years at age. Early life events and lifestyle correlate with the composition of the gut microbiota in early school age children, including dietary patterns. However, the impact of dietary intake on metabolic responses differs between children according to gut microbiome enterotype. This suggests that it is important to consider stratification according to enterotypes in dietary intervention studies.

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2.3.6. Distinct Early Immune Phenotypes Associating with Later Disease Development

Susanne Brix

Technical University of Denmark, 2800 Lyngby, Denmark

No abstract available: Dr. Brix discussed the relationship between early immune profiles and the developmental trajectory to later childhood diseases, with a focus on the great heterogeneity in innate immune responses in relation to the risk of atopic dermatitis. Her research described non-overlapping atopic dermatitis-related immune phenotypes, and observed that 67% of atopic dermatitis (AD) cases were accounted for by four immune phenotypes. She concluded that the immune trajectory to childhood asthma, allergic rhinoconjunctivitis, and atopic dermatitis is imprinted in early life; that there are distinct immune phenotypes for each disease; and that selective perinatal risk factors define each disease-linked immune phenotype. Various genetic and environmental factors may influence disease trajectories, but importantly, most of the phenotypes were reflected in adverse immune reactions to microbial components from ssRNA-holding vira and bacteria.

2.3.7. Quantitative Profiling of IgG-Coated Gut Bacteria from IBD Patients

Carsten Eriksen [1,2], Daisy Jonkers [3], Simone Jensen [1], Pi W. Bondegaard [1], Heike Becker [4], Karsten Kristiansen [2,5], John Penders [6] and Susanne Brix [1]

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We propose a new method combining quantitative bacterial enumeration with the profiling of immunoglobulin G (IgG) isotype-specific coating by flow cytometry to study inflammatory responses directed against gut bacteria. By analyzing fecal samples collected from 11 Crohn's disease (CD),

11 ulcerative colitis (UC) patients with active disease (determined by fecal calprotectin levels), as well as 20 healthy controls, we here provide novel insight into the disease phenotypes of patients suffering from inflammatory bowel diseases (IBDs).

The profiling revealed a shift in the IgG2:IgG4 and IgG2:IgG1 coating ratio in UC patients compared to the CD patients and healthy controls. A shift away from the healthy coating profile dominated by IgG1 and IgG4-coating toward an IgG2-coating profile links to a more pro-inflammatory Type 1-driven immune response. Exploration of clinical parameters showed a positive association between the number of IgG2-coated bacteria from UC patients and C-reactive Protein (CRP), as well as the simple clinical colitis activity index (SCCAI), while a negative association was observed between the number of IgG4-coated bacteria and CRP and SCCAI. We propose the use of quantitative profiling of an IgG-subtype coating of bacteria as a way to identify inflammatory interactions between the host and gut bacteria by non-invasive means. By applying the methodology to fecal samples from IBD patients, we were able to identify novel gut inflammatory responses to bacteria and associations to distinct disease phenotypes.

2.3.8. Maternal Lifestyle Factors and Infant Gut Microbiome

Merete Eggesbø [1], Nina Iszatt [1], Siddhartha Mandal [2], Cecilie Dahl [3] and Maggie Stanislawski [4]

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[4] Colorado School of Public Health, Colorado, Denver, CO 80045, USA

Gut microbiota forms an integral part of the human 'supraorganism' and develops in early life. It is critical to understand how maternal factors such as weight, diet, and toxicants may alter early gut microbiota. We used data from the NoMIC (Norwegian Microbiota) cohort, n = 552 (2002–2005). Mothers provided milk samples—their own—and infants' fecal samples, and in a subset, we estimated the nutritional content of trace elements based on a FFQ. Microbial composition was assessed by Illumina sequencing and calculation of the number of OTUs (Operational Training Units), Shannon diversity, phylogenetic diversity, beta diversity, differential abundance of taxa, and short-chain fatty acids (SCFAs). In the first paper, we show that maternal pre-pregnancy overweight and obesity, as well as excessive gestational weight gain, are associated with marked taxonomic differences in the maternal gut microbiota, although they are not associated with overall differences in the infant gut microbiota over the first two years of life [1]. However, the presence of specific microbes in maternal gut was related to presence in the newborn gut for many taxa, including some lean-associated taxa. Maternal diet during pregnancy affects gut microbiota around the time of delivery, and we explored this in a second paper. Of all of the nutrients studied, Vitamin D dietary intake was the single most influential nutrient affecting diversity and composition [2], which was also supported by another study [3]. Dietary fat also had a pronounced effect on the phyla composition, with different types of fat partially shifting it in the opposite direction. Thus, dietary advice and possible nutrient supplementation provides an opportunity to influence infant gut microbiome. Finally, in a third paper, we show that low gut microbiota diversity in moms increases the risk of preterm delivery [4]. Interactions between human milk toxicants and infant microbiota will be presented separately [5]. In conclusion, we show that lifestyle factors play a role in determining the maternal and infant gut microbiome, pointing to important areas that are worth exploring further.

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3. Wang, J.; Thingholm, L.B.; Skiecevičienė, J.; Rausch, P.; Kummen, M.; Hov, J.R.; Degenhardt, F.; Heinsen, F.A.; Rühlemann, M.C.; Szymczak, S.; et al. Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. *Nat. Genet.* **2016**, *48*, 1396–1406.
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5. Iszatt, N.; Janssen, S.; Lenters, V.; Dahl, C.; Stigum, H.; Mandal, S.; Peddada, S.; Eggesbø, M. Environmental contaminants in breast milk are associated with gut bacteria composition and their metabolites in infants one month old. In preparation.

2.3.9. Delayed Gut Microbiota Development in High-Risk Asthma Infants is Temporarily Modifiable by *Lactobacillus* Supplementation

Juliana Durack, Nikole E. Kimes, Din L. Lin, Marcus Rauch, Michelle McKean, Kathryn McCauley, Ariane R. Panzer, Jordan S. Mar, Michael D. Cabana and Susan V. Lynch

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Gut microbiota dysbiosis and metabolic dysfunction in infancy precede childhood atopy and asthma development. Here, we examined gut microbiota maturation over the first year of life in infants at high risk for asthma (HR), and whether it is modifiable by early-life *Lactobacillus* supplementation. We performed a longitudinal comparison of stool samples collected from HR infants randomized to daily oral *Lactobacillus rhamnosus* GG (HRLGG) or placebo (HRP) for six months, and healthy (HC) infants. The meconium microbiota of HRP participants is distinct, follows a delayed developmental trajectory, and is primarily glycolytic and depleted of a range of anti-inflammatory lipids at six months of age. These deficits are partly rescued in HRLGG infants, but this effect was lost at 12 months of age, six months after the cessation of supplementation. Thus, we show that early-life gut microbial development is distinct, but plastic, in HR infants. Our findings offer a novel strategy for early-life preventative interventions

2.3.10. The Bacterial Exposome and Protection of Chronic Inflammatory Reactions—New Experimental Insights

Harald Renz

No abstract available: Dr. Renz discussed the ways in which the 'microbial exposome' (the collective exposure of indoor and outdoor biomes, including plant and diet-associated factors) influence the residential communities of the human microbiome. These in turn influence the development of the mucosal immune system and systemic disease predisposition. He used the example of how traditional farming environments have been shown to influence human immune development and reduce allergic risk, and how animal models have been used to modulate allergy development using the intranasal application of environmental bacteria from these farming environments (*A. lwoffii*). This consistently induces local and systemic innate immune response to prevent the allergic phenotype in mice. Collectively, these findings underscore the importance of biodiversity for human health.

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2.3.11. Restoring Neonatal Gut Biodiversity after Postnatal Antibiotics Exposure (RESTORE Trial)

Shailender Mehta and Katherine Collins

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Antibiotic use is one of the most important determinants of the early infant's gut microbiome. It is well understood that antibiotics destroy the probiotic, commensal microbes in addition to pathogenic microbes. While the microbe numbers may restore following antibiotic exposure, the diversity of the species remains impaired long after the completion of the antibiotics, creating a long-term state of *dysbiosis* [1]. The first few months of life have been described as the window period for the development of the gut microbiome, which coincides with the greatest period of plasticity of the immune system [2]. The delay in the maturation of the microbe-immune interface due to gut dysbiosis has been repeatedly linked with the development of atopic disease [3]. Probiotics are immunostimulatory, and have been shown to significantly contribute to the developing immune function of a neonate, promote tolerance, and therefore reduce atopic disease and disease states [4]. Restoring the microbiome through probiotics theoretically has significant health benefits to antibiotic-exposed infants. Most importantly, minimizing the time that an infant spends in dysbiosis using probiotics may help to reduce the likelihood of the development of asthma, eczema, and allergies, as well as obesity, diabetes, and inflammatory bowel disease [5]. We are currently undertaking a double-blind placebo controlled randomized clinical trial of multistrain probiotic in the neonatal period for antibiotics-exposed term infants with the aim of rapidly restoring their gut biodiversity (as determined through fecal microbiome analysis) and studying their immune function at the same time points. We anticipate the results to be available before the *in*VIVO meeting next year.

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4. Hörmannsperger, G.; Clavel, T.; Haller, D. Gut matters: Microbe-host interactions in allergic diseases. *J. Allergy Clin. Immunol.* **2012**, *129*, 1452–1459.
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2.3.12. Interleukin 2 Promotes Gut Homing of Human Naïve Treg Cells Early in Life

Peter S. Hsu [1,2,3], Catherine L. Lai [1,2,4], Mingjing Hu [4], Brigitte Santner-Nanan [4], Jane E. Dahlstrom [5,6], Cheng Hiang Lee [7,8], Ayesha Ajmal [5], Amanda Bullman [5], Susan Arbuckle [9], Ahmed Al-Saidi [4], Lou Gacis [1], Reta Nambiar [1], Andrew Williams [1], Melanie Wong [1], Dianne E. Campbell [1,2,3] and Ralph Nanan [4]

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Regulatory T (Treg) cells play an important role in maintaining gut immune tolerance. However, the development and tissue homing characteristics of Treg cells in children has not been studied in detail. Here, we studied the development and homing characteristics of human peripheral blood Treg cell subsets and potential mechanisms inducing homing molecule expression in healthy children. We found contrasting patterns of circulating Treg cell gut and skin tropism, with abundant gut homing Treg cells at birth and increasing skin homing Treg cells later in life. We show that Treg cells in cord blood were much more sensitive to the IL-2 induced upregulation of gut homing molecules compared to adult Treg cells. Our results suggest that early in life, naïve Treg cells may be driven for gut tropism by their increased sensitivity to IL-2, implicating a potential role of IL-2 in gut immune tolerance during this critical period of development.

2.3.13. Differences in Fecal Microbiota and Soluble Inflammatory Biomarkers in Long-Term Adolescent/Young Adult Hodgkin Lymphoma Survivors and Their Unaffected Twins

Nancy Huang [1], Jun Wang [2], Marta Epeldegui [1], Amie Eunah Hwang [2], Venu Lagishetty [1], Yang Yu [2], Laura Buchanan [2], Joshua Millstein [2], Bharat N. Nathwani [3], Guoquin Yu [4], Thomas M. Mack [2], David V. Conti [2], Otoniel Martinez-Maza [1], Jonathan P. Jacobs [1] and Wendy Cozen [2]

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Hodgkin lymphoma (HL) is one of the most common malignancies among adolescents/young adults (AYA) in economically developed settings. Although the survival rate is high, severe late effects are common. Risk decreases with increasing siblings and oral exposures early in life. Immune dysregulation is a hallmark. Since fecal bacteria modulate immune responses, we compared the fecal microbiome and serum markers of inflammation in 24 long-term AYAHL survivors and their lifetime unaffected twins. DNA extraction from stool samples was performed using bead beating in conjunction with the MO BIO Powersoil kit. First, 16S V4 ribosomal DNA sequencing was performed using an Illumina HiSeq 2500. Raw sequence data was processed in QIIME (Quantitative Insights Into Microbial Ecology) and 97% OTUs picked using the Silva database. Differences in the relative abundance were determined using DESeq2, based on negative binomial models with twin pair as a covariate. Blood samples were collected for 18 twin pairs. Luminex multiplex assays were performed for 15 biomarkers. Differences in serum biomarker levels were assessed with T-tests, and correlations were calculated using Spearman correlation coefficients. All of the *p*-values were adjusted for multiple comparisons. The AYAHL survivors had lower alpha diversity compared to their unaffected twin (Shannon index $p = 0.0483$). Significant differences in the relative abundance of the following were observed between AYAHL survivors and their unaffected twins: *Streptococcus* ($p = 9.7 \times 10^{-5}$), *Sellimonas* ($p = 0.005$), *Erysipelotrichaceae*, ($p = 0.020$), *Faeclitalea* ($p = 0.035$), *Veillonella* ($p = 0.040$), *Faecalibacterium* ($p = 0.026$), *and Eubacterium oxidoreducens* ($p = 0.028$). All but the last two were more abundant in survivors. Serum IL6 ($p = 0.03$) and VEGF (Vascular endothelial growth factor) ($p = 0.04$) levels were higher in AYAHL survivors compared to unaffected twins. There were statistically significant correlations ($p < 0.003$) between differences in Erysipelotrichaceae (known to be increased after extensive antibiotic use) and serum IL6 and IL2Ra levels. It is unknown if these differences are markers of an abnormal immunophenotype that predates diagnosis, or if they are a persistent result of treatment.

2.3.14. Gut Microbial Composition and Diversity in Young Children with Recurrent Asthma-Like Symptoms: A Case-Control Study

Liene Bervoets [1], Kim van de Kant [2], Niels van Best [1,3], Michiel Bannier [2], Paul Savelkoul [1], Edward Dompeling [2] and John Penders [1]

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[3] Institute of Medical Microbiology, RWTH University Hospital Aachen, 52074 Aachen, Germany

Asthma is the most common chronic disease in childhood. Although asthmatic symptoms are common in preschool children, only 30% will eventually develop true asthma. The remaining children are asymptomatic at age six, but suffer from transient, viral-associated wheeze. The ultimate objective of the Asthma DEtection and Monitoring (ADEM) study is to develop a non-invasive technique for the early diagnosis of asthma in young preschool children with recurrent asthma-like symptoms (wheezing). This could eventually result in an earlier and better treatment of childhood asthma. The aim of the present study is to investigate if the gut microbiome can differentiate between wheezing and non-wheezing preschool children, and can eventually be used to predict the development of true asthma at six years of age.

In this prospective case-control study, 202 children with wheezing and 50 children without wheezing between two and three years of age were included. Children were followed up until the age of six years. Data obtained by standardized questionnaires on respiratory symptoms were collected. Fecal samples were collected and subjected to high-throughput sequencing of the V3–V4 region of the 16S rRNA gene for the analysis of microbial composition and diversity.

Preliminary analysis shows that the relative abundance of certain microbial taxa significantly differs between the wheezing and non-wheezing group. No significant differences were found in microbial diversity.

2.3.15. Butyrate: The Missing Link between the Gut Microbiome and Asthma

Alissa Cait, Erick Cardenas, Pedro Dimitriu, David Levy-Booth, Nelly Amenyogbe and William W. Mohn

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Asthma has become the most common childhood disease in developed countries, with major social and economic consequences. The causes of asthma are complex and poorly understood, but there is a growing body of evidence that implicates dysbiosis of the gut microbiome as a driving force behind the development and severity of asthma and allergy. We previously identified in mice that antibiotic treatment caused a perturbation of the microbiome marked by the reduced production of the short chain fatty acid (SCFA) butyrate. We found that mice on antibiotics, thus lacking exposure to butyrate, have a pro-inflammatory immune phenotype with heightened Th2 responses in a model of asthma. We subsequently found that exogenous supplementation of SCFA to these mice did not significantly alter the gut dysbiosis, but was sufficient to ameliorate allergic severity. In infants, we previously found a small association between the gut microbiome in the first 100 days of life and the development of asthma using a 16S-based approach. We hypothesized that we would identify a more profound microbiome signature if we looked in a targeted way at the genes involved in butyrate production. Consistent with our hypothesis that butyrate is the key link between the gut microbiome and allergy development, we identified a metagenomic signature present in the three-month-old fecal samples of children who go on to develop asthma with a specific depletion in the bacterial genes required for the breakdown of indigestible carbohydrates in breast milk (human milk oligosaccharides) and the genes

required to ferment these into butyrate. Together, our data suggests that microbial-derived butyrate plays a pivotal role in the calibration and development of the infant immune system, and without this molecule, the immune system will polarize toward a Th2 inflammatory phenotype for life. This finding has potential practical applications in the prevention of asthma.

2.4. Session 4: Transgenerational Perspectives—Policy Meets Biology

The following topics were presented as part of the session. While the abstracts are not all available, this session will be submitted as a separate publication in *Challenges*.

2.4.1. KEYNOTE: Transgenerational Perspectives of Environmental Impact

Susanne Krauss Etchman

Research Center Borstel, Leibniz Lung Center, 23845 Sülfeld, Germany

No abstract available: Dr. Krauss Etchman challenged the "traditional" concept that maternal exposures are largely the pathway to the transgenerational transmission of disease risk. She examined data that paternal influences are also significant in the early programming that determines offspring disease susceptibility in later life. She showed epidemiological evidence from Swedish famine years that suggests that germ cell susceptibility to reprogramming, and its subsequent effects on future generations' disease risk, is greatest during the slow growth period of preadolescence, including the ALSPAC (Avon Longitudinal Study of Parents and Children) study data showing that early paternal smoking is associated with greater body mass index (BMI) at nine years of age in sons, but not daughters. These effects may be more significant for exposures before the completion of puberty, implicating spermatogenesis and small RNAs. MicroRNAs control transcripts and are influenced by environmental stimuli. They are essential for development and spermatogenesis, and are likely to regulate gene expression post-fertilization. In animal models, sperm microRNAs can recapitulate phenotypes, and it is possible that sperm cell small RNAs could act as mediators of epigenetic inheritance. If this is the case, sperm cells could gather somatic information that is delivered to the next generation(s) as a mechanism of paternal programming.

2.4.2. Epigenetic Research: Building Maps for Predicting and Preventing Disease

John W. Holloway

University of Southampton, Southampton SO17 1BJ, UK

No abstract available: Dr. Holloway discussed the epigenetic processes that alter transcription without affecting the DNA sequence, allowing animals (including humans) to change gene expression in response to their environment. He explored examples of how early life exposures (such as maternal smoking) can shape the offspring epigenome, and how these effects may still be evident in the epigenome decades later. He also showed examples of how the early life epigenome can predict childhood phenotype, namely food allergies. There are also emerging examples of how the epigenome lies on the causal pathway between early environment and disease (such as the relationship between maternal B12 and childhood IQ). He also identified important unanswered questions, such as:

- Does the methylome interact with the genome to determine disease?
- If so, what exposures determine the methylome?
- Can the epigenome be modified by postnatal exposures (treatments)?
- What is the mechanism and the key susceptibility windows for inter/transgenerational effects?

2.4.3. Preconception Maternal Helminth Infection Transfers via Nursing Long-Lasting Cellular Immunity against Helminths to Offspring

Matthew Darby [1], Benjamin Dewals [2], Dunja Mrjden [1], Claire Mackowiak [3], Delphine Sedda [3], Donald Nyangahu [1], Heather Jaspan [1,4], Murray Selkirk [5], Kai Toellner [6], Valerie Quesniaux [3], Bernhard Ryffel [3], Adam F. Cunningham [6], Frank Brombacher [1,7,*] and William G. C. Horsnell [1,3,6,*]

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[3] Laboratory of Molecular and Experimental Immunology and Neurogenetics, UMR 7355, CNRS-University of Orleans and Le Studium Institute for Advanced Studies, Rue Dupanloup, 45000 Orléans, France
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[6] Medical Research Council Centre for Immune Regulation, School of Immunity and Infection & Institute of Microbiology and Infection, University of Birmingham, Birmingham B15 2TT, UK
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* Corresponding author

Maternal immune transfer via nursing is the most significant source of protection from infection in early life. However, whether maternal transfer of immunity by nursing can permanently alter offspring immunity is poorly understood. We identify in this study maternal immune imprinting of offspring nursed by mothers who had a preconception helminth infection. Here, the nursing of pups by helminth-exposed mothers transferred protective cellular immunity to these offspring against helminth infection. Notably, this protection was associated with the systemic development of protective Th2 T cell populations, which corrected susceptibility to this infection in Th2-impaired IL-4R-/offspring. Protection from infection was also maintained into maturity and associated with incorporation (via nursing) by the offspring of maternally derived Th2-competent CD4 T cells. Therefore, our data reveals that maternal exposure to a globally common source of infection prior to pregnancy provides long-term nursing-acquired immune benefits to offspring by the incorporation and maintenance of maternally derived pathogen experienced lymphocytes.

2.4.4. Where Do We Focus Resources for the Future: Early Puberty as a Window for Improving Policy and Practice

Cecilie Svanes

Centre for International Health, University of Bergen, 5007 Bergen, Norway

Abstract not available: Dr. Svanes discussed the developmental origins of health and disease paradigm (DOHaD) for its potential to have a global influence on policy and practice, giving a practical example of obesity. Obesity in pregnancy is associated with poorer pregnancy outcomes and offspring health. Identifying susceptible time windows may have consequences for policy and practice, including more specific programs that aim at caring for these high-risk pregnancies. Furthermore, it needs to be recognized that some of the risk might possibly be caused by obesity in susceptible time windows in the mother and father before pregnancy. She concluded that:

- Mechanistic studies and first human studies suggest that **early puberty** may be an important susceptibility window for personal and offspring health

- We need further research, including mechanistic studies, experimental mice studies, human studies, exposures/outcomes, and behavioral research.
- Policy and practice may need profound changes—i.e., more focused resources on school health services

2.5. Session 5: Mind and Body—Links between Emotion and Immunity

2.5.1. Mindfulness Meditation and Health: Emotion, Stress, and Inflammatory Pathways

Emily K. Lindsay

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Stress and loneliness are well-established psychosocial risk factors for poor health and early mortality, while positive emotions and social relationships have health-protective effects. Interventions that mitigate these psychosocial risk factors and boost protective resources could have important health implications. Mindfulness interventions, which train people to monitor the present-moment experience with an orientation of acceptance and equanimity, have been associated with improvements in a wide range of mental and physical health outcomes. Less is known about the active mechanisms driving these effects. We have theorized that mindfulness interventions exert their effects on health through stress-buffering pathways [1], and that acceptance is a critical emotion regulation mechanism underlying these reductions in stress [2].

We conducted a randomized controlled trial to explore these predictions [3]. First, 153 stressed community adults were randomly assigned to complete one of three structurally equivalent 14-lesson smartphone interventions: (a) mindfulness training with instruction in both attention monitoring and acceptance skills, (b) mindfulness training with instruction in attention monitoring skills only, or (c) active control training. By dismantling mindfulness interventions into their active components, this study provides novel experimental evidence that acceptance training is a central mechanism of mindfulness interventions for reducing biological stress reactivity and daily life loneliness, as well as for boosting positive emotions and increasing social engagement in daily life. Overall, accumulating evidence suggests that mindfulness interventions may be beneficial for health, and that acceptance training is particularly important for changing one's perspective in ways that mitigate psychosocial risk factors and boost protective resources.

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2.5.2. Positive Emotions and Immunity: The Anti-Inflammatory Effects of Positivity for Health and Resilience

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No abstract available: Dr. Stellar is among a growing group of researchers who argue that our emotions are an important predictor of health and well-being. The majority of the past work on emotions has focused on the impact of *negative* emotion. This has been valuable, because we now better understand the detrimental effects of negative emotion; it has been a catalyst for the development of interventions to reduce negative affect. However, there has been a lack of focus on positive emotions,

and thus on understanding their independent effects on health and well-being. There is now a new field of research to investigate the biological pathways between positive emotion and health, including through the immune system; specifically, through modulating pro-inflammatory cytokines. Studies are now showing that positive emotions predict lower levels of pro-inflammatory cytokines (IL-6) in human studies. This has been replicated and extended to show that specific positive emotions were particularly good predictors of lower IL-6; particularly joy, contentment, pride, and awe. The emotion of awe consistently showed the strongest protective relationship with IL-6. Awe is "a combination of wonder and amazement inspired by authority or by the sacred or sublime". Most people report experiencing awe in response to the beauty of nature, inspiring people, art and music, religious and spiritual experiences, and even having big ideas. Despite the diversity of experiences that elicit awe, there are common themes. It occurs when we encounter something vast and grand that challenges your view of the world, and it makes us feel more interconnected with the world and others in it. She concluded:

1. Take time to feel positive emotions
2. Awe is not a luxury, it's important for health
3. Nature is a great way to feel awe.

2.5.3. The Influence of Aussie Optimism Mental Health Promotion Programs on Inflammatory Markers for Children Aged 0–5 Years

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Prevalence rates for mental health disorders are increasing and the age of first onset is decreasing, with many more mental health difficulties observed in children than ever before. The burden associated with mental health difficulties is enormous, particularly when they first appear in childhood and are left to persist into adulthood. As such, prevention programs have been developed to improve mental health and well-being so that mental health disorders may be avoided. It is now known that many mental health disorders have their origins in childhood, with early experiences and environmental conditions contributing significantly to health and well-being outcomes in the lifespan. This new knowledge provides an opportunity to intervene earlier than adolescence, as had been previously deemed appropriate.

Successful prevention strategies have included the development of social, emotional, and cognitive skills in both universal and targeted samples utilizing cognitive behavioral therapy approaches. Reductions in depressive and anxiety symptoms, increases in prosocial behaviors, emotion knowledge, internalizing behaviors, and to some extent reductions in externalizing behaviors are among the assessed outcomes in studies using these strategies with the Aussie Optimism programs. However, more recently, the connection between mental and physical health has been studied, with important discoveries linking emotion experiences with physiological changes, such as inflammatory markers. This paper describes the development of new Aussie Optimism intervention programs for infants and young children up to the age of five and their parents/carers, which includes the assessment of inflammatory markers in the children before and after an intervention that aims to promote mental health and well-being.

2.5.4. Exploring the Gut–Brain Axis and the Role of Probiotics

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In the body, the maintenance of optimal fitness and defense against external threats is maintained by the coordinated action of the nervous, immune, and endocrine systems. Relatively recently, it has

emerged that host-associated microbes are important modulators of this neuroimmunoendocrine supersystem, influencing individual components and communication between components.

The major site of interaction between microbes and the neuroimmunoendocrine supersystem is the gastrointestinal tract, where the highest concentration of immune cells in the body and a network of 200–600 million neurons come into contact with the trillions of bacteria, fungi, and viruses that constitute the human gut microbiota. The influence of the gut microbiota extends beyond the gastrointestinal tract, modulating systemic immunity and altering the activity of the peripheral and central nervous systems. The influence of gut microbes on the central nervous system results in changes in brain chemistry function and behavior, and indicates the existence of a microbiota–gut–brain axis [1].

Despite the complexity of the gut microbiota, exposure to a single microbial strain can alter brain neurochemistry, resulting in anxiolytic and antidepressant-like effects and protect against certain stress-induced changes in immunity, brain function, and behavior [2,3]. It has also demonstrated that clinically relevant doses of penicillin in early life induce long-term effects. In addition to disrupting the gut microbiota, penicillin increases brain cytokine levels and alters behavior, leading to increased anxiety-like behaviors and impaired sociability [4].

This work suggests the potential role of early-life antibiotic use in the development of neuropsychiatric disorders, and effects that may be attenuated by beneficial bacteria. It also indicates the possibility of microbe-based interventions for stress-related disorders.

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2.5.5. Probiotics in Pregnancy and Postnatal Depression

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Empirical treatment with probiotics preceded the current worldwide interest in the microbiomes and their effects on many aspects of health. In a series of birth randomized controlled trials, we have examined the effects of two probiotics: L rhamnosus HN001 and B Lactis HN019. L rhamnosus HN0001 has shown significant protective effects against eczema from birth to age 11 years, and some evidence of a reduction in both atopic sensitization and asthma in later childhood. B lactis HN019 had no significant effects. In a separate study, L rhamnosus HN001 has shown a protective effect against gestational diabetes and reduced postnatal depression. The mechanism of these effects await elucidation.

2.5.6. Assessment of Brain-Derived Neurotrophic Factor in Hair to Study Stress Responses: A Pilot Investigation

Hani Harb [1,2], Marcela González-de-la-Vara [3,4], Lara Thalheimer [4], Undine Klein [4], Harald Renz [1], Matthias Rose [5], Johannes Kruse [3], Daniel Piotr Potaczek [1] and Eva Milena Johanne Peters [4,5]

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To study pathogenic stress effects in health and disease, it is paramount to define easy access parameters for the non-invasive analysis of biological change in response to stress. Hair samples successfully provide this access for the study of hypothalamus–pituitary–adrenal axis (HPA) changes. In this study, we assess the hair expression and corresponding epigenetic changes of a neurotrophin that is essential for autonomic nervous system function and mental health: brain-derived neurotrophic factor (BDNF). In three independent studies in healthy academic volunteers (study I: German students, $N = 36$; study II, German academic population sample, $N = 28$; study III: Mexican students, $N = 115$), BDNF protein expression or BDNF gene (BDNF) histone acetylation was determined. Simultaneously, mental distress and distress-associated somatic complaints were assessed by self-report. In study I, we found a negative correlation between hair-BDNF protein level and hair-cortisol, as well as between hair-BDNF and somatic complaints, while hair-cortisol correlated positively with mental distress. In study II, we found a negative correlation between H4 histone acetylation at the BDNF gene P4-promoter and somatic complaints. Regression analysis confirmed the confounder stability of associations in both studies. In study III, we confirmed study I and found lower hair-BDNF protein levels in volunteers with high somatic complaints, who also reported higher mental distress during the end-of-term exams. The results indicate that BDNF protein levels can be detected in clipped hair and are associated with somatic complaints and stress in life. In addition, we concluded that plucked hair can provide material for the study of epigenetic changes in stress-affected tissues. These tools can prove valuable for future studies on distress, both under experimental and field conditions.

2.5.7. Mind and Body: Human Physicality in Personal and Planetary

Frank Forencich

No abstract available: Frank Forencich discussed the importance of mindful physicality for health. This physical awareness is more than exercise and activity, but rather is a form of connectivity and awareness of our environment and others. In particular, conscious physical awareness is part of our connection with natural environment. Technology culture had interfered with this relationship, and centered awareness on our brains over our bodies. This is a world of unique and often health-hostile conditions including artificial light, noise, abnormal social relationships, abnormal physical demands, and abnormal foods. The challenge is to bring our ancient inclinations into harmony with this new world. Here, there are also many lessons to learn from indigenous cultures.

2.5.8. Early Anesthetic Exposure and the Risk of Attention Deficit Hyperactive Disorder

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Background and aims: Although attention deficit hyperactive disorder (ADHD) is predominantly a genetic condition, approximately 40% variance may be due to environmental factors. Early environmental factors that may result in inflammation include exposure to general anaesthetic, which can impact on brain development. Our study investigated the risk of early exposure to one or

more anaesthetics in children who were subsequently diagnosed and treated with stimulant medication for ADHD.

Method: Population information was collected on 10,850 non-Aboriginal children <18 years (cases) who had been prescribed stimulant medication in WA (Western Australia) for ADHD and were recorded on the Monitoring of Drugs Dependency System (MODDS). A stratified random sample of birth records with no linkage to MODDS formed a comparison group (25,240). Case and comparison records were linked to the Midwives Notification System and the Hospital Morbidity Database, which identified children who received an anaesthetic during their hospital admission. De-identified linked data files were provided for analysis.

Results: 23% of non-Aboriginal children who were subsequently diagnosed with ADHD and 16% of their non-ADHD counterparts had received a general anaesthetic under four years of age. Children who received one anaesthetic under four years of age had an increased risk of being diagnosed with ADHD compared with their non-ADHD counterparts (OR 1.40 (95% CI 1.31–1.50). Having one or more general anaesthetics under four years of age increased this risk almost twofold (OR 1.87; 95% CI 1.68–2.08) when adjusted for sex, maternal age, birth weight, marital status, socioeconomic status, and year of birth.

Conclusions: Although population studies are unable to show the causal direction of environmental exposures, there is evidence that early exposure to anaesthetic and multiple exposures may increase the risk of being diagnosed with ADHD. Inflammation during a general anaesthetic may be an important underlying environmental risk factor associated with a subsequent diagnosis of ADHD.

2.6. Session 6: The Future of Food—Ultra-Processing Meets Nutritional Ecology

2.6.1. KEYNOTE: Healthy and Sustainable Diets for Humanity: Why Food Processing Matters

Jean-Claude Moubarac

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No abstract available: Dr. Moubarac discussed the role of food processing in the context of progressively more reductionist food 'science' and the politics of dietary advice. Food processing is now the main shaping force of the global food system, and the main determinant of the nature of diets and related states of health and well-being. Some level of food processing per se is beneficial and essential; however, ultra-processing is mostly detrimental to humanity, the microbiome, and the planet. He discussed the 'Nova food classification', which is based on the nature, extent, and purpose of food processing. Food processing, as understood by Nova, involves physical, biological, and chemical processes applied to foods after their separation from nature, and before they are submitted to culinary preparation (cleaning, peeling, seasoning, cooking, etc.) or prior to their consumption in the case of items that do not require culinary preparation. The Nova food classification defines foods as:

1. Unprocessed or minimally processed foods
2. Processed culinary ingredients
3. Processed foods; this recognized that food processing is beneficial when its purpose is to preserve foods and enable the handmade preparation of diverse and delicious meals. These foods are generally consumed at regular hours, in meals, at a table, and with company. This includes handmade culinary preparations
4. Ultra-processed food (UPF) products. This refers to industrial food and drink formulations made mostly from refined substances extracted or derived from foods and additives. Ingredients and production techniques reduce cost while making products convenient (durable and ready-to-eat) and hyper-attractive. These foods are marketed through sophisticated and aggressive marketing.

Ultra-processing replaces cooking and promotes consumption, because these foods are ready-to-consume and available throughout the day, between meals, on the go, as snacks, and are often

consumed alone. UFP are typically high-energy density foods with increased levels of free sugars, sodium, saturated fats, and trans fats. They are also low in nutritional quality, vitamins, minerals, fiber, and protein. The obesogenic attributes of ultra-processed products are not necessarily captured by their nutritional profile. Dr. Moubarac discussed the clear evidence linking ultra-processed products to obesity and non-communicable diseases (NCDs), including how the annual sales per capita of UPF and drink products was associated with mean body mass index (BMI) scores in 12 Latin American countries between 2000–2009. The consumption of ultra-processed products affects the normal mechanisms that regulate appetite and behavioral control. A food system based on ultra-processed food consumption threatens food cultures and contributes directly to the climate crisis. This is not a failure of individual willpower. This is a failure of political will to take on big business. He concluded with dietary advice:

- Always prefer minimally processed foods and freshly handmade dishes made from them to ultra-processed foods
- Give preference to plant-based minimally processed foods
- Use salt, oils, and sugars in moderation, and explore other spices in culinary preparations.

2.6.2. KEYNOTE: The Nutrition Transition in Indigenous Populations from Flour, Sugar, and Lard to Ultra-Processed Foods

Noreen Willows

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No abstract available: Dr. Willows discussed the transition from health-promoting subsistence lifestyles to Western-style ultra-processed foods (UFP) in indigenous populations. This includes a change from whole, minimally processed foods with high diversity (>550 plant species and >527 animal species consumed for food) to less diverse refined foods including refined wheat flour, sugar, salt, and lard. There are significant nutritional differences in domesticated versus wild animals (e.g., beef versus caribou, deer or moose; chicken versus wild geese) with more total fat and SFA (saturated fatty acids), less PUFA (polyunsaturated fatty acids) and MUFA (monounsaturated fatty acids), and fewer micronutrients such as iron. Similarly, there are differences in nutritional value in the transition from whole grains to refined grains, and from boiled lake fish to frozen fish sticks. There are also significant implications in terms of costs, requirements for potable water, and implications for cultural practices. Processed food is also associated with an increase in landfill waste, with the transition from organic, biodegradable, waste to non-biodegradable waste. Studies show that UPF contributed 53.9% of the dietary calories of First Nations peoples on reserves, which was mostly from: fast food and ready-to-eat dishes, commercial breads, carbonated energy and fruit drinks and fruit juices, deli and processed meats, and salty snacks. Nutrition transition resulting from colonization has been associated with: the diminished procurement of food from local food systems; increased sedentariness; a diminished stewardship of the land; disconnection from cultural practices; an increased intake of non-nutrient-dense store-bought foods and a decreased intake of whole foods; micronutrient inadequacies; an excess intake of sugar, sodium, and saturated fat; obesity; coronary artery disease; high blood pressure; type II diabetes; dental caries; and lower life expectancy.

The way forward is through indigenous food sovereignty movements and habitat restoration. This recognizes that indigenous communities have the right to preserve and practice their cultural traditions surrounding the production of food. This should ensure the allocation of adequate land for hunting, fishing, and gathering to protect, conserve, and restore indigenous food systems. It must address social determinants of health so that people can respond to their own needs for healthy indigenous foods. This is also needed to heal and reconcile relationships between indigenous peoples and stakeholders (Canadian citizens and their government).

2.6.3. The Western Lifestyle and Chronic Degenerative Diseases: Learning from the Diets and Lifestyles of Traditional Populations

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Chronic degenerative diseases, including cancer, coronary heart disease, stroke, hypertension, diabetes, osteoporosis, and autoimmune and neuropsychiatric diseases have reached epidemic proportions in virtually every country, but appear to be rare in various non-Westernized populations, which cannot be attributed to genetics or a low life expectancy, but rather to their traditional lifestyle, namely a diet composed of minimally processed whole foods, regular exercise, adequate sun exposure and sleep patterns, and low exposure to xenobiotics. Therefore, it is proposed that: (1) the underlying causes of most chronic degenerative diseases are the profound changes in diet and lifestyle that occurred after the Industrial Revolution and the Modern Age, which led to multiple pathophysiological changes; (2) in order to establish public health guidelines that help prevent those diseases, the common beneficial characteristics of the diets and lifestyles of traditional populations should be identified.

2.6.4. Influence of Sockeye Salmon Restoration on Syilx Well-being

Suzanne Johnson, Malek Batal, Noreen Willows, Rosanne Blanchet and Pauline Terbasket

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After being almost extirpated, sockeye salmon has been brought back to the Okanagan River Sub-basin (of the Columbia River) system through the restoration efforts of the Syilx Okanagan Nation, to the extent that a social, ceremonial, and economic fishery has been revived. This presentation will provide an overview of the multifaceted approach to restoration that has addressed the determinants of health, including social, environmental, economic, and cultural continuity. Restoration efforts have included community leadership and engagement, active participation in regional water management and flow decisions, the design and development of fish passage over hydroelectric dams, river habitat restoration, ceremonial salmon fry release into rivers and lakes, and the cultural revitalization of social gatherings, ceremony, and N'syilxcen language transmission. Increased salmon abundance has supported food, social, and ceremonial needs and an anticipated transition to participatory fishery, economic pilot, and recreation initiatives that respect a sustainable food sovereignty and food security model.

Salmon is a crucial food source for the Syilx. The nutritional health benefits of salmon are well known. The omega-3 fatty acids found in salmon have a protective role against the development of cardiovascular diseases in indigenous populations. Salmon can also be considered a cultural keystone species, given its role as a food 'Chief' in key governing teachings of the Syilx. Thus, the existence of salmon is imperative for the continuation of language and cultural teachings, and its 'near loss' can be considered to have contributed to an 'ecological grief' resulting in poor health and depression in Syilx communities. The restoration of determinants of health, including culture, have also been shown to have a positive impact on physical health. A multimethods study is examining the determinants and outcomes of the reintroduction of Okanagan sockeye salmon. The study will also explore how the experiences of individuals participating in restoration efforts have contributed to Syilx well-being.

2.6.5. Mood Effects Associated with Switching to a Mediterranean Diet

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Introduction: A Mediterranean diet is characterized by a higher intake of vegetables, fruits, and nuts, and a lower intake of meat and dairy products (except long-preservable cheeses) when compared to the "Western" diet. The purpose of this study was to examine the effects of a 10-day Mediterranean dietary intervention on mood.

Methods: N = 53 young female adults, aged 22.3 (3.6) years old, were randomly assigned to a control group or a dietary intervention group. Those who received the intervention had to adhere to the Mediterranean diet for 10 days. Both groups completed a daily food diary. Mood assessments were made on Day 1, Day 5, and Day 10, including the Bond–Lader visual analogue scales (VAS) scales assessing alertness, calmness, and being content, and the Profiles of Mood States (POMS) questionnaire, including subscales on tension/anxiety, anger/hostility, fatigue/inertia, vigor/activity, confusion/bewilderment, and a total mood disturbances score. Pre-intervention and post-intervention mood data within the Mediterranean diet group and within the control group were compared.

Results: Relative to Day 1, in the Mediterranean diet group on Day 10, scores on the POMS subscales of tension/anxiety, anger/hostility, fatigue/inertia, confusion/bewilderment, and the total mood disturbances score were significantly lower ($p < 0.05$), whereas vigor/activity scores were significantly higher ($p < 0.05$). In line, Bond–Lader VAS scale scores on alertness and being content were significantly higher on Day 10 in the Mediterranean diet group ($p < 0.05$). No significant pre-treatment and post-treatment differences were seen in the control group.

Conclusions: A Mediterranean diet for just 10 days is associated with significant positive mood effects, including significantly increased levels of alertness being content, and increased vigor/activity, and reduced feelings of anxiety, anger, fatigue, and confusion.

2.6.6. Plasmacytoid Dendritic Cells Protect from Viral Bronchiolitis and Asthma through Semaphorin 4a-Mediated T Reg Expansion

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Respiratory syncytial virus bronchiolitis is a major independent risk factor for subsequent asthma, but the causal mechanisms remain obscure. We identified that transient plasmacytoid dendritic cell (pDC) depletion during primary pneumovirus infection alone predisposed patients to severe bronchiolitis in early life and subsequent asthma in later life after reinfection. pDC depletion ablated interferon production and increased viral load; however, the heightened immunopathology and susceptibility to subsequent asthma stemmed from a failure to expand functional neuropilin-1+ regulatory T (T reg) cells in the absence of pDC-derived semaphorin 4A (Sema4A). In adult mice, pDC depletion predisposed patients to severe bronchiolitis only after antibiotic treatment. Consistent with a protective role for the microbiome, the treatment of pDC-depleted neonates with the microbial-derived metabolite propionate promoted Sema4A-dependent T reg cell expansion, ameliorating both diseases. In children with viral bronchiolitis, nasal propionate levels were decreased and correlated with an IL-6high/IL-10 low microenvironment. We highlight a common but age-related Sema4A-mediated pathway by which pDCs and microbial colonization induce T reg cell expansion to protect against severe bronchiolitis and subsequent asthma.

2.6.7. Large-Scale Retrospective Analyses of Fetal Ultrasound Parameters: a Novel Tool for DOHaD-Related Research

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Abstract: For a multitude of practical and ethical reasons, access to fetal parameters represents a major challenge in research on the *Developmental Origins of Health and Disease* (DOHaD). Routine antenatal ultrasound images harbor a rich and predominantly untapped source of information relating to the developing fetal immune, metabolic, and central nervous systems. Hence, the utilization of automated image processing and machine learning (artificial intelligence)-based analytic tools enable large-scale retrospective analyses of fetal organ size and structures from existing large data repositories of ultrasound images.

With this unique approach, we aim to correlate parameters obtained on ultrasound images with perturbations in the antenatal period as well as with health outcomes later in life. The reliability of such analyses depends on the accurate identification and measurement of anatomical structures in ultrasound images of different organ and acquisition view planes. However, manual identification and measurement is a time-consuming process requiring expert sonographers with a considerable risk of interobserver and intraobserver variability. We designed an automated technique to accurately identify ultrasound fetal planes through state-of-the-art machine learning algorithms. Furthermore, we have automated measurements of fetal biometrics through shape modeling and computer vision algorithms. The development of these automated tools can be envisaged as a computerized system to support the retrospective analysis of fetal structures from 2D B-mode US images. To date, we have performed several stages of preliminary clinical and engineering experiments. In our next phase, we will demonstrate that this method will be useful for analyzing fetal development measurements on a large scale, and explain how these automatically derived imaging parameters can be correlated to antenatal and postnatal parameters.

2.6.8. Cluster Analysis of Factors Influencing Food Sensitization and Food Allergy in Urban and Rural African Children Requested

Mike Levin

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SAFFA (South African Food sensitisation and Food Allergy) is a study that compares patterns of allergic sensitization between rural and urban communities in South Africa. He presented the significant differences in urban:rural aeroallergen sensitization (13.1% versus 3.8%) and in food sensitization (11.54% versus 4.8%). These are likely to be multifactorial, including different environmental conditions, delivery methods, cooking and heating methods, parental smoking, contact with domestic and farm animals, infections, tuberculosis, and the use of antibiotics. Further studies are planned to examine the relative contributions of different risk (and protective) factors in urban and rural environments with excess risk modeling.

2.6.9. Development of a Dietary Screening Questionnaire to Predict Excessive Weight Gain in Pregnancy

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Excessive gestational weight gain (GWG) is a risk factor for several adverse pregnancy outcomes, including macrosomia. Diet is one of few modifiable risk factors identified. However, most dietary

assessment methods are impractical for use in maternal care. This study evaluated whether a short dietary screening questionnaire could be used as a predictor of excessive GWG. The dietary data was collected in gestational weeks 11–14 using a 40-item food frequency screening questionnaire. The dietary data was transformed into 13 predefined dietary risk factors for inadequate diet. Stepwise backward elimination was used to identify a reduced set of factors that best predicted excessive GWG. This set of variables was then used to calculate a combined dietary risk score (range 0–5). Information regarding outcomes, GWG (n = 1326), and birth weight (n = 1651) was extracted from maternal hospital records. In total, 36% had excessive GWG, and 5% of infants were macrosomic. A dietary risk score (characterized by: a non-varied diet, non-adequate frequency of consumption of fruits/vegetables, dairy and whole grain intake, and excessive intake of sugar/artificially sweetened beverages and dairy) was associated with a higher risk of excessive GWG. Women with high ($\geq$4) versus low ($\leq$2) risk scores had a higher risk of excessive GWG (RR = 1.24, 95% CI = 1.01; 1.52) and higher odds of delivering a macrosomic offspring (OR = 2.28, 95% CI = 1.18; 4.38). The results indicate that asking simple questions about women's dietary intake early in pregnancy could identify women who should be prioritized for further dietary counseling and support.

2.6.10. Effect of Early Egg Introduction on the Development of Ovalbumin-Specific Regulatory T and B Cells in At-Risk Infants

Catherine Li Lai [1,2,3,4], Debra J. Palmer [4,5], Cristina Gamez [4,5], Ralph Nanan [3], Susan L. Prescott [4,5], Dianne Campbell [1,2] and Peter Hsu [1,2]

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Background: Egg allergy affects around 9% of Australian children. Recent studies show that the early introduction of allergenic foods, including egg, prevents the development of food allergies later in life. However, the underlying immune mechanisms involved in the acquisition of natural tolerance have not been clarified, although the role of regulatory T (Treg) and B (Breg) cells are implicated.

Aims: To characterize ovalbumin-specific Tregs and Bregs in at-risk infants randomized to receive egg or placebo from four to six months of life in the BEAT and STEP cohorts.

Methods: Peripheral blood mononuclear cells (PBMC) from infants aged five months (STEP, prior to egg introduction) and 12 months (BEAT and STEP after egg introduction) months were used for phenotypic and functional analysis. The cells were analyzed by multi-color flow cytometry for ex vivo FoxP3+ Treg phenotype. In vitro assays were also conducted to compare cytokine production, ovalbumin-specific Breg frequency, and ovalbumin-specific FoxP3+ Treg responses between the egg and placebo groups. Flow cytometry data was analyzed in Flowjo.

Results: Pooled data between BEAT and STEP studies showed an increasing trend in ovalbumin-specific Tregs (CD4+CD137+CD40L-FoxP3+ cells) in the egg-treated group at 12 months. No clear differences were observed in ovalbumin-specific Tr1, Th2 and Breg cells between the two groups.

Conclusion: Early egg introduction appears to be associated with the induction of ovalbumin specific Treg cells. Further and ongoing analyses are required to confirm this and other immune changes related to development of natural tolerance to foods during infant development.

2.6.11. The Influence of Vitamin D on Immune Development in the First Six Months of Life

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Background: The incidence of childhood allergic disease has dramatically increased worldwide. The early environment plays a key role in the development of the immune system and consequently on allergy risk, with eczema as the earliest manifestation. Low levels of vitamin D have been linked to allergies in children. Low vitamin D status is a potential consequence of modern lifestyle changes, in particular reduced sunlight exposure. However, intervention trials investigating the effect of vitamin D supplementation during infancy as an allergy prevention strategy are lacking.

Aims: To determine the effects of early postnatal infant vitamin D supplementation and sunlight exposure on infant immune development and the development of eczema.

Methods: In this randomized controlled trial, 195 high-risk infants were orally supplemented with either 400 IU vitamin D/day or placebo from birth to six months of age. Uniquely, a personal ultraviolet (UV) dosimeter was worn to measure infant UV exposure during the first three months of life. Blood samples were collected at three and six months of age to determine relationships between oral vitamin D intake and UV light exposure with blood 25(OH)D concentration, immune cell function responses to allergens, and the development of eczema by six months of age.

Conclusions: The study is in progress, and preliminary data will be presented at the meeting. This study will provide essential pilot data for future investigations of early life dietary and environmental exposures, focusing on possible links between vitamin D status, sunlight exposure, and childhood allergic disease outcomes.

2.6.12. A Low Prevalence of Pediatric Food Allergy (FA) among Old Order Mennonites (OOM) Is Related to Robust Mucosal IgA Production

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Background: Several studies, including ours in the Old Order Mennonites (OOM) community, have found farm life protective against the development of atopic diseases. The OOM lifestyle includes the consumption of unpasteurized farm milk, large families, home births, and long periods of breast-feeding. However, the effect of farm life on food allergy (FA) and the development of the mucosal IgA responses have not been assessed.

Objective: 500 surveys were distributed to OOM families. Surveys queried individual FA in children as adapted from the National Health and Nutrition Examination Survey (NHANES) 2007–2010 ("self-reported FA"). Further phone contact determined if the child was also avoiding the food ("likely/possible FA"). Saliva was collected from 31 OOM and 37 Rochester non-OOM infants at six months, and total IgA was measured by ELISA.

Results: The response rate was 30.8%. Among 524 OOM children, the rates of self-reported allergy to egg ($p < 0.05$), soy ($p < 0.001$), tree nuts ($p < 0.001$), fish ($p < 0.01$), and shellfish ($p < 0.001$) were significantly lower than reported in NHANES. The rates of likely/possible allergy to peanut ($p < 0.05$), wheat ($p < 0.01$), fish ($p < 0.05$), and shellfish ($p < 0.001$) were also lower than reported in NHANES. The weaning foods in OOM include fruits and yogurt, which was often homemade, at seven months of age on average, with egg and peanut introduced at eight and 21 months. OOM infant saliva had higher levels of IgA than Rochester saliva ($p < 0.01$).

Conclusion: OOM have a robust mucosal IgA production and low rates of FA, despite the delayed introduction of highly allergenic foods such as peanut. The mechanisms related to protective immune responses are being further characterized, including microbiome and breast milk composition.

2.6.13. Early Life Gut Microbiota Associates with IgE-Mediated Food Allergy

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The rapid rise in Immunoglobulin E-mediated food allergy (IgE-FA) incidence points to environmental rather than genetic causes. A leading hypothesis is that environmental factors induce alterations in intestinal microbiota composition, which results in improper immune development. In this work, we associated early life intestinal microbiota with IgE-FA in children enrolled in the Wayne County Health, Environment, Allergy, and Asthma Longitudinal Study (WHEALS) birth cohort based in Detroit, Michigan ($N = 1258$). Using stool samples collected at approximately one and six months of age, infant gut bacterial microbiota were measured by 16S rRNA sequencing, while fungal microbiota were measured by ITS2 sequencing. IgE-FA was defined using a panel of board-certified allergists to systematically identify egg, milk, and peanut IgE-FA, based on detailed parental interviews, allergen-specific IgEs, and skin prick testing at age two. Of the 590 children with sufficient information to determine IgE-FA, 447 (76%) had at least one microbiota sample. Of these, 44 (9.8%) were classified as IgE-FA. PERMANOVA was used to test for microbiota compositional differences between IgE-FA and no IgE-FA; alpha diversity trajectories were fit using linear mixed models. Differences in specific taxa were tested using zero-inflated negative binomial regression, with a false discovery rate threshold of 5%. Early life bacterial gut composition—but not fungal gut composition—was significantly associated with IgE-FA (unweighted UniFrac p-value = 0.005, $R^2 = 0.003$). Additionally, compared to no IgE-FA, IgE-FA children exhibited significantly lower bacterial richness and phylogenetic diversity throughout the first six months of life (p-values = 0.025, 0.049, respectively). In taxa tests at one month of age, all of the significant taxa had lower abundances in IgE-FA children: these were primarily *Lactobacillales* (lactic acid bacteria), but also included *Bifidobacterium* and *Bacteroidales*. These findings provide further evidence that early life gut microbiota plays a role in the development of IgE-FA, and may have implications for the prevention of IgE-FA in children.

2.7. Session 7—The Quality and Influences of Our First Food (a Session on Breast Milk and Lactation Presented by LactoActive)

2.7.1. Human Milk Oligosaccharides as Primers for Infant and Long-Term Health

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Human milk oligosaccharides (HMOs) are a group of more than 150 structurally distinct complex sugars that together represent the third most abundant component of human milk. In contrast,

bovine milk, which is the basis for most infant formula, contains only about 40 oligosaccharides that are less complex in structure, and altogether about 100 to 1000 times less abundant than oligosaccharides in human milk. HMOs are prebiotics that serve as metabolic substrates for specific bacteria that are potentially beneficial to infant health. HMOs are also antiadhesives that block potential pathogens from attaching to epithelial surfaces as well as antimicrobials that prevent potential pathogens from growing. Thus, the prebiotic, antiadhesive, and antimicrobial effects of HMOs contribute to shaping the infant microbiome with potential immediate and long-term implications for infant health and development. In addition to these indirect effects that are mediated through the microbiome, HMOs may also have direct effects on host epithelial and immune cell responses. Our lab uses a combination of preclinical models and cohort association studies to uncover the full potential of HMOs. To assess HMO efficacy and determine structure–function relationships, we isolate HMOs from pooled donor human milk to capture all known HMOs in one prep. First, we test the efficacy of these pooled HMOs in suitable in vitro and/or in vivo models. Then, if we observe an effect, we fractionate HMOs by multidimensional chromatography to determine structure–function relationships. HMO preps are often contaminated with excess lactose, salt, and endotoxins, which leads to a misinterpretation of what true HMO effects are. Thus, our preparative HMO platform is designed to remove contaminants and apply rigorous quality control to obtain HMO preps of the highest quality. We successfully applied this approach of HMO efficacy testing and stepwise structure–function elucidation in tissue culture as well as in animal models. For example, we have shown that the HMO lacto-N-tetraose (LNT) inhibits the growth of group B streptococcus (GBS) in culture, or that disialyllacto-N-tetraose (DSLNT) reduces necrotizing enterocolitis in a neonatal rat model. In both cases, we elucidated the chemical space around the effective HMOs and confirmed that the results have implications on health and diseases in humans. In addition, and often complementary to HMO efficacy testing in preclinical models, we analyze HMO composition in milk samples from large mother–infant cohorts to investigate the role of HMOs in different health and disease contexts. Our analytical HMO platform applies parallel solid phase extraction technology, 2-aminobenzamide-labeling, and high and ultra-high-pressure liquid chromatography with sensitive fluorescent detection (HPLC-FL). The analysis yields absolute and relative quantification of HMOs in less than 20 μL of milk, and we currently have the capacity to process ~300 samples per week, which enables association studies in large human cohorts with hundreds and thousands of samples. So far, this combined approach of preclinical testing and cohort associations has revealed two different scenarios of how HMOs might work. In some cases, individual HMOs are required and the effects are highly-structure specific, dose-dependent, and likely mediated by specific receptors on either the host cell or on a microbe. For example, we identified that DSLNT is protective in a neonatal rat model of necrotizing enterocolitis, and the same HMO is also less abundant in milk that is fed to preterm infants that later develop this devastating disease, showing a clear overlap in the results from preclinical efficacy testing and cohort association studies. In other cases, effects cannot be linked to a single HMO, but rather depend on a specific ratio of different HMOs to each other: the overall HMO composition matters. For example, we discovered that a specific HMO composition profile is associated with lower risk for infants to develop food sensitization later in life. These are just a few examples for the roles of HMOs. Eventually, our goal is to investigate which maternal genetic and environmental factors influence HMO composition and how HMO composition impacts the health and development of infants and mothers.

2.7.2. Environmental Contaminants in Breast Milk Are Associated with Gut Bacteria Composition and Their Metabolites in One-Month-Old Infants

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Infants are exposed to both environmental toxicants and multiple microbiome-altering factors. These factors may adversely affect child health, with a potential for interaction. We investigated whether exposure to environmental contaminants in breast milk impacts the infant gut microbiome composition and function at one month. We measured environmental toxicants in breast milk, fecal short-chain fatty acids (SCFAs), and gut microbial composition from 16S rRNA gene amplicon sequencing using samples from 293 mother–child pairs in the Norwegian Microbiota Cohort (NoMIC). We tested 28 chemical exposures: polychlorinated biphenyls (PCBs), polybrominated flame retardants (PBDEs), perfluoroalkyl substances (PFASs), and organochlorine pesticides. We calculated infant gut alpha and beta diversity, the differential abundance of taxa, metatranscriptome predictions, and SCFAs. We assessed chemical exposure and alpha diversity/SCFA using elastic net regression modeling and generalized linear models, adjusting for confounders, and variation in beta diversity (Bray-Curtis, UniFrac), taxa abundance (ANCOM), and predicted metatranscriptomes (PiCRUSt) in low, medium and highly exposed groups.

Results: The gut microbiome of infants exposed to more environmental toxicants through breast milk has divergent functionality and composition. Toxicants explain up to 40% of the variance in SCFAs at one month. Perfluorinated compounds increase SCFAs, with a compound-specific effect on composition. Brominated flame retardants were associated with reduced SCFAs and a less diverse microbiome. In general, all of the classes of toxicants reduced the abundance of microbes belonging to the phyla Firmicutes (*L. gasseri*, *V. parvula*), Bacteroidetes (*B. vulgatus*, *fragilis*, and *faecichinchillae*), and Actinobacteria (*E. lenta*, *C. pseudodiphtheriticum*).

Conclusions: Toxicant exposure influences microbial function, in part through changes in composition. Further investigation is required to understand the significance of our findings for child health.

2.7.3. Metabolites in Mother's Milk: An Update from the LactoActive Project

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No abstract available: Dr. Kozyrskyj presented data on comparative studies using breast milk samples from collaborating *in*VIVO birth cohorts, including samples from the USA (n = 18), Norway (n = 40), and South Africa (n = 10) of general (mixed) allergic risk, and from Japan (n = 12) and Australia (n = 29) at high atopic risk. The aim was to identify the key metabolites of the breast milk metabolome, and determine the differential abundance of these metabolites across maternal atopy status, infant sex, location, and maternal ethnicity. Dr. Kozyrskyj presented data showing clustering by location; breast milk lactose levels were higher in South African than Norwegian or Australian healthy women. Analyses are ongoing.

2.7.4. Impact of Milk on the Metabolic Phenotype of the Developing Neonate

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The link between food and health is complex, particularly for the developing neonate. The period after birth is the time when long-term programming is occurring in the neurologic, immune, and metabolic regulatory systems. Breast-feeding is known to have short and long-term benefits,

and yet, the intricate relationship of this unique food with the neonate is not fully understood. We have previously reported profound differences between breast-fed and formula-fed infants with respect to growth trajectory, immunological development, succession of the gut microbiome, and metabolism that indicate the development of unique metabolic phenotypes as a consequence of diet. Changing one component can have measurable impacts on the blood, urine, and fecal metabolomes, as well as on fecal microbial ecology. To investigate how the composition of infant formula affects the succession of the gut microbiome and the overall host metabolism, fecal microbial ecology, measured through 16s rRNA sequencing, and comprehensive metabolic profiling of serum and feces measured through 1H NMR metabolomics, were analyzed in the context of different formula diets, and compared with breast-fed controls. Our results highlight the need for a greater understanding of human milk and how it shapes immunity and metabolism in the developing neonate.

2.7.5. Immunological Factors in Human Milk and Infant Body Composition over the First 12 Months of Life

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Breast-feeding has been implicated in the establishment of infant appetite regulation, feeding patterns, and body composition (BC), and is also associated with a reduced risk of developing a range of infectious diseases during childhood and chronic non-communicable diseases (NCDs) later in life. The aim of this study was to investigate the relationships between maternal and infant BC and human milk (HM) immunological factors during the first 12 months of lactation.

The BC of breast-feeding dyads (n = 20) was measured at two, five, nine, and/or 12 months postpartum with ultrasound skinfolds (US; infants only) and bioelectrical impedance spectroscopy (infants and mothers). Then, 24-h milk intake and concentrations of HM lactoferrin, lysozyme, and sIgA were measured, and daily doses were calculated (CDI). Statistical analysis used linear mixed effect models, and the results were adjusted for the false discovery rate.

No associations were seen between the concentrations/CDI of immunological factors and maternal BC. No associations between infant BC and concentrations of lactoferrin, lysozyme, and sIgA were seen. The higher CDI of lactoferrin and sIgA was associated with lower infant fat-free mass index measured with US (lactoferrin: p = 0.002; sIgA: p = 0.008), while a higher CDI of lysozyme was associated with larger infant fat mass (p = 0.004) and higher fat mass index (p = 0.004) measured with US.

These results show that there is a differential effect of HM immunological factors on infant BC during the first 12 months of life. Given the antibacterial, antiviral, and anti-inflammatory effects of the factors analyzed, and the link that exists between inflammation and obesity, there is a potential to improve the outcome for the infant through interventions, such as the continuation of breast-feeding during the first 12 months of life and beyond, which may facilitate favorable developmental programming that may reduce the risk of NCD later in life.

2.7.6. Human Milk Composition: Are "Lactotypes" Myth or Reality?

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No abstract available: Dr. Munblit presented preliminary data suggesting that there may be distinctive 'lactotype' types that reflect differences in the profile of immunologically active molecules in human milk (HM) samples, and that these may be associated with protection or predisposition to infant disease, in particular early-onset conditions such as allergy. Hey summarized the need for ongoing research in this field, including: large and well-standardized studies of HM composition (integrated data on immune markers, human milk oligosaccharides (HMOs), PUFAs, microbiomes, and metabolites), defining lactotypes, and assessing the variations between women residing in different countries; the application of omics approaches (metabolomics, proteomics, genomics, etc.) to delineate the most important components of HM in relation to allergic diseases; understanding the relevance of geographical location/lifestyle/diet on the composition of human milk and how to account for these important confounders; developing new intervention strategies for HM composition modification and indirect preventative effects of disease prevention.

Suggested Reading

1. Munblit, D.; Peroni, D.G.; Boix-Amorós, A.; Hsu, P.S.; Land, B.V.; Gay, M.C.; Kolotilina, A.; Skevaki, C.; Boyle, R.J.; Collado, M.C.; Garssen, J. Human Milk and Allergic Diseases: An Unsolved Puzzle. *Nutrients* **2017**, *9*, 894.

2.7.7. Impact of Maternal Probiotic Supplementation on Human Milk Oligosaccharide Composition

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Rationale: Human milk oligosaccharides (HMOs) provide substrates to shape the infant's gut microbiota and affect the maturation of the intestinal mucosal immune system. We have previously identified an association with increased levels of certain HMOs and protection against the development of food allergy and atopic diseases in infants. However, the regulation of HMO levels is incompletely understood.

Methods: We utilized stored frozen colostrum samples from the previously published large randomized probiotic interventional study of pregnant mothers from Helsinki, Finland carrying children with hereditary allergic predisposition. The children born from these mothers were followed up for five years for the development of allergic disease. In the probiotic group, from the 36th week of gestation, mothers took twice daily *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* ssp. *shermanii* JS in capsules. Then, 81 colostrum samples were randomly selected, with equal distribution between the placebo and treatment probiotic groups. The concentrations of 19 HMOs were determined using HPLC.

Results: The concentrations of 3-fucosyl lactose (413 μmol/mL versus 312 μmol/mL, $p = 0.0077$) and 3′-sialyllactose (833 μmol/mL versus 516 μmol/mL, $p = 0.006$) were significantly higher in colostrum from the maternal probiotic supplementation group compared to the non-supplemented group. Levels of DFLNH ($p = 0.0049$), LNT ($p = 0.012$), LNFP I ($p = 0.026$), and 6′-sialyllactose ($p = 0.028$) were lower in colostrum from probiotic-supplemented mothers.

Conclusions: Maternal probiotic supplementation during late pregnancy may alter the HMO composition in colostrum, including a shift from 6′-sialylation to 3′-sialylation. Maternal diet may be

an important factor in modulating colostrum HMO levels that should be considered when assessing HMO levels.

2.7.8. TGF-Beta in Human Milk and Allergic Outcomes in Children: A Systematic Review

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Background: Human milk (HM) cytokines, and in particular transforming growth factor-beta (TGF-ß), appear to be essential in developing and maintaining appropriate infant immune responses. However, the role of TGF-ß in the prevention of allergic diseases remains controversial. This systematic review aims to provide a comprehensive analysis of published studies on the association between HM TGF-ß and allergic outcomes in infancy/early childhood.

Method: An extensive search was conducted in MEDLINE, EMBASE, and the Cochrane Library for prospective, retrospective and cross-sectional human studies published in English. The risk of bias was assessed in duplicate using the Cochrane Risk of Bias tool and the National Institute for Clinical Excellence methodological checklists for intervention (IS) and observational studies (OS), respectively.

Results: Of the 353 hits identified in the database search, 103 relevant papers were screened. Of these, 27 that met the selection criteria were reviewed, and 21 studies (7 IS and 14 OS) were included. Among the health outcomes measured, studies assessed the association of HM TGF-ß and the risk of asthma and/or wheezing (10), allergic rhinoconjunctivitis (2), eczema (17), allergic sensitization (14), and the development of the food allergy (7). Results indicated that TGF-ß1 shows either neutral or protective effect for infant allergic outcomes (9/14 OS (64%)—neutral, 5/14 (36%)—protective effect), while TGF-ß2 shows either neutral or negative effect (4/5 OS (80%)—neutral, 1/5 (20%)—negative effect; 3/5 IS (60%)—neutral, 2/5 (40%)—negative effect). There was a high level of heterogeneity among the studies, and some studies carried a high risk of bias.

Conclusions: While TGF-β is an important factor in HM involved in the regulation of inflammation, its contribution to the prevention of allergy during infancy has yet to be confirmed. Further studies are needed in order to elucidate the effect of these regulatory cytokines on allergy development employing a consistent timing of collection, validated assay methods, and the accurate phenotyping of outcomes.

2.7.9. Effects of Milk Fat Globule Membrane Supplementation and Postnatal Growth Restriction on the Developing Rat Pup Microbiota

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Objectives: The milk fat globule membrane (MFGM) is responsible for delivering fat in human milk to the newborn infant. This trilayer membrane contains a variety of lipids (both polar and non-polar) and glycosylated proteins originating from the secreting mammary cell. This milk fraction is typically removed during the processing of infant formula. Considering that infant feeding modality can have a significant impact on an infant's microbiota, our aim was to determine how MFGM may influence early microbiome development utilizing a rat pup model.

Methods: Sprague–Dawley rats were mated, and the resulting litters were randomized on postnatal day (PD) 2 to either normal (N; n = 10 pups/dam) or restricted growth (R; n = 16 pups per dam) litter sizes. Pups were supplemented with 100 mg/kg BW of MFGM or a non-fat milk control (NFM) daily beginning on PD2 and until PD13. On PD14, pups were killed and cecal and colon contents were collected and pooled into sterile tubes containing RNA later. Following isolation, the V4 region of the 16S rRNA gene from each sample was amplified and sequenced using the Illumina Miseq platform. Sequences were analyzed using DADA2 as implemented in QIIME2 pipeline (version 2017.8). Alpha diversity was analyzed using Chao1 richness and the Shannon index using R (version 3.4.1). Beta diversity was analyzed using weighted UniFrac distances in combination with Adonis and PCOA (Principal Coordinate Analysis) in R. Differential abundance testing was completed using gneiss as implemented in QIIME2.

Results: At PD14, normal growth pups were on average 6.3 g larger than the restricted growth pups (p = 0.0001). Firmicutes and proteobacteria dominated all of the fecal samples. Restricted growth decreased species richness as measured by Chao1, regardless of MFGM or NFM treatment. The treatment and growth interaction was significant for Chao1 species richness. Growth, but not treatment, also impacted beta diversity. The cluster analysis produced with gneiss indicates that clostridia is one of the main taxa driving differences between the treatment and growth groups.

Conclusions: The results from this study indicate that growth restriction and MFGM supplementation modulate the microbiota of the developing rat pup.

2.7.10. Leptin Concentration in Human Breast Milk and Infant Body Composition: Results of the Ulm Birth Cohort Study and the Ulm SPATZ Health Study

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Background: Leptin in human breast milk has been implicated as a potential regulator of early-life metabolic programming. To add to current knowledge, we investigated the influence of breast milk leptin on child body composition up to two years within two independent birth cohorts.

Methods: The Ulm Birth Cohort Study (UBCS) and the Ulm SPATZ Health Study each consist of approximately 1000 newborns and their mothers recruited from the general population in the University Medical Center in Ulm, Germany, from 2000–2001 and 2012–2013, respectively. Leptin concentration was measured in skimmed breast milk collected around six weeks postpartum in both cohorts, and at six months and one year among long-term breast-feeding mothers in the SPATZ cohort only. Age-adjusted infant weight-to-length ratio z-scores (WTLz) were calculated from measurements recorded during regular pediatric appointments at about five weeks, four months, six months, one year, and two years postpartum. Linear regression was used to investigate associations of categorized (quintiles) leptin concentration with WTLz, adjusting for maternal pre-pregnancy body mass index (BMI), age, breast-feeding frequency, and preceding period WTLz.

Results: Breast milk leptin concentrations were available for 754 and 668 mothers of singleton infants in UBCS and SPATZ, respectively. Overall, median leptin concentration was lower (p-value < 0.001) in UBCS [median (IQR): 175.0 (270.2)] compared with SPATZ [266.5 (346.0)]. In both cohorts, six-week leptin concentrations were inversely associated (p-trend < 0.001) with five-week WTLz [β comparing

fifth to first quintile: −0.35, (95% CI −0.57 to −0.12) for UBCS and −0.35 (−0.60 to −0.11) for SPATZ]. No significant associations were observed with WTLz thereafter.

Conclusions: We observed strong evidence implicating breast milk leptin as a potential mediator of concurrent early infant growth up to six weeks postpartum, but not for concentrations in more mature breast milk (preliminary results, data not shown) or with later growth periods.

2.7.11. sCD14 Concentration in Human Breast Milk and Its Potential Role in Child Atopic Dermatitis: Results of the Ulm Birth Cohort Studies

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Background: Soluble CD14 (sCD14) is one of many factors in human breast milk that may influence the programming of the immune response in the breast-fed child. Although previous studies have mostly found little association between sCD14 concentration in breast milk and atopic outcomes, recent evidence continues to support a role of sCD14 in immune-related disease.

Objective: We aimed to clarify whether an association exists between sCD14 concentration in human breast milk and child atopic dermatitis (AD) diagnosis by three years of age within the context of two large birth cohorts.

Methods: Data were obtained from the Ulm Birth Cohort Study (UBCS) and the Ulm SPATZ Health Study, which were methodologically similar birth cohort studies, each consisting of approximately 1000 newborns and their mothers recruited from the general population shortly after delivery in Ulm, Southern Germany, respectively from November 2000 to November 2001 and April 2012 to May 2013. sCD14 concentrations were measured by different ELISAs (UBCS: IBL, SPATZ: R&D) in breast milk samples collected at six weeks post-delivery in both studies, and additionally at six months and one year in SPATZ. Children's AD diagnosis was assessed using parent and pediatrician reports at one, two, and three years of age.

Results: Complete exposure and outcome data were available for 659 UBCS and 489 SPATZ children. In both cohorts, sCD14 concentration was significantly associated with breast-feeding frequency ($p < 0.01$). We observed no association between sCD14 concentration and child AD diagnosis in either study.

Conclusions: Our results do not support an association between sCD14 concentration in mature breast milk and AD among breast-fed children.

2.7.12. Appetite Hormones in Human Milk and Maternal and Infant Body Composition over the First 12 Months of Lactation

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Human milk (HM) components, such as appetite hormones, may influence infant appetite regulation and body composition (BC), while breast-feeding is associated with a reduced risk of developing non-communicable diseases (NCD) during childhood and later in life. A holistic approach is required to establish if appetite hormones in HM play a role in both the programming and prevention of NCD, and investigate associations between the concentrations/calculated daily intakes (CDI) of HM adipokines in the first 12 months postpartum and maternal and term infant BC.

The BC of breast-feeding dyads (n = 20) was measured at two, five, nine, and/or 12 months postpartum with ultrasound skinfolds (US; infants only) and bioimpedance spectroscopy (infants and mothers). Then, 24-h milk intake was measured; HM was analyzed for whole milk adiponectin and skim milk leptin (SML), and whole milk leptin (WML) and the CDI of adipokines were also calculated. Statistical analysis used linear mixed effect models, and results were adjusted for the false discovery rate.

No significant associations were seen between maternal BC and either concentrations or the CDI of adiponectin, WML, and SML. No significant associations were seen between concentrations of these adipokines and infant BC. Higher CDI of adiponectin were associated with lower infant fat-free mass (FFM) (p = 0.005), FFM index (p = 0.009), and fat mass (FM) index ($p < 0.001$), and higher FM ($p < 0.001$) and %FM ($p < 0.001$) measured with ultrasound (US). The higher CDI of SML was associated with higher infant FM ($p < 0.001$), FFM index ($p < 0.001$), and %FM (p = 0.002) measured with US. No associations were seen between infant BC and the CDI of WML.

These results show that there is a differential effect of HM appetite hormones on the development of infant FM and FFM during the first 12 months of life. This time is a critical window of infant programming, and HM may potentially influence the risk of later disease and obesity via the modulation of BC.

2.7.13. Relationships between Breast-Feeding Patterns and Maternal and Infant Body Composition over the First 12 Months of Lactation

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Obesity is increasingly identified as a risk factor for non-communicable chronic disease (NCD) in children and adults. NCD is also linked to the unfavorable developmental programming of appetite control. Breast-feeding has been implicated in the establishment of infant appetite regulation, feeding patterns, and body composition (BC). A holistic approach is required to elucidate the relationships between infant and maternal BC and contributing factors, such as breast-feeding parameters, which may play a role in both obesity programming and prevention.

Associations between maternal BC and breast-fed term infant BC (n = 20) and the breast-feeding parameters during the first 12 months of lactation were investigated. BC was measured at two, five, nine, and/or 12 months postpartum with ultrasound skinfolds (US; infants only) and bioimpedance spectroscopy (infants and mothers). Then, 24-h milk intake and feeding frequency were measured. Higher feeding frequency was associated with larger 24-h milk intake ($p \leq 0.003$). Higher 24-h milk intake was associated with: greater infant fat mass (FM) (US: $p \leq 0.002$), greater %FM (US: $p \leq 0.008$), greater FM index (FMI) (US: $p \leq 0.001$), and lower fat-free mass index (FFMI) (US: p = 0.015).

Lower feeding frequency was associated with both larger FFM (US: $p \leq 0.001$) and FFMI (US: $p < 0.001$). Greater maternal adiposity was associated with smaller infant FFM measured with US (maternal BMI: $p < 0.010$; %FM: $p = 0.004$; FMI: $p < 0.011$). Maternal BC was not associated with feeding frequency or 24-h milk intake.

These results show that there are significant differences in infant BC depending on maternal BC and breast-feeding parameters in first 12 months of life. Thus, there is a potential to exploit these differences for long-term benefit, through interventions during preconception, pregnancy, and in the first 12 months of life, which may facilitate developmental programming that could reduce the risk of NCD later in life.

2.7.14. A Role for Early Oral Exposure to House Dust Mite Protease in Food Allergy Susceptibility

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With dramatic increases in the burden of infant food allergy, there is a mounting imperative to understand the factors affecting gut mucosal immune development, particularly those adversely affecting the capacity to mount oral tolerance. We recently demonstrated that allergens from the house dust mite Dermatophagoides pteronyssinus (Der p) are present in human milk, and thereby could potentially affect gut mucosal immunity in offspring. Here, we observed that mice exposed to Der p allergens through breast milk showed increased gut permeability, IL-33 secretion, group 2 innate lymphoid cells activation, and Th2 cell differentiation in the small intestine lamina propria at two weeks of life. This pro-Th2 gut mucosal environment hindered the induction of antigen-specific FoxP3 regulatory T cells upon oral exposure to egg-derived antigen ovalbumin (OVA) through breast milk. In the long term, the Der p-induced imbalance in gut mucosal immunity abolished the possibility of preventing food allergy by OVA exposure through breast milk. The neutralization of Der p protease activity indicated that this enzymatic activity was necessary and sufficient for Der p-induced gut mucosal immune dysregulation and increased food allergy susceptibility. Finally, we observed a consistent relationship in humans. In a birth cohort of 100 infants, IgE-mediated egg allergy prevalence at one year was 4.7 times higher in infants exposed to Der p through breast milk compared to infants exposed to OVA through breastmilk (RR 3.4; CI: 0.5–21.5; $p = 0.04$, chi-square one side).

The evidence that protease from house dust mite, an ubiquitous source of respiratory allergens, could profoundly affect gut immune ontogeny and the risk for food allergy, should promote research for new strategies to prevent food allergy in early life.

2.8. Session 8: ONE Health—Encouraging Cross-Disciplinary Approaches to Symbiotic Mutualism

2.8.1. Antimicrobial Resistance: Linking Science to Policy Development to Curb AMR in Humans and Animals in Canada

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Antimicrobial resistance (AMR) is a global public health crisis threatening to push the world into the post-antibiotic era. Recent estimates suggest that by 2050, the annual burden of human deaths attributable to AMR could exceed 10 million, with a cumulative cost to global economic output in the order of $100 trillion (USD) [1]. Despite much work to understand and combat AMR, we continue toward the precipice where these drugs are no longer effective. This will force us to rethink our lifestyles, from minor wounds sustained during activities to procedures that we take for granted, such as caesarian sections and joint replacements. This also affects animal health and welfare in production animals, from which we derive food and companion animals, which are important members of our families.

The complicated epidemiology of AMR and its genetic determinants absolutely requires a One Health approach to devise solutions and mitigation strategies. Current policy work includes human and animal health stakeholders, but the environmental piece remains elusive. In 2017, Canada released its strategic framework to tackle AMR [2] under the World Health Organization (WHO) Global Action Plan on AMR. The development of this Canadian framework included representatives from the animal and human health sectors of all federal, provincial, and territorial government departments. However, those developing the framework recognized the need for future engagement with the environmental sector to address this potential reservoir for AMR development, maintenance, and transmission. A recent systematic review found that interventions to reduce antimicrobial use in food-producing animals did reduce AMR in bacterial isolates from both animals and humans, but it did not eliminate it [3]. This suggests that gaps exist in our understanding of the complex epidemiology of AMR, and supports the need for a One Health approach.

Recent evidence suggests that our construct of "antimicrobials" and "disinfectants" compared to other chemical compounds may be an oversimplification of how we consider their antimicrobial effects and the resulting environmental implications of their use. A recent in vitro study co-exposed *Salmonella* Typhimurium or *E. coli* isolates to different antimicrobials and active ingredients of common commercial herbicides (e.g., glyphosate, 2,4-D or dicamba) [4]. The response in the selected isolates varied from increasing to decreasing levels of resistance to each antimicrobial. Another new in vitro study evaluated the effect of 1197 human non-antimicrobial drugs on 40 bacterial isolates representative of the human gut microbiome [5]. They reported that one in four of these non-antimicrobial drugs, irrespective of drug class, inhibited the growth of at least one gut strain, and could be a concern for AMR development.

Together, these results complement a growing feeling that the evaluation of antimicrobial selection pressure is not as simple as single "bug-drug" combinations. Antimicrobials, as we traditionally define them, are likely not the only compounds to impart this selective pressure. Action at all levels to develop mitigation strategies for AMR must include a broad environmental lens and scientific evidence. This is the very essence that makes AMR such a challenging One Health problem, requiring engagement from all sectors as full participants to move toward global solutions.

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2.8.2. Cleaning Products, the Infant Gut Microbiome, and Disease Risk: CHILD Birth Cohort

Mon H. Tun [1,2], Hein M. Tun [2], Justin J. Mahoney [2], Theodore B. Konya [3], David S. Guttman [4], Allan B. Becker [5], Piush J. Mandhane [2], Stuart E. Turvey [6], Padmaja Subbarao [7], Malcolm R. Sears [8], Jeffrey R. Brook [3], Wendy Lou [3], Tim K. Takarao [9], James A. Scott [3], Anita L. Kozyrskyj [1,2] and the CHILD Study Investigators

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Background: A greater emphasis on cleanliness has led to the widening use of disinfectants in the home, which leave their imprint on our microbial environment. There is evidence that household cleaning products adversely affect respiratory health, but no existing studies have reported on how they impact the gut microbiota of infants or their future health. In this session, new results from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort were presented on household cleaning product use, infant gut microbial composition, and overweight risk at age three. They were prefaced by mention of additional early life factors that cause dysbiosis of the infant gut, and followed by recommendations on how this can be prevented or reversed.

Methodology: Presented data originated from a large sub-sample of infants in the CHILD population-based birth cohort. At three to four months postpartum, home cleaning product use was determined from questionnaires, and the gut microbial composition of infant fecal samples was assessed by 16S rRNA sequencing. An overweight child at age three was defined as having a BMI z-score >97th percentile. Covariates such as mode of delivery, breast-feeding, and antibiotics exposure were retrieved from questionnaires or birth charts.

Results: A well-known signature of cesarean birth, especially when hospitalization is extended, is the reduced Bacteroidetes of the infant gut. Further, mothers in the CHILD study were more likely to clean with disinfectants after cesarean delivery. A high-frequency use of household disinfectants affected infant gut microbial composition by elevating the abundance of Lachnospiraceae in a dose-dependent manner. The Lachnospiraceae were found to mediate the association between postnatal disinfectant exposure and children who were overweight at age three.

Conclusions: The CHILD study reveals that exposure to household disinfectants in early life can alter infant gut microbiota and increase the risk of overweight children. Pet ownership during

pregnancy and early breast-feeding has the capacity to prevent/revert infant gut dysbiosis following birth interventions.

2.8.3. Early Life Fungal and Bacterial Microbiome in Asthma Development

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No abstract available: Dr. Arietta discussed the developmental changes in early microbial colonization that are associated with the modern Western lifestyle, and the patterns of dysbiosis (including both the altered microbial communities and associated microbial metabolic signatures) associated with an increasing predisposition to asthma and allergic diseases. She also explored how the microbiome regulates fecal fungal growth, and how microbial dysbiosis may be associated with increased fungal growth. Asthma-related microbial dysbiosis appears to be related both bacterial and fungal alterations. Fungal overgrowth may also explain immune dysregulation in asthma and allergic diseases.

2.8.4. The Microbiome (and Resistome) in International Travelers and Rural Populations in Developing Regions

John Penders

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No abstract available: Dr. Penders discussed novel approaches to understand the emergence, dissemination, and potential prevention of antimicrobial resistance (AMR). He reviewed research on the Vietnamese population and changes in the microbiome (resistome) in travelers to the region. Data show a high prevalence of targeted resistance AMR genes (including *mcr-1*) in Vietnamese individuals and their companion animals. Traveler's resistome has been shown to rapidly adapt to the resistome profile of the local Vietnamese community, with the acquisition of resistance gene *MCR-1*. Further studies are needed using functional metagenomics to identify novel resistance genes; sequence-based metagenomics to examine full resistance potential; and targeted metagenomics to determine the selected resistance genes for investigation in epidemiological analysis. The spread of resistance to antimicrobials (such as colistin and extended beta-lactam resistance) not only endangers the treatment of infectious disease, but it also has implications for non-communicable diseases in already vulnerable populations.

2.8.5. Prenatal Exposures and the Infant Microbiome, Allergy, and Adiposity: Lessons from the WHEALS Cohort

Ganesa Wegienka

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No abstract available: Dr. Wegienka discussed associations between various prenatal factors, body size and allergic outcomes, highlighting the complex and interrelated nature of these relationships. The importance of any single factor can vary in the presence/absence of other factors and the need to address these 'effect modifications' to tease apart relationships to understand mechanisms. The challenge is how can we address these relationships with an epidemiological approach, given that assessing statistical interactions consume statistical power, and it is difficult to interpret multiway interactions. Latent class analyses can be used to identify "prenatal profiles" as defined by combinations of maternal and environmental factors. These "prenatal profiles" can then be examined for relationships to outcomes. This provides a way to combine many variables used to identify groups that are more similar to each other with respect to the studied characteristics. She concluded that even without

statistically significant results, it is still important to consider effect modification in analyses to add to the understanding of interrelatedness—"*don't just cling to p-values*".

2.8.6. Association between Pacifier Cleaning Methods and Child Total IgE

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Microbial-related exposures in early life stimulate immune development and may protect against allergic disease manifestations later in life. Parental pacifier sucking is one such early life exposure that may offer protection through the transfer of oral microbes from parent to offspring.

We investigated whether pacifier-cleaning methods reported at six months of age were associated with differences in serum IgE trajectory over the first 18 months of life (blood collected at cord, six months, and 18 months), using maternal–child pairs from the Detroit-based Microbes, Allergy, Asthma, and Pets (MAAP) cohort (N = 141). Linear mixed effect models were used to model total IgE trajectories (log transformed for normality).

Of 128 mothers completing an interview when children were six months old, 74 (58%) reported current child pacifier use. Of these 74, 30 (41%) reported pacifier cleaning by sterilization, 53 (72%) reported handwashing the pacifier, and nine (12%) reported parental pacifier sucking. No differences in maternal, household, and early-life characteristics were found by any pacifier cleaning method (all $p > 0.05$). Pacifier sterilization or handwashing were not associated with serum IgE trajectory (interaction p-values = 0.95, 0.99; main effect p-values = 0.72, 0.41, respectively). However, a significant time of interaction was detected for pacifier sucking ($p = 0.083$), indicating that the trajectory shape differed between children of pacifier-sucking versus non-pacifier sucking parents. Specifically, parental pacifier sucking appeared to suppress serum IgE levels beginning around 10 months of age ($p = 0.048$), and continued to diverge through 18 months ($p = 0.015$).

These results suggest that parental pacifier sucking may lessen early-life IgE production, indicating altered immune development in a fashion that lessens allergy risk. Further research is needed to assess whether these differences are due to the transfer of parental oral microbes. These findings support a previous Swedish study reporting a protective effect of parental pacifier sucking, and may have implications for the prevention of allergic diseases in children.

2.8.7. Exposure to Tobacco Smoke in Prenatal and Early Postnatal Alters Infant Gut Microbiota and Increases Risk of Childhood Overweight

Hein M. Tun [1], Sarah L. Bridgman [1], Theodore Konya [2], David S. Guttman [3], Radha S. Chari [4], Catherine J. Field [5], Allan B. Becker [6], Puish J. Mandhane [1], Stuart E. Turvey [7], Padmaja Subbarao [8], Malcolm R. Sears [9], James A. Scott [2], Anita L. Kozyrskyj [1] and the CHILD Study Investigators

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Introduction: The association between smoking exposure (during and after pregnancy) and childhood overweight has been reported previously. However, the underlying mechanism is not yet clear. In this study, we investigate the effect of household tobacco smoke exposure in prenatal and early postnatal periods on the infant gut microbiota composition and overweight risk at age three.

Methodology: This study included 999 infants from the Canadian Healthy Infant Longitudinal Development (CHILD) study cohort. Smoking exposure status (both maternal and other household members) was categorized into four groups: no exposure (78.2%); exposure only during pregnancy (1.5%); exposure only postnatally (10.7%); and exposure during pregnancy and postnatally (4.6%). At age three, children with a BMI-z score >97th percentile were classified as overweight. The gut microbiota of infants at three to four months was assessed using high-throughput 16S rRNA sequencing. Other covariates, including maternal pre-pregnancy weight, ethnicity, birth mode, breast-feeding, and antibiotics exposure were retrieved from standardized questionnaires completed by mothers. The mediation effect of microbiota measurements was evaluated. Statistical analyses were performed in SAS V9.4.

Results: Exposure to tobacco smoke postnatally was significantly associated with child overweight at three years of age (OR: 3.61, 95% CI: 1.36–9.60). The association was significant after adjusting for other covariates, including maternal overweight. Firmicutes richness and an abundance of *Lachnospiraceae* was significantly increased in infants exposed to tobacco smoke postnatally or both prenatally and postnatally ($p < 0.05$). Independent to tested covariates, the highest tertile of Firmicutes richness provided a twofold higher risk of overweight at age three (aOR: 1.91, 95% CI: 1.01–3.60). A mediation analysis revealed potential mediation by gut microbiota, especially Firmicutes richness, in the association between postnatal smoking exposure and the risk of childhood overweight at age three (95% CI: 0.01–0.09).

Conclusions: Our study highlights that exposure to household tobacco smoking in early life can alter infant gut microbiota at three to four months, and may increase the risk of childhood overweight and obesity.

2.8.8. Exposure to *Ascaris* spp. Is Associated with Lower Lung Function among Males in a Norwegian Cohort

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Background: Ascariasis is the most common helminth infection, with an estimated worldwide prevalence of 25%. Data about affluent countries is scarce, and the role of helminths is believed to be overlooked. During its natural life cycle, *Ascaris* travels through the lungs to reach the intestine, causing tissue damage. We therefore hypothesize that *Ascaris* might affect lung function. It has been proposed, and also shown in mural models, that gender differences may play a crucial role in the host's response to ascariasis, i.e., resulting in a higher worm load in males.

Objective: To describe the association of anti-*Ascaris lumbricoides* IgG4 seropositivity with lung function in Norway, stratified by gender.

Methods: Serum levels of *Ascaris* spp. IgG4 were established by ELISA in two cohorts: parents born 1945–1972 (n = 171) and their offspring born 1969–1996 (n = 246). Spirometry, clinical, and interview data were recorded during clinical examination. Logistic regression models were used to assess the relationship between exposure to *Ascaris* and lung function. All of the models were adjusted for age, height, and smoking.

Results: Anti-*Ascaris* spp. IgG4 was detected in 29.2% of parents and 10.6% of offspring. The prevalence was higher among male offspring (12.9%) compared to female (7.7%) offspring. *Ascaris* seropositivity was associated with lower FVC (forced vital capacity) [−328.2 mL (95% CI: −627 mL, −29.4 mL; p = 0.032)] and FEV1 (forced expiratory volume in one second) [−243.7 mL (−491.3–4 mL; p = 0.054)] among the male offspring, suggesting a restrictive pattern. Adjustment for BMI, age squared, and smoking did not alter the associations. There was no association of *Ascaris* with lung function in women or the middle-aged parents' generation.

Conclusions and Clinical Relevance: Exposure to *Ascaris* among young Norwegians was associated with substantially lower lung function in younger male participants, but not among females. These findings highlight the need to explore further the role of helminths on lung health, also in Western countries, and with a particular focus on gender differences.

2.8.9. General Causal Factors in the Development of Allergies in Mammals

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Allergies are reported to be more prevalent in urban than in rural human populations. Furthermore, several factors that probably increase our microbial exposure such as farming environment, siblings, and regular contact with cattle and pets, tend to be associated with allergy protection. Allergic diseases are not restricted to humans. Also, our companion animals, dogs, suffer increasingly from allergies and many other non-communicable diseases that are analogues to those common in humans.

We have conducted two projects, a large survey (n = 5622) and an explorative study (n = 169 + 167) with biological samples, in which we asked how environmental factors and lifestyle associate with allergies in dogs and their owners. In this explorative project, we collected skin and gut microbiota samples as well as blood serum (for analysis of Immunoglobulin E and C-reactive protein) from dogs and their owners.

In both datasets, dogs were more allergic in urban than in rural environments. This finding was also true when the effect of breed, which is a strong predisposing factor in dogs, was controlled. The composition of skin microbiota in dogs was associated with their living environment and lifestyle, while gut microbiota was associated with their diet and medications. Interestingly, allergic diseases, skin microbiota, and living environment were interrelated in dogs.

In both datasets, an allergic dog was more likely to have an allergic owner than a healthy dog was. This indicates that the shared factor in the living environment or lifestyle can explain the higher prevalence of allergic diseases in urban environments in both species. In ongoing analyses, we explore this finding deeper, and see how skin and gut microbiota relates in dogs and their owners, and whether it is associated with the mutual presence of allergies. We also search the shared environment or lifestyle factor that can potentially explain this relation. The results of these new analyses were presented.

2.8.10. Association between Antibacterial Chemicals, Oral Microbiome, and Lung Function

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Antibacterial chemicals have been associated with allergic disease, and convincing evidence point toward an association between oral microbiota and lung health. We aimed to describe the association between paraben exposure and oral microbiome, and secondly the association between oral microbiome and lung health.

Interview data, lung function (FEV_1 and FVC), urine samples, and gingival fluid samples were collected from 288 adults (48% females, median age: 28 years) from the RHINESSA (Respiratory Health In Northern Europe, Spain and Australia) study in Bergen, Norway. Urine biomarkers of paraben exposure were quantified with mass spectrometry and microbiome by high-throughput sequencing (Illumina MiSeq) and assigned taxonomy by the Human Oral Microbiome Database. Differential abundance in the gingival microbiome for paraben exposure and lung function was evaluated by the analysis of composition of microbiomes (ANCOM) methodology.

Propyl (PPB) and methyl-parabens (MPB) were detected in 95% of the urine samples, and ethyl (EPB) and butyl (BPB) were detected in 62% and 38% of the urine samples, respectively. Women were significantly more exposed than men, and urine levels increased with the reported frequency of use of cosmetic products. Several gingival bacteria, mainly within the Firmicutes and Proteobacteria phyla, were associated with FEV_1 and FVC, of which some were also associated with paraben exposure. The relative abundance of *Mitsuokella* spp. increased with FEV_1 and FVC, and with exposure to PPB. *Peptostreptococcacea [XI][G-7]* spp. was associated with BPB exposure and inversely correlated with FVC, and *Haemophilus* spp. was associated with EPB and correlated positively with FEV_1.

Among the bacteria associated with paraben exposure and lung function, species within the genera *Peptostreptococcae* and *Mitsuokella* have been associated with poor oral health, and *Haemophilus* spp. includes species that are known respiratory pathogens as well as commensal bacterial species from the upper respiratory tract. These preliminary results suggest that exposure to antibacterial chemicals may modify the association between oral microbiome and lung health.

2.9. Session 9: Stress, Sleep, Inflammation, and Aging

2.9.1. Stress, Aging, and Our Biological Clock—Lessons from Telomeres: Telomere Length in Early Life

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Telomere length may predict the lifespan and susceptibility of developing age-related diseases, and is considered to be a marker of biological aging. At birth, telomere length is highly variable due to differences in genetics and environmental exposures that occur during embryonic and fetal development [1]. It has been hypothesized that the origins of health and disease in later life may be determined early in life or even during the prenatal life. Therefore, the programming of telomere biology at birth and during early life may be an important biological pathway underlying the developmental origins of later life health and disease. Knowledge on factors that determine telomere length at birth is scarce. However, recently, important factors explaining telomere length variation at birth are being explored. In the ongoing population-based prospective Environmental Influence on Aging in Early Life (ENVIR*ON*AGE) birth cohort study in Belgium, we evaluated different early life

factors associated with telomere length at birth. We observed that each 1-kg/m^2 increase in maternal pre-pregnancy BMI was associated with a 0.50% shorter cord blood and a 0.66% shorter placental telomere length [2]. Besides pre-pregnancy BMI as a newborn telomere length predictor, we observed a negative association between prenatal particulate matter (PM) air pollution exposure and newborn telomere length. Each 5 μg/m^3 increase in maternal residential $PM_{2.5}$ (particles with an aerodynamic diameter $\leq$2.5 μm) exposure during the entire pregnancy was associated with an 8.8% shorter cord blood and a 13.2% shorter placental telomere length [3]. Up to now, we identified that maternal overweight before pregnancy and maternal exposure to air pollution during pregnancy may influence newborns' predisposition to accelerated biological aging. Healthy weight and air before and during pregnancy may promote the molecular longevity of the next generations.

Suggested Reading

1. Martens, D.S.; Nawrot, T.S.; Air Pollution Stress and the Aging Phenotype: The Telomere Connection. *Curr. Environ. Health Rep.* **2016**, *3*, 258–269.
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2.9.2. Noise Stress during Pregnancy and Birth Outcomes

Hind Sbihi [1], Hugh Davies [1], Perry Hystad [2], Leanne Cusack [2], Ulrike Gehring [3], Michael Brauer [1] and Stuart Turvey [1]

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Rationale: Most of the evidence for an adverse effect of noise exposure on pregnancy outcomes comes from cross-sectional occupational studies. Little is known about the effects of environmental noise exposure, which is an established environmental stressor, on pregnancy outcomes.

Plausible biological mechanisms include stress and sleep disturbance. Stress has been hypothesized to affect fetal growth through the endocrine system, which has been confirmed in human and animal studies; sleep disturbance has been found to be associated with adverse pregnancy outcomes. Moreover, there is evidence for an increased risk of hypertension in subjects exposed to noise, which could increase the risk for adverse pregnancy outcomes as a result of pre-existing hypertension or pregnancy-induced hypertension.

Methods and Studies: Using linked administrative health databases, we developed geospatial environmental exposures surfaces, including air pollution, noise, and greenness. Noise exposure was based on transportation-related information, including road traffic, railway data, aircraft noise exposure forecasts, and building heights and footprints. Air pollution was estimated using land-use regression models, and greenness was derived using a biomass index (Naturalized Difference Vegetation Index, NDVI) from satellite imagery. All of the individual exposures were linked to the residential addresses of over 68,000 pregnant mothers in the Vancouver metropolitan area (British Columbia, Canada).

Results: Our findings from a large population-based prospective cohort study with rigorous exposure assessment and objective outcomes add to the growing evidence that motorized traffic adversely affects pregnancy outcomes, and indicate that traffic affects birth weight not only through air pollution but also through noise, whereas effects on pregnancy duration are limited to air pollution. Furthermore, observed air pollution effects on small-for-gestational age and term birth weight were partly attributable to noise. However, greenness acted as a protective buffer.

This positive effect of green spaces on birth outcomes regardless of other spatially covarying environmental exposures suggests additional pathways of influence. These were subsequently examined in a national birth cohort study: the Canadian Healthy Infant Longitudinal Development (CHILD). Here, we established that accounting for all of the aforementioned urban environmental exposures in addition to psychosocial and parental hereditary risk factors did not affect the protective impact of greenness on birth outcomes.

Conclusions: In light of the studies presented, we demonstrate the need to control for spatially covarying environmental exposures in epidemiological studies on the effects of the built environment on pregnancy outcomes. Further, we showed that when accounting for all of the putative environmental pathways, the protective effect of greenness remains. Taken together, these studies have led to our current investigation within the CHILD study on the potential role that the gut microbiome plays in the association between the built environment (including traffic air pollution and greenness) and child early-life immune-mediated health.

2.9.3. Neurodevelopment: The Importance of Sleep and Fruit Consumption

Piush Mandhane

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No abstract available: Dr. Mandhane presented data from the CHILD cohort, identifying factors associated with cognitive development. This included data suggesting relationships between maternal dietary patterns (including fruit intake) during pregnancy and infant cognitive development at one year. Postnatal factors that were discussed included night-time and daytime sleep trajectories in relation to early childhood impacts on learning and behavior. He also examined infant microbiome clusters and infant development.

2.9.4. Age-Associated Microbial Dysbiosis and Inflammation: Normal Aging or Lifestyle Changes?

Dessi Loukov

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No abstract available: Dr. Loukov discussed the impact of environmental influences on longevity, in particular the importance of socioeconomic status and education in determining opportunities for "healthy" behaviors. There is growing evidence that at least some of these influences may be mediated through the effects of lifestyle and behavior on the microbiome.

In 1908, Ilya Metchnikov proposed a link between intestinal health and longevity. Recent evidence supports this notion. Microbial dysbiosis may increase intestinal permeability, the translocation of bacterial products, and systemic inflammation, thereby contributing to disease and senescence. Animal studies indicate that the aging microbiome influences age-associated intestinal permeability and inflammation. This relationship is likely to be bidirectional, as preventing inflammation in the host (TNF KO mice) reduces microbial dysbiosis, intestinal permeability, and frailty. Immune-senescence highlights the importance of addressing lifestyle and environmental factors that promote inflammation and dysbiosis. Many of these factors are determined by socioeconomic status, adding a new dimension to the pathways of health inequalities and social justice.

2.9.5. Associations between Infant Short Sleep Duration and the Gut Microbiota Composition at Three Months of Age

Brittany A. Matenchuk [1], Theodore Konya [2], David S. Guttman [3], Allan B. Becker [4], Malcolm R. Sears [5], Stuart E. Turvey [6], Padmaja Subbarao [7], James A. Scott [2], Anita L. Kozyrskyj [1], Puish J. Mandhane [1] and the CHILD Study Investigators

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No abstract available: In children, sleep and gut microbiota composition are independently linked to future risk for asthma and obesity. The relationship between sleep duration and negative health outcomes may be explained by an altered gut microbiota composition. This study aims to explore the relationship between short sleep duration and gut microbiota composition in the three-month-old infant. Preliminary results were presented.

2.9.6. Improving Frailty and Vulnerability in Later Life: Applying Lessons from the Newborn?

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As a consequence of better medical care and living conditions, the population is aging in both developed and developing countries. However, aging is a major predisposing condition for acute infectious disease and chronic debilitating disease [1], and thereby is a cause of major economic burden for the society and suffering for the individual and their family. We propose here that looking at the other extreme of life, i.e., early postnatal life, could be a source of inspiration for insuring healthy aging. Actually, neonates and elderly people share a lack of autonomy and a homeostatic imbalance as a result of two opposite processes: organ development and organ degeneration, respectively. However, a major difference is that neonates benefit from a major support for their health: breast-feeding. This support is so well adapted to the needs of the developing child that breast-feeding is recognized as the most efficient way of preventing under-five disease and death [2]. This major success of nature probably relies on the comprehensive and adapted care that breast-feeding is providing to the neonate. As an example, the successful prevention of infection in neonates by breast milk is most probably achieved by the multiple functions provided by breast milk, including immune defense by the transfer of antibodies and a cocktail of non-antigen specific antimicrobial molecules, strengthening of the mucosal barrier by the transfer of growth factors, and gut microbiota eubiosis by the presence of prebiotics and probiotics [3]. Elderly people have a fragile barrier, low immune response to antigen challenge, altered microbiota; a holistic approach as the one provided by breast milk may be far more efficient for infection prevention than vaccination only. From this example, we propose to analyze how breast-feeding achieves homeostasis in the developing child to discover new ways of maintaining homeostasis in an aging population.

Suggested Reading

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