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Oxford Textbook of Nature and Public Health

The role of nature in improving the health of a population

Edited by
Matilda van den Bosch
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Dedication

Anthony J. McMichael: a champion for environmental health

Tony McMichael died soon after writing Chapter 7.5 in this book. Born 1942, he was inspired by microbiologist turned planetary health ecologist René Dubos to 'think global act local'. Best known for his leadership in global ecology, climate change, and health, McMichael also pioneered the harm done by lead. He was prolific: 300+ papers, 160+ chapters, 3 sole-authored books, and 9 that were co-edited.

After graduating in medicine, McMichael was elected president of the Australian National Union of Students in 1968. By 1994, he was Epidemiology Professor at the London School of Hygiene and Tropical Medicine. He instigated and led the health chapter in the second report of the Intergovernmental Panel on Climate Change.

If we are to survive as an advanced and compassionate species, the work of people like McMichael will be recognized as fundamental to the shift that we must accelerate.

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Dedication

Stephen R. Kellert

Nature lost an important friend and advocate with the passing of Stephen R. Kellert on 27 November 2016. Kellert was a pioneering scholar in exploring the biological origins of our environmental values, and the many important ways children and adults interact with, and benefit from, contact with the natural world. He is probably best known for his work in support of the concept of biophilia: the belief that humans have an innate connection and need to affiliate with nature.

Kellert was not simply an academic, but one who cared deeply about seeing these biophilic principles put into practice and utilizing them to improve design of the built environment.

Kellert leaves behind both a biophilic design movement, and a cadre of friends and colleagues who he helped to infect with his enthusiasm for biophilia. Kellert organized the first major national meeting on biophilic design, later leading to the important book, *Biophilic Design: Theory, Science, and Practice of Bringing Buildings to Life* (2008). Many of us who attended that meeting began to see our own work through a biophilic lens, and we became Kellert disciples on a mission to foster a renewed sense of the wonder and beauty of nature, and its special power to heal and to bring meaning and rootedness in a turbulent world. His passion, intellect, and vision for what might be, will be missed by us all.

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Foreword

We live in epochal times.

The origins lie far back in time. Our genus, *Homo*, dates back more than two million years, our species roughly 200,000. Through evolutionary time, we have outlasted many of our Homo cousins—neanderthalensis, heidelbergensis, floresiensis, and more (Harari, 2014). That long process shaped us in complex ways, including endowing us with a deep connection to nature (Wilson, 1984). But we may not fully understand and appreciate that connection; we are arguably wired more for fight or flight than for foresight and wisdom (Buss, 2015; Kahneman, 2011).

Cultural history provides further context. Our civilization arose roughly 13,000 years ago, when the Younger Dryas cooling at the end of the Pleistocene gave way to post-glacial warming, marking the beginning of the Holocene. Our ancestors shifted from hunting and gathering to what we recognize as modern life—agriculture and manufacturing, art and culture, towns and cities. Human well-being improved in many ways, although there were also costs, such as less diverse diets and less contact with nature (McMichael *et al.*, 2017).

Recent industrial history provides still further context. The current human predicament dates from just a few hundred years ago, when we learned how to unleash vast amounts of energy that had been locked in fossil fuels over geologic time. This ushered in the Great Acceleration (Steffen *et al.*, 2015)—a time of unprecedented growth in population, urbanization, manufacturing, and of ecological degradation. So great was the impact that we have destabilized the very systems that maintain our planet. Rising atmospheric concentrations of greenhouse gases, especially carbon dioxide, are altering the climate. Biodiversity is diminishing as species go extinct at alarming rates. The pH of the ocean is falling. In many parts of the world, nitrogen and phosphorus cycles have been profoundly altered, soil degraded, forests extirpated, river flows interrupted, fresh water supplies depleted. Human impacts on earth systems define the epoch in which we live: the Anthropocene (Steffen *et al.*, 2007).

In many ways, the Anthropocene has been good to us. Our numbers have grown, as has our life expectancy. We have conquered ancient health problems such as polio, and we have limited the damage done by many diseases, from leprosy to tuberculosis to syphilis. But the story is not all rosy. Deep disparities persist; the wealthy enjoy far better health than the poor. And the Great Acceleration brought with it an epidemiologic transition, in which chronic and degenerative diseases supplanted infectious diseases around the world (Barrett *et al.*, 2015; Omran, 1971; Zuckerman *et al.*, 2014). Cardiovascular diseases, chronic respiratory diseases, and cancers—the so-called 'non-communicable diseases'—became the predominant killers. The factors that contribute to these conditions—obesity, high blood pressure, unhealthy diets, sedentary lifestyles, stress—became routine realities for far too many people.

Other conditions have also become common, causing suffering if not death, and the explanation is not always clear. Allergies, asthma, and autoimmune diseases such as lupus are on the rise, and may reflect, at least in part, an alteration of the human relationship with the microbial world (Versini *et al.*, 2015; Velasquez-Manoff, 2012). Back pain, neck pain, and headaches are disturbingly common (Vos *et al.*, 2016). So are autism, attention deficit-hyperactivity disorder (Vos *et al.*, 2016), anxiety, depression, and substance abuse (Whiteford *et al.*, 2015). In a world of increasing plenty, even in the wealthiest and most peaceful countries, large proportions of people report being unhappy and unsatisfied with their lives (Helliwell *et al.*, 2016).

Part of the solution can be found in this book.

We humans have a longstanding affiliation with the natural world, one embedded in evolutionary time (Wilson, 1984). Like all deep, authentic relationships, it is not always happy: sabre-toothed tigers chased us, snakes bit us, bees stung us, storms lashed us. But the natural world has also been a source of sustenance, succour, and inspiration. And now, it is increasingly clear that a feature of modern life—indeed, a corollary of our frenzied charge into the Anthropocene—is the breaching of this relationship.

The litany of problems is familiar. Urbanization has reduced opportunities for nature contact—not urbanization per se, but bad urbanization, featuring sterile, lifeless settings, and vast distances between where people live and where they can access greenspace. People in 'developed' nations spend the vast majority of their time indoors—in the United States, more than 90% (Klepeis *et al.*, 2001). Technology has taken centre stage in many people's lives, supplanting nature contact; children younger than age eight have an average of almost two hours of screen time each day (Rideout, 2013), a figure that nearly quadruples, to more than 7.5 hours, during their teenage years (Rideout *et al.*, 2010). Adults go even further, averaging a stunning 10 hours and 39 minutes of 'total media consumption' each day (Nielsen, 2016). Park visitation, hunting, fishing, camping, and children's outdoor play have all declined substantially over recent decades (Pergams and Zaradic, 2008; Clements, 2004;

Frost, 2010). 'Nature deficit disorder', while not a formal diagnostic term, denotes a widespread ailment (Louv, 2005).

Nature contact offers an astonishingly wide range of benefits for human health and well-being, from improving birth outcomes and reducing obesity, relieving depression to prolonging life. The relevant body of science is growing rapidly, and many published reviews have summarized it (Bowler *et al.*, 2010; Lee and Maheswaran, 2011; Russell *et al.*, 2013; Martens and Bauer, 2013; Hartig *et al.*, 2014; James *et al.*, 2015; Seymour, 2016). It is essential to document these benefits, and there is no more comprehensive collection of that documentation than in this book.

It is also essential to understand how nature benefits health and well-being—through what biomedical, social, and cultural pathways it operates. As with pharmaceuticals, this biomedical understanding will enable us to provide the most effective 'doses' of nature, in the most effective ways, to those who will benefit the most. Innovative science, from brain imaging to immune function tests, is propelling the needed research. This book admirably summarizes what we now know about the mechanisms that underlie nature benefits.

But scientific understanding is not enough. We need to implement what we know. We need to apply evidence to designing, creating, and maintaining opportunities for nature contact in ways that demonstrably make people healthier, happier, and more self-actualized. This is a task for the design professions—architects, urban planners, and landscape architects. It is a task for educators, school board members, and child care professionals. It is a task for parks and recreation professionals. It is a task for health professionals. It is a task for parents, and for elected officials. This book offers a rich selection of strategies and tactics for translating research into action.

We need a moral dimension to this work. In far too many ways, modern societies are stratified and unequal. Small minorities in most societies control vastly disproportionate shares of resources, and large numbers of people live in deprivation. Nature contact is not just an amenity; it is a birthright. Moreover, given evidence that nature contact disproportionately benefits those who are less well-off (Mitchell and Popham, 2008; Mitchell *et al.*, 2015), it may be an effective way to help rectify health disparities.

And cradling all of this—the science, the implementation, the social justice—we need culture change. A deeply felt appreciation of the natural world and of the human place in it, a sense of reverence and humility, an openness to awe and wonder, the ability to think in systems, a commitment to creating and preserving legacy—these must be promoted as cultural norms. They can be found in the wisdom of indigenous peoples worldwide, in philosophy, art, poetry, and popular culture, from ancient Greece to the New England transcendentalists (McLuhan, 1994). In these troubled times, when planetary health hangs in the balance, when, as Bill McKibben memorably wrote (McKibben, 1989), the 'end of nature' seems possible, may this fine book provide the evidence, the wisdom, and the inspiration to help renew the human relationship with the natural world, enabling health and well-being now and for generations to come.

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Contents

† It is with regret we report the death of Anthony J. McMichael during the preparation of this textbook.
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Abbreviations

AAA	animal-assisted activities
AAE	animal-assisted education
AAI	animal-assisted interventions
AAT	animal-assisted therapy
ACT	artemisinin-based combination therapy
ADHD	attention deficit and hyperactivity disorder
AQBAT	Air Quality Benefits Assessment Tool
AR	allergic rhinitis
ART	Attention Restoration Theory
ASD	acute stress disorder
BDNF	brain-derived neurotrophic factor
BFV	Barmah Forest Virus
BMI	body mass index
CBNRM	community-based natural resources management
CFM	collaborative forest management
CNS	central nervous system
CRED	Center for Research on the Epidemiology of Disasters
CRH	corticotropine-releasing hormone
CRP	C-reactive protein
DAF	directed attention fatigue
DALY	disability-adjusted life year
DHF	dengue haemorrhagic fever
DOHaD	Developmental Origins of Health and Disease
EA	environmental assessment
EE	environmental enrichment
EF	ecological footprinting
EIA	environmental impact assessment
ELC	European Landscape Convention
ELF	early life stress
EPA	Environmental Protection Agency
ES	ecosystem services
ESS	Emotional State Scale
ESSP	Earth Systems Science Partnership
FAO	Food and Agriculture Organization
FoF	fear of falling
FSS	functional somatic syndrome
FSSD	Framework for Strategic Sustainable Development
GAD	generalized anxiety disorder
GBD	global burden of disease
GDM	gestational diabetes mellitus
GI	green infrastructure
HCWH	Health Care Without Harm
HD	Huntington's disease
HEAL	Health and Environment Alliance
HEAT	health economic assessment tool
HFA	Health For All
HGT	horizontal gene transfer
HIA	health impact assessment
HL	Hodgkin's lymphoma
HRV	heart rate variability
HSE	Health and Safety Executive
IAHAIO	International Association of Human–Animal Interaction Organizations
IARC	International Agency for Research on Cancer
ICIMOD	International Centre for Integrated Mountain Development
IPA	International Play Association
ISAAT	International Society for Animal Assisted Therapy
ITDP	Institute for Transportation and Development Policy
LEED	Leadership in Energy and Environmental Design
MUS	medically unexplained symptoms
MVPA	moderate-to-vigorous physical activity
NAI	nature-assisted interventions
NBI	nature-based interventions
NCD	non-communicable disease
NFC	near field communication
NGF	nerve growth factor
NGO	non-governmental organization
NK	natural killer
NRPA	National Recreation and Park Association
OFFE	Olfactory Function Field Exam
OPEC	Outdoor Play Environment Categories
PAHO	Pan American Health Organization
PANIC	Physical Activity and Nutrition in Children
PAR	predictive adaptive responses
PFA	Perceptual Fluency Account
PHC	Primary Health Care
PSR	Physicians for Social Responsibility
PTSD	post-traumatic stress disorder
QALY	quality-adjusted life year
QoL	quality of life
RMSF	Rocky Mountain spotted fever
ROS	reactive oxidative species
RRT	Reward Restoration Theory
RRV	Ross River Virus
RSPB	Royal Society for Protection of Birds

SAVE	sociocultural appraisals, values, and emotions
SCCYP	Scotland's Commissioner for Children and Young People
SCI	spinal cord injury
SCL	skin conductance level
SES	socioeconomic status
SET	Supportive Environment Theory
SETAC	Society of Environmental Toxicology and Chemistry
SIDS	Small Island Developing States
SIRCC	Scottish Institute for Residential Child Care
SMR	standardized mortality ratios
SNS	sympathetic nervous system
SPUGS	small public urban green spaces
SRT	Stress Reduction Theory
TBE	tick-borne encephalitis
TBI	traumatic brain injury
TEEB	The Economics of Ecosystems and Biodiversity
TWS	tsunami warning system
UHI	urban heat island
UNEP	United Nations Environment Programme
USDA	United States Department of Agriculture
WHO	World Health Organization

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SECTION 1

Why is nature a health factor?

CHAPTER 1.1

Setting the scene and how to read the book

Matilda van den Bosch and William Bird

Healthy nature, healthy people

For virtually all our development humans have been totally dependent on nature. With increasing industrialization and urbanization human beings have become partly disconnected from natural environments, both physically and mentally. The disconnection is now being viewed as a threat to health and this book explains how this disconnection displays through several pathways and eventually defined health outcomes. Equally, contact with natural environments may serve as a remedy for many contemporary health issues.

Public health does not depend only on the health of other human beings, but also on the health of our surrounding natural ecosystems. This notion is, for example, included in the concept of ecological public health (Rayner, 2012). Ecological public health embraces complex and dynamic biological, material, social, and cultural dimensions of the human, living, and physical world. This opens up questions of non-linearity, evolutionary mismatch and biological feedback, and other aspects of nature and human behaviour. To put it simple—it is obvious that we cannot expect to live healthy lives, unless also the ecosystems, on which we depend, are healthy and functional (Lang and Rayner, 2012). To fully acknowledge this, and to create knowledge aimed for action, the various interactions between humans and natural environments must be explored and illuminated. This means all kinds of interactions with all kinds of humans and with all kinds of nature.

This book considers various interactions between humans and nature and the influence on health. This implies all potential health benefits, all trade-offs, all medical and healthcare options, all policies, and all directly and indirectly related topics of the relationship between humans and nature. By presenting the multiple facets of this relationship, a fascinating and challenging complexity will be revealed. This complexity mirrors the kind of health issues we are facing today.

A changing disease scenario

A new disease scenario is challenging global health, due to changes in lifestyles as well as social and environmental conditions. Non-communicable diseases (NCDs) are currently dominating the global disease burden. This means that diabetes, cancer, cardiovascular and chronic obstructive pulmonary diseases, obesity, and mental disorders have surpassed infectious diseases as the main health issues globally (WHO, 2014). However, this obviously varies between populations and regions of the world. In sub-Saharan Africa, infectious diseases, like HIV/AIDS and malaria, are still the major threats to health, though also here the NCDs are rapidly increasing in prevalence (Naghavi and Forouzanfar, 2013). This is, at least partly, a consequence of urbanization, energy consumption, and adoption of Western world lifestyles (Potts, 2012).

Environmental change, sustainability, and public health

Biodiversity loss and climate change have a major impact on human health (Watts *et al*., 2015) and this demonstrates the complex interdependence between the environment and health and well-being. In order to halt further environmental degradation and climate change we need to change ways of living and find mutual and sustainable solutions for health of people and nature. As part of a new sustainable development agenda from 2015, countries adopted a set of goals to end poverty, protect the planet, and ensure prosperity for all over the coming 15 years. Of the 17 Sustainable Development Goals (SDGs) only one explicitly mentions health (goal no. 3: 'Good health and well-being'), but all goals trespass the traditional disciplinary silos and make it clear that every goal is dependent on the fulfilment of the others (Waage *et al*., 2015). This means that environmental threats to human health are considered as well as environmental solutions which can reinforce human health and well-being. For example, a subgoal under goal no. 3 declares that by 2030 access to green spaces shall be secured particularly for women, children, and other vulnerable population groups. This is a clear indication that exposure to nature is starting to be recognized as vital for human health.

A guide to the book

Section 1: Why is nature a health factor?

This book seeks to explore how natural environments and ecosystems contribute to human health and well-being. This exploration will start by laying out a foundation of fundamental concepts like system science, the life course approach, the Developmental Origins of Health and Disease (DOHaD), stress, and evolution. While the contents of this first section may at a first glance appear peripheral to the book's topic, outlining these concepts contributes to a more profound understanding of what nature means to human health and how we can approach it in thought and action. It may be

possible to exclude this section and go directly to the theories and evidence around nature's impact on health, but for putting theories, evidence, and practice into a conceptual, planetary, philosophical, and outreaching context this foundation will be highly supportive.

In Chapter 1.2, 'A life course approach to public health: why early life matters', Felicia Low and her colleagues describe the full range of early life exposures and the implications for future health. They also explain recent research which expands beyond heritability of disease risk, because genetic variation is a poor explanation for the increasingly common NCDs. In order to promote health we need to understand how and why disease prevalence varies between populations and how the impact of environment contributes to shaping health and disease patterns. As it becomes clear that negative environmental exposures during prenatal and early life determine a person's health development throughout the entire life, it is plausible that early exposure to natural environments, with opportunities for physical activity and recreation, can contribute to healthier and longer lives. Keeping in mind that natural environments may represent ideal settings for healthy behaviours, the DOHaD paradigm is a way to incorporate nature into the life course approach to public health research and actions. It also clarifies the urgent need to consider health and interventions for improving public health from a much wider and more inclusive perspective than what is currently the prevailing situation within many medical curricula.

By introducing systems science in Chapter 1.3, 'Systems thinking for global health and strategic sustainable development', we want to further emphasize how inter- or transdisciplinary thinking is necessary for achieving health for all—both people and planet. By outlining a framework for strategic sustainable development (FSSD), Karl-Henrik Robèrt and his colleagues show how resilient environments and global health are intimately intertwined. In doing so, they provide tools for implementing systems science for efficient solutions in complex systems. As we have already concluded that current health and environmental issues are of increasingly complex characters, such tools are of fundamental value for public health understanding and action, not the least for increasing the understanding of nature's value for health development.

A basic understanding of the stress concept is useful in any work on current diseases and relation to the environment. Particularly when considering how and why nature may have a positive influence on health, stress is a central feature. In Chapter 1.4, 'The physiology of stress and stress recovery' Peter Währborg and colleagues share their experience from lifetime research and work around stress physiology and disease development.

Stress has been defined as a state where our bodily equilibrium is threatened (McEwen, 1998). While this is an evolutionary developed physiological reaction, as we need to respond adequately to acute risks to our survival, the same reactions tend to be harmful if an acute stress reaction is not followed by recovery and return to equilibrium. The further we alienate ourselves from our species' evolutionary origin the risk for such sustained stress states seem to increase.

Many chronic diseases can, at least partly, be attributed to dysfunctional or prolonged stress reactions (McEwen, 2008). While we are developed for a life connected to nature, we are today mostly spending our days in urban indoor settings experiencing stress from factors like economic uncertainties, management of conflicts, or hostile urban realms without opportunities for recovery. None of these situations are likely to be alleviated by physiological stress reactions, such as excretion of stress hormones, increased heart rate and blood pressure, and redirection of blood flow from brain to muscles. This is one of the basic premises for why nature may play a fundamental role for our health, as it can contribute to recovery and return to a balanced physiological state. While increasing the understanding of this fundament, this text can also work as a reference chapter when the stress concept is mentioned throughout the book.

Building on Chapter 1.4, Chapter 1.5 'Unifying mechanisms: nature deficiency, chronic stress, and inflammation' by William Bird and colleagues develops the theories around the fundamental relevance of chronic stress and chronic inflammation for health and disease. This text brings us further into the role of cell metabolism, mitochondria, and genetic material for understanding linkages between environment, stress, and inflammation. The authors present recent research demonstrating the intricate links between our inner biochemical environments and the outer world and how these links interact to determine various states of health.

Section 2: How nature can affect health—theories and mechanisms

Next section presents the development of the scientific field around nature and health relations; from early theories and hypotheses in, for example, environmental psychology to later research exploring biological mechanisms behind human reactions to nature exposure.

In Chapter 2.1, 'Environmental psychology', Agnes van den Berg and Henk Staats give a broad overview of the topic's rise and progress within the environmental psychology discipline. In this chapter, the historic development of human-nature research is revealed, including theories around aesthetics and preferences. Many of these values tend to be subjectively perceived and are thus important to understand for drawing conclusions on what particular environments may be beneficial across different populations and cultures. While keeping this relative perspective in mind, several of the theories also refer to the concept of biophilia, drawing on human evolution in natural landscapes. Biophilia proposes that there is an inherent human bond to natural environments, recognized for survival, restoration, and protection (Wilson, 1984). The authors describe how the field has developed over time and how empirical findings have spurred new theory advancement, essential for coming research.

Mardie Townsend and her colleagues continue the exploration of psychological concepts of nature and well-being in Chapter 2.2, 'Therapeutic landscapes, restorative environments, place attachment, and well-being'. The historical outlook on these notions dates back to several centuries BC. While therapeutic landscapes and restorative environments may initially appear as abstract models, this chapter defines and explains distinctions between the two and clarifies the relation to theories outlined in the previous chapter. As the authors further illuminate and concretize place attachment, sense of place, and ecopsychology the link to well-being and public health is revealed. Case studies are used to illustrate the concepts. The chapter also describes current challenges to the psychological relation between human and nature, a relation that may be more important to recognize now than ever before.

In Chapter 2.3, 'Microbes, the immune system, and the health benefits of exposure to the natural environment', Graham Rook presents theories on the importance of microbial biodiversity for healthy immune system development. Those theories are supported by findings of differences in immune function depending on childhood exposure to natural and biodiverse environments

(Kondrashova *et al*., 2013). These ideas thus represent another biological mechanism or pathway between nature and health. It also provides a possible explanation for the rise of autoimmune diseases in later years, correlating in time with increasing urbanization and disconnection from nature.

Following this, Heidi Janssen and her colleagues explain how the expanding research on enriched environments (Chapter 2.4, 'Environmental enrichment: neurophysiological responses and consequences for health') may relate to nature and health mechanisms. While much of the research in this field is based on rat studies and an enriched environment may not fully correspond to a particular natural setting, the intriguing mechanisms occur likely to parallel human reactions to nature. Therefore, it is important to follow this research line and the chapter demonstrates how certain positive clues, providing multisensory stimulation in the environment, affect neuroanatomical and physiological functions, which improve behavioural and health outcomes. For example, neurogenesis and neuronal survival are enhanced by a richness in environmental stimuli (Sale *et al*., 2009). Certain features of enriched environments, such as complexity and novelty, are abundant in nature and may thus represent an inherently enriched environment.

In Chapter 2.5, 'Biological mechanisms and physiological responses to sensory impact from nature', Caroline Hägerhäll and colleagues take us from psychology to physiology. Drawing on both old and novel theories and hypotheses they describe empirical findings which demonstrate how humans are biologically affected by nature. Adding such findings to epidemiological results on causality provides a firm evidence base for health effects of nature exposure. The authors draw partly on their own research on visual, auditory, and olfactory sensory input from nature, demonstrating specific physiological responses as measured by neuroimaging and other physiological monitoring methods.

Much of our health and well-being is determined by our behaviour. In Chapter 2.6, 'The role of nature and environment in behavioural medicine' Leonie Venhoeven and colleagues describe how input from nature may influence our behaviour and how this affects our health both directly and indirectly. While behavioural medicine has traditionally studied behaviours with direct impact on health, such as physical activity and social interactions, this chapter outlines theories and research around environmentally related behaviour. For example, pro-environmental behaviour is described and how this may be triggered by contact with nature, and the influence this may have on health. This highlights an intriguing chain reaction where pro-environmental behaviour can have an effect on individual well-being, but may also indirectly affect public health through prevention of further environmental degradation and climate change. Once again, the dynamics and interrelatedness in the area of nature and public health are exposed.

Section 3: Public health impact of nature contact—pathways to health promotion and disease prevention

In Section 3, major pathways through which natural environments are in general believed to affect public health, are described. This section provides an abundance of arguments for why investments in green spaces across different populations are necessary for maintaining and improving public health. Such arguments are important in any health policy making and should increase collaboration across environmental and health sectors and disciplines. By providing empirical evidence on the importance of urban greenery for public health, nature gains a step in the ever increasing competition around urban land.

One mediating factor between nature and health outcomes is physical activity. In Chapter 3.1, 'Promoting physical activity—reducing obesity and non-communicable diseases', Billie Giles-Corti and her colleagues first outline the multiple health risks that are associated with physical inactivity and how this issue has increased over time. By doing so, it becomes obvious that even minor interventions that can promote physical activity are of substantial value in a larger population perspective. It has been recognized that the availability, quality, and design of public green spaces may play an important role for community levels of physical activity (Sallis *et al*., 2016; Almanza *et al*., 2012). The chapter presents findings on the value of nature and green spaces for children, adolescents, adults, and elderly in promoting physical activity and thereby preventing obesity and other NCDs. Whether there is a connection between access to green spaces and physical activity or not has recently come to debate. Potential explanations and ideas around some inconsistency in results are presented and discussed by the authors.

Another potential factor contributing to the health and nature relation is stress. This is discussed by Matilda van den Bosch and her colleagues in Chapter 3.2, 'Preventing stress and promoting mental health'. Similar to physical inactivity, stress is a major risk factor in today's disease scenario and often attributed to the increasing prevalence of mental disorders (McEwen, 2012). Early theories from environmental psychology and related disciplines already suggested that restoration and stress recovery may have an important explanatory role to play. The evolutionary fundaments for this are explained in for example Chapter 2.1 and physiological mechanisms are outlined in the chapter on stress (1.4). This chapter explains how nature may affect stress and how this may reduce the prevalence of mental disorders, currently a major public health issue across the world (Vos *et al*., 2015).

Finally, nature's potential for building social capital is elaborated on in Chapter 3.3, 'Promoting social cohesion and social capital—increasing well-being'. In this chapter Birgit Elands and her colleagues present their own and others' work, demonstrating how green areas seem to facilitate social interactions and thereby creating individual and community well-being. Social isolation is today considered a risk factor of the same magnitude as smoking with similar odds for morbidity and mortality (Holt-Lunstad *et al*., 2015). Thus, if green spaces encourage social networking there is a vast potential for health gains. Open green spaces are often visited by various population groups, thereby offering opportunities for interactions across cultural and social borders. The authors also discuss how certain types of green spaces, for example community or allotment gardens, are particularly suited for social interactions and how appropriate planning of green spaces is necessary for encouraging social interactions.

Section 4: Public health impact of nature contact—intervention and rehabilitation

The contents of this book are much focused on classical public health approaches, such as health promotion and disease prevention. The following section describes how nature has been incorporated in healthcare for treatment of various conditions. In this context, animal-assisted interventions and other correlating complex interventions are included.

In Chapter 4.1, 'Using nature as a treatment option', Anna María Pálsdóttir and colleagues provide definitions and examples of the

broad spanning field of interventions using nature in various forms to treat and cure illnesses. Gardens have traditionally been used in mental healthcare, but many other forms of nature interactions, such as farming and wilderness experiences, exist as therapeutic means. The chapter provides an overview of how nature can be both an arena for interventions and have therapeutic effects in itself. Concepts such as horticultural therapy, green care, and wilderness therapy are described and related to respective diagnoses for which efficiency has been demonstrated.

The human–animal bond is an inherent and profound feature of humankind. Therefore, it is not surprising that interactions with animals may be restorative and help recovering from various diseases. In Chapter 4.2, 'The human–animal bond and animal-assisted intervention', Aubrey H. Fine and Shawna J. Weaver demonstrate how animals and pets can be used in healthcare. They also outline various theories and describe how research has tried to uncover the biological fundaments behind the health effects of, for example, petting an animal. Some of this has been related to release of the hormone oxytocin, which is associated with feelings of happiness and trust (Rodrigues *et al.*, 2009).

Finally, Cecilia Stenfors and her colleagues give an outlook on other non-pharmaceutical or surgical interventions that may be used in healthcare. In the chapter 'Similarities, disparities, and synergies with other complex interventions—stress as a common pathway' (4.3), commonalities between nature therapies and other complex interventions, based on for example meditation or cultural utterances, are revealed. Many parallels, both psychological and physiological, seem to lead back to stress and stress recovery processes. By recognizing both commonalities and distinctions, individually tailored therapies and synergistic effects may be achieved.

Section 5: Public health impact of varied landscapes and environments

In Section 5, various types of nature and respective effects on health and well-being are described. It may appear unnatural to try and divide something as complex and dynamic as nature into separate entities. Obviously, this is a construct far from the real world—urban woodlands dynamically transfer into wilderness, lakes, and seashores are embedded in forests or parks—nature as a whole involves all parts to various extents and in various shapes. The chapters in this section evidently do not ignore this fact, but by a small act of nature dissection some particular features of specific environments can be revealed and our understanding of the whole may thus increase.

First, Simon Bell and Qing Li describe the wonders of 'The great outdoors: Forests, wilderness, and public health' (5.1). Forests may, by some, be considered the ultimate representation of nature—the wild, the untouched, and containing many of the basics for our survival. However, today only very few, if any, forests are untouched by human hand and the health benefits may be of a different, less basic kind, at least in the Western part of the world. In spite of this, forests still seem to be places where people go to search for peace and to find an escape from the hectic daily grind and stress of city living. This chapter draws on theories and research to highlight some particular health benefits that may be achieved by visiting forests; for example, effects on the neuroendocrine immune system and thereby reduced stress by so-called 'forest bathing' (Shinrin-yoku).

Another distinct type of nature is water in its various shapes and forms. Mathew White and his colleagues describe how access to landscapes including water affect health in Chapter 5.2, 'Blue landscapes and public health'. Water continues to have a special value for humankind in terms of survival, culture, and religion. Many symbolic rituals, such as baptism, are centred on elements of water. This may indicate an innate preference for water with an instant well-being effect. Research on blue landscapes has not yet developed as much as for green landscapes (although bearing in mind that green and blue are not always to be considered as separate from each other), but recent studies suggest that health effects of visiting, for example, a seashore, may be even stronger than visiting a merely green landscape. Many effects seem to relate to stress recovery.

In the chapter 'Technological nature and human well-being' (5.3) Peter Kahn shares his view and research on so-called technological nature, to be found in the interface between human dependence on healthy ecosystems and the current exponential growth of technological solutions. Technological nature can take many forms, from nature films on television to geocaching in the woods. Kahn discusses what happens to human beings and our health if we replace real nature with simulated natural settings. It becomes clear that many of the sensory experiences and dynamics gained by interacting with nature in the mountains, the forests, or the water landscapes are falling short in technological nature interactions. And while we may manage to adapt to technological forms of nature, it may not be a beneficial adaptation—neither for us nor the environment.

Section 6: Varied populations and interactions with nature

In the complex landscape of nature and human health associations it is often found that different people react differently to nature. This is fairly evident considering our various backgrounds and various needs across the lifespan. Although individual differences evidently exist, it seems possible to draw some general conclusions on reactions to nature depending on population group. In Section 6, different responses to interactions with nature depending on age, and socioeconomic or cultural belonging are described together with the implications this has for how nature can best be integrated in planning, care, and living environments.

Nancy Wells and her colleagues start this section with Chapter 6.1, 'Children and nature'. Children's relation to nature is of specific value—not only for the developing individual itself, but also for the environment. If no connection to nature is established in early years it will be hard for the growing individual to develop a sense for the environment, which may lead to further environmental destruction and biodiversity loss. For the child itself, outdoor nature exposure contributes to an almost endless line of various benefits—for cognitive, social, and motoric development, for play and physical activity, for concentration capacity and academic performance, and for preventing myopia, vitamin D deficiency, stress, and obesity.

Older people may suffer from anxiety disorders, often aggravated by multimedication. In Chapter 6.2, 'Nature-based treatments as an adjunctive therapy for anxiety among elders', Mark B. Detweiler and his colleagues describe how we can prevent anxiety and reduce pharmaceutical use among older people by increasing access and exposure to nature in daily life. First a general outlook on anxiety among elders and neurobiological mechanisms is provided and this is then linked to how and why nature interactions may be of specific importance for this group.

Difference in health depending on socioeconomic status and general vulnerability is a major public health issue, which requires actions across several disciplines and authorities (Marmot *et al.*, 2012). In Chapter 6.3, 'Vulnerable populations, health inequalities, and nature', Richard Mitchell and his colleagues explain why we need to incorporate measures of particular vulnerability in any public health action and how this may imply an environmental aspect, in particular access to nature. It is generally found that people of less wealth and education respond more positively in terms of improved health outcomes to nature exposure than do already healthy and wealthy populations. This means that nature may counteract some of the health differences determined by socioeconomic group belonging. The chapter presents evidence on the buffering effect of nature on health inequalities and outlines suggestions for environmental justice for public health.

Finally, Caroline Hägerhäll presents a cultural exposé in Chapter 6.4, 'Responses to nature from populations of varied cultural background'. This chapter discusses the topic of whether there is any common preference for nature independent of cultural and ethnical belonging, or whether such preferences are socially determined. The research on this subject is scarce and the chapter is a first scientific attempt to bring together current existing knowledge on definitions and conceptualizations of and preferences for natural environments in a cross-cultural perspective.

Section 7: Threats, environmental change, and unintended consequences of nature—protecting health and reducing environmental hazards

So-called disservices from and harmful effects of nature and ecosystems have recently become a topic in focus. In science it is necessary to be critical and to strive to falsify hypotheses in order to prevent harmful consequences and optimize prioritizations based on research results. From this perspective, it may be possible to understand why a focus on the negative aspects of nature has become relevant. However, nature and healthy ecosystems are the fundaments for our survival and health. Apart from nutrition and other basic provisional needs, this is obvious from the level of microbiota and neurocognitive development to spiritual and emotional well-being (van den Bosch and Nieuwenhuijsen, 2017). Anthropogenic impact on nature, has come to disturb many ecosystem functions, leading to, for example, prolonged seasons of more allergenic pollen grains and harmful effects of various natural disasters, such as hurricanes and vector-borne diseases. Section 7 takes a closer look at these events, showing that while interactions with nature can sometimes be unsafe, the damaging effects are mainly due to human interference with nature in the first place. What we need to do is therefore to prevent further harmful impact on nature by humans and learn to interact with nature in a healthy way. This is different than saying that nature is dangerous and brings disservices to human beings. The section also discusses these issues from the perspective of what we have to lose in terms of health and well-being by further biodiversity loss and climate change, as well as from the perspective of a sometimes unbalanced risk perception.

In Chapter 7.1, 'Allergenic pollen emissions from vegetation—threats and prevention', Åslög Dahl first outlines the biology of pollen and allergenic plant species, pollen counts, and impacts of anthropogenic disturbance by, for example, climate change. Matilda van den Bosch then describes the basics of allergenic diseases and their impact on health. Finally, Thomas Ogren shares insights in how to plan for less allergenic environments by more careful selection of, for example, street trees and by applying more functional botanical sexism.

Another threat that is possible to encounter in nature, and also in urban green and blue spaces, are vector-borne diseases. In Chapter 7.2, 'Vector-borne diseases and poisonous plants', David Wong outlines those threats and includes advice on how we can act sensibly and thereby reduce the risks and prevent harms from such vectors and plants. The chapter's main focus is from an outdoor recreational perspective, as people who engage in such activities are evidently at increased risk. However, by adequate prevention measures and education, the potential risks from these conditions are by far outweighed by the vast amount of health benefits to be achieved from outdoor recreation.

Through unsustainable practices and climate change the incidence of natural disasters has increased globally. In Chapter 7.3, 'The health impact of natural disasters', Eric K. Noji and Anas A. Khan discuss how natural hazards such as earthquakes, hurricanes, floods, droughts, and volcanic eruptions are considered as disasters, while these events are in fact only natural agents that transform a vulnerable human condition into a disaster. Ignorance of, for example, appropriate building codes in combination with poverty and social inequalities, improper land use, rapid population growth in poor regions, and global climate change and biodiversity loss can create a hazardous environment with severe negative impact on health in particularly low- and middle-income countries. This chapter provides the most up-to-date knowledge on natural disasters, evaluation, impacts, risk reduction, and prevention.

David J. Ball and Laurence N. Ball-King provide an overview of how we have, with time, become disconnected from nature and how this has led to a sometimes exaggerated fear of nature in Chapter 7.4, 'Risk and the perception of risk in interactions with nature'. The chapter includes perspectives on risk perception and what may cause unbalance in how we perceive threats versus opportunities. The authors also discuss current impediments for realizing the many benefits of nature and what we can do to act against these streams.

The final chapter of this section is written by the late Anthony McMichael, who completed it in his last days. The devotion of such precious time to authoring the chapter 'Population health deficits due to biodiversity loss, climate change, and other environmental degradation' (7.5) is a symbol of the urgency of the topic. While this book has focused on the many health benefits we can gain from nature, this chapter takes another view by showing all the losses we are indisputably to face by further disconnection from nature and continued destruction of Earth and its ecosystems. By a holistic approach, the text displays how traditional scientific and medical assumptions and methods are no longer appropriate if we aim to avert the multiple catastrophic effects on environment and human health, following climate change and environmental degradation.

Section 8: The nature of the city

We live in a rapidly urbanizing world. This major demographic shift has had and will continue to have wide implications on public health. This perfectly well demonstrates how the environment impacts health in a multitude of ways. Section 8 takes a closer look at the urban environment, how nature is or is not integrated in cities, and the effects on health for various populations.

In Chapter 8.1, 'The shift from natural living environments to urban: population-based and neurobiological implications for public health' Florian Lederbogen and colleagues discuss how the shift from rural to urban environments has equally created a shift in the general disease scenario. This is exemplified by population studies on diabetes prevalence in China and India, and by neuroscientific findings on differences in brain anatomy and function between rural and urban populations.

Timothy Beatley and Cecil Konijnendijk van den Bosch walk us through the city in Chapter 8.2, 'Urban landscapes and public health'. They discuss the challenges and opportunities in creating healthy and resilient urban environments and how various disciplines and sectors must collaborate to reach this goal. This comes together in the socioecological approach, where human behaviour is understood as a factor of interactions with physical and sociocultural surroundings. The authors argue that by strategically implementing a socioecological approach we can come closer to creating urban landscapes that promote public health and well-being. Within this context urban green and blue spaces are considered central, as expressed through concepts like green urbanism and biophilic cities.

This reasoning continues in Chapter 8.3, 'Nature in buildings and health design' by the late Stephen R. Kellert. The chapter draws on the concept of biophilia, the supposed innate connection between humans and nature, based on our evolutionary origin (Wilson, 1984). This means that by incorporating natural features in buildings and design we may foster health and well-being in a largely urbanized world. This may be particularly important in healthcare facilities. Apart from providing an environment which is perceived as pleasant and corresponding to our biological functions, biophilic design may encourage positive interactions with the natural world contributing to the overall coherence of the human ecosystem.

Another concept which is often used in the discussion of creating resilient and healthy cities is green infrastructure (GI). Cecil Konijnendijk van den Bosch and Raffaele Lafortezza go into depth with this topic in Chapter 8.4, 'Green infrastructure—its approach and public health benefits'. GI is commonly understood as an interconnected network of natural areas with various benefits to the society. Although the concept is rooted in planning and environmental sectors, it has a large bearing on public health. The principle of GI is to gain benefits for both people and the environment through pro-active urban planning and management where natural resources are strategically included.

Closely related to the concept of green infrastructure is ecosystem services. Elisabet Lindgren and her colleagues reveal the various benefits and services provided by urban ecosystems in Chapter 8.5, 'Ecosystem services and health benefits—an urban perspective'. Human beings are all part of ecosystems and this fact may be expressed through the terms of ecosystem services, as this clarifies all direct and indirect health benefits we gain from ecosystems. In this chapter the particular challenges of global urbanization to functional ecosystem services are outlined and discussed. This is diversified across different types of urban environments—affluent mature cities, affluent growing cities, and low-income growing cities.

Taking us to the border between environmental health and policy making, Evelyne de Leeuw and Premila Webster give an overview of the WHO Healthy Cities Project in Chapter 8.6, 'The healthy settings approach: Healthy cities and environmental health indicators'. A basic principle of the project is to move health high on social and political agendas in urban policies, sometimes expressed as Health in All Policies. From an urban green planning perspective, this means that environmental workers and policy makers should consider the health aspects of any planning or management strategy around built versus green environments. Equally it would imply that public health workers and decision makers collaborate closely with urban planners and create shared visions and goals for healthy, green, and resilient cities. The Healthy Cities concept draws attention to the close connection between people's health and their surrounding environment and among many other goals, it states that a healthy city should strive to provide ecosystems that are stable and sustainable.

Section 9: Natural public health across the world

Much of the research on associations between public health and nature has been conducted in Western parts of the world with comparatively high resources for both science and development. While low- and middle-income countries are rapidly developing Western-based lifestyles, they are still facing unique issues and challenges in regard to associations between health and nature. It is of particular value to increase the focus on other parts of the world, partly in order to avoid similar mistakes that have been made in the Western world. Such mistakes include, for example, densification of cities at the cost of biodiversity and natural spaces, without considering long-term effects on public health.

In Section 9 we make a first attempt to bring together existing knowledge on nature and public health relations in other parts of the world—Africa, Latin America, and Small Island Developing States.

Emmanuel K. Boon and Albert Ahenkan take us to Africa in Chapter 9.1, 'Africa and environmental health trends'. In Africa, natural resources are central to people's livelihoods and health, especially in the relatively large rural populations. To a higher extent than in, for example, Europe, the provisioning ecosystem services are of strong importance for population health. However, forests and other natural areas also play an important role for cultural services, such as tourism and recreation, spiritual healing, leisure, and religious practices. General natural resource management is becoming an increasing topic of concern in Africa, in the tracks of deforestation, population growth, and urbanization. While threats and opportunities from nature vary across the continent, there are also commonalities, such as increasing beneficiary and community participation, developing and sharing environmental friendly technologies, and formulating appropriate environmental policies for improved public health. Another specific theme of the African region is traditional medicine (also called botanical medicine), which is defined as the use of whole plants or part of plants to prevent or treat illness.

Following this we continue to another continent in Chapter 9.2, 'Latin America and the environmental health movement', authored by Ana Faggi and her colleagues. In Latin America green spaces have by tradition been considered places for everyone to meet and socialize and are associated with healthy environments, as well as culture and multiculturalism. During the influence of French and English models in the late nineteenth century, urban green spaces and large parks were established to prevent health issues associated with city living. Today, Latin America has the most urbanized population in the world—public green spaces are under high pressure and urban development is far from sustainable. The planning of urban green spaces is not coherent and the green infrastructure

urgently requires investments for achieving health benefits. Often, deprived neighbourhoods have very poor quality or a complete lack of green spaces. While the health–nature relationship is poorly recognized in policy campaigns and in the grey literature, some recent activities seem to acknowledge the value of green spaces for mental health and other health benefits. This chapter provides a few examples of such activities, including the showcase of Curitiba, Brazil, with 64.5 m^2 of green area per citizen.

Finally, Evelyne de Leeuw and her colleagues take us to Small Island Developing States (SIDS) in Chapter 9.3, 'Healthy islands'. In nation-state islands, nature and ecosystem health meet population health in a particular way. The WHO has initiated a programme which connects SIDS' (in the Pacific Ocean) environmental development with public health, the Healthy Islands programme. The programme has several interconnected priority areas, including ecological sustainability and social and emotional well-being. Apart from NCDs, the most serious threat to health on these islands is climate change.

Section 10: Bringing nature into public health actions

This book seeks to contribute to a paradigm shift in how we look at health in relation to the natural environment. The aim is to provide knowledge in order to create a deeper understanding of what health means, how we can change our approach to current major health issues, and improve public health today and in the future. This knowledge and understanding must be created through a transdisciplinary strategy where scientists from various disciplines collaborate with stakeholders and practitioners, through all phases from the initial research problem identification to the solution. This final section aims to bring us into action by providing a few examples of the roles that various actors can play in distributing and applying the knowledge around nature and public health.

In Chapter 10.1, 'The role of the health professional', the physicians Robert Zarr and William Bird share their experiences from clinical practice where natural spaces have been incorporated in the treatment and care of patients with various chronic conditions. They also provide examples of well-established health promoting programmes, which draw on nature exposure in order to maintain and improve health in a population.

Cinnamon P. Carlarne and Jeffrey M. Bielicki share insights around legal and regulatory strategies related to the environment in Chapter 10.2, 'The role of environmental law'. Many environmental law makers recognize that natural spaces are important for human well-being for several reasons, including recreation and mental health. This is mirrored in for example National Park System and National Forest System in the United States and many other natural resource laws. Similarly, land use laws affect many factors with important ramification for public health, for instance transportation, levels of noise, and ease of access to public green spaces. Environmental lawmakers must continue and increase interactions with other sectors for understanding and improving the interplay between law, nature, and human well-being.

Related to environmental law and policies are impact assessments. In Chapter 10.3, 'Environmental assessment and health impact assessment', Salim Vohra and colleagues provide an overview of how the practice of environmental impact assessments has grown with the recognition of human health impact. While most health impact assessments of planned environmental interferences concern negative health outcomes, recently also health impact assessments of, for example, urban park establishments, have locally been applied while looking at health gains. This can have an important bearing for quantifying the health effects of green spaces and thereby provide a common ground for practical implementation in urban planning.

David Nowak presents a practical ecosystem evaluation tool in Chapter 10.4, 'Quantifying and valuing the role of trees and forests on environmental quality and human health'. While recognizing that not everything can be calculated in money, monetary tools may facilitate practical implementation of environmental strategies for public health. By accounting for the ecosystem services in monetary terms, better planning, design, and economic decisions may be made towards utilizing nature as a means to improve human health.

Finally, Chapter 10.5, 'The role of civil society and organizations', authored by Matilda van den Bosch and colleagues presents a selection of non-governmental and civil society organizations, which through various channels work for improved practice regarding human and nature relationships. The organizations outlined in the chapter are all committed to increasing the awareness of human health and nature relations, from various perspectives. They are non-profit organizations, with independent status, and contribute to engaging civil society and people in putting the important matters of nature and health higher on the political agenda. This may be one tool for indirectly bridging the science–policy gap and to increase the incorporation of positive environmental impact on health in healthcare, and to more strongly prevent the major losses expected by the degradation of natural resources.

Conclusion

The final paragraph of Charles Darwin's *Origin of Species* begins with a beautiful reflection on nature and our dependence of functional interactions between all species: 'It is interesting to contemplate a tangled bank, clothed with many plants of many kinds, with birds singing on the bushes, with various insects flitting about, and with worms crawling through the damp earth, and to reflect that these elaborately constructed forms, so different from each other, and dependent upon each other in so complex a manner, have all been produced by laws acting around us.' (Darwin, 1859)

These laws define numerous rules, including growth and reproduction, and variability. By the latest century's reduced respect for nature and its laws, and by our lost connection to nature, we seem to disrupt or insult those laws. We do so at growing peril to ourselves and to nature itself.

We want this book to challenge the way we view the impact that nature has on human health and why this is so important. Connection, respect, and reverence celebrate the relation between us and nature and represent the interface between science and philosophy. Inherent in the recognition of nature as a public health asset must be a realization of how much we all have to lose by disconnecting from or degrading natural environments. If we realize this, forests, lakes, seashores, urban parks and woodlands may continue to provide settings for recovery and recreation, while simultaneously delivering basic services for our health and survival.

How shall we move forward and who is responsible for increasing the visibility of nature in the public health agenda? We all are. We, the people of the planet Earth, have a responsibility to drive decisions that account for the health of forthcoming generations

of human beings and ecosystems. We are the people that must reframe our thinking and our values to change and develop new societies, economies, and policies that embrace an understanding of the inherent beauty of nature and how much we have to lose by destroying her.

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CHAPTER 1.2

A life course approach to public health: why early life matters

Felicia M. Low, Peter D. Gluckman, and Mark A. Hanson

Developmental origins of health and disease

Research efforts to illuminate the underlying heritability of disease risk, which had traditionally relied on twin and adoption studies, received a tremendous boost in the early 2000s upon completion of the Human Genome Project. The availability of the full three billion base pair-sequence comprising the human genome was touted as a breakthrough in elucidating the determinants of human disease, and, accordingly, in devising appropriate therapeutic strategies. When applied to common complex non-communicable diseases (NCDs), however, it soon became apparent that such aspirational promises could not be fully met. Genome-wide association studies attempting to identify functional mutations associated with disease found that single nucleotide polymorphisms could be clearly linked to monogenic Mendelian diseases such as cystic fibrosis. However, genetic variation was a poor explanator at the population level for increasingly common disorders involving a non-Mendelian heritable component (Kaiser, 2012; Drong *et al.*, 2012), especially obesity and associated NCDs such as type 2 diabetes (T2D), cardiovascular and chronic lung disease, other components of the metabolic syndrome, and some mental health problems.

With the gradual realization that narratives based solely on a gene-centric viewpoint were no longer viable, greater attention was paid to the mounting interdisciplinary evidence showing that exposures in early life are important influences on an individual's vulnerability to disease risk in later life. Today, a significant corpus of research encompassing epidemiological, clinical, and experimental work, underpinned by a cogent theoretical framework, overwhelmingly supports the integral role of extrinsic factors acting in early life in modulating later life vulnerability to NCDs. This paradigm has been formalized as the Developmental Origins of Health and Disease (DOHaD) concept and is supported by an international learned society and associated scholarly journal (Gluckman and Hanson, 2006b; International Society for Developmental Origins of Health and Disease, n.d.). Cues as varied as maternal and childhood nutrition, stress, and toxins or chemicals have been implicated in an increased risk of a broad range of pathologies, including components of the metabolic syndrome, respiratory disease, atopy, osteoporosis, mood and cognitive disorders, and some types of cancer. While this phenomenon is often referred to as developmental 'programming', we note that such terminology raises connotations of genetic determinism, and that individuals may be more appropriately described as 'primed' or 'conditioned' to respond differently to later environmental exposures (Hanson and Gluckman, 2014).

The modern day epidemics of obesity and other NCDs exert a profound impact on public health in both developed and developing societies, and the magnitude of the problem is only set to grow (Capizzi *et al.*, 2015). In this chapter we provide an overview of DOHaD and discuss the concept of developmental plasticity underpinning it, effected in part by epigenetic processes that serve as a molecular bridge between an inducing cue and later phenotypes. We discuss how a life course approach, which is informed by developmental plasticity and gives particular focus to optimizing early life conditions, presents a fundamentally new and scientifically sound paradigm for reducing both an individual's and a population's risk of obesity and its co-morbidities.

Historical overview

The idea that early life factors could have a delayed, detrimental impact on later life health was mooted as early as the 1930s, when a study reported unusual trends in mortality rates in Great Britain consistent with the hypothesis that poorer conditions during childhood were linked to lower life expectancy (Kermack *et al.*, 1934). However, despite attracting some attention at the time, the clinical significance of the work was underappreciated and this line of enquiry largely languished. Several decades later, in the 1970s–1980s, a number of clinical studies correlating pre and perinatal conditions to risk of obesity, metabolic and cardiovascular disease, were reported (Plagemann, 2005). In rats, experimentally inducing foetal growth restriction or gestational diabetes in the mother induced pancreatic dysfunction and multiple metabolic changes in the pups (Aerts and Van Assche, 1979). Some epidemiological reports in the same period broached the possibility that pregnancy complications such as undernutrition (Ravelli *et al.*, 1976) and pre-eclampsia (Higgins *et al.*, 1980) had effects on offspring adiposity and blood pressure. Then, in the late 1980s–early 1990s, a team led by English epidemiologist David Barker published a series of large-scale analyses showing that low birth weight was associated with increased adult mortality from cardiovascular disease and risk of impaired glucose tolerance or T2D (Barker *et al.*, 1989b; Barker *et al.*, 1989a; Hales *et al.*, 1991; Osmond *et al.*,

1993). The concerted efforts of Barker and his colleagues to publicize the phenomenon spurred an upsurge of interest in this field of research, his key role being reflected in the eponymous naming of the 'Barker hypothesis' by the *British Medical Journal* in 1995 (Paneth and Susser, 1995).

Further work from epidemiologists, clinicians, and experimental physiologists began to reinforce the validity of the notion that there is indeed an early life component to adult disease risk. Large studies linked lower birth weight with increased risk of hypertension, stroke, and higher body mass index (BMI) (Curhan *et al.*, 1996; Rich-Edwards *et al.*, 2005), while asymptomatic children who had experienced intrauterine growth retardation were shown to be markedly insulin resistant compared to normal birth weight peers (Hofman *et al.*, 1997). Multiple animal models of rats, mice, and sheep provided supportive data by demonstrating that quantitative or qualitative manipulations of maternal diet led to dysregulations in metabolic and cardiovascular physiology (Langley and Jackson, 1994; Vickers *et al.*, 2000; Ozaki *et al.*, 2000; Goyal *et al.*, 2010). However, over time it emerged that the association between low birth weight and disease risk was only part of a broader range of developmental phenomena linking events in early life to later ill health. Birth weight itself was not on the causal pathways involved, except insofar as it was a proxy for conditions that might have affected the developing foetus *in utero*. Indeed, distinct pathways reflecting different mechanisms appeared likely, with the recognition that foetal macrosomia, such as that associated with maternal gestational diabetes, also had long-term consequences for the offspring's later health (van Assche *et al.*, 2001).

Evolution of a conceptual framework

The idea that adverse exposures during development could lead to later disease, without necessarily having immediate manifestations of ill health, was intriguing and well-supported by empirical data. However, it ran counter to prevailing medical belief, which was resistant to making associative connections between prenatal/infant and adult health. Instead, emphasis remained on the combination of genetic risk and unhealthy adult lifestyle as the major contributors to NCDs. It became evident that there was a need to conceptualize the phenomenon of DOHaD within an acceptable framework to engender its greater acceptance. Barker, together with Nicholas Hales, drew an analogy from the 'thrifty genotype' hypothesis that was proposed by James Neel (1962) as one of the first attempts at explaining the growing NCD epidemic in modern environments. Neel had posited that genes promoting metabolic 'thrift' became selected in the course of human evolution as an energy-conserving strategy to cope with famine situations, and that they had repercussions in the modern context of abundant nutrition. In their framework, Hales and Barker hypothesized that poor early life nutrition induces a nutritionally 'thrifty phenotype', resulting in low birth weight and insulin resistance, and placing the individual at greater risk of metabolic disease in an environment of nutritional plenitude (Hales and Barker, 1992, 2001).

Although valuable for bringing evolutionary and adaptive considerations to the fore in the discourse on disease risk, this model had several limitations. It considered birth weight as a causal factor operating on a single 'programming' pathway, and failed to appreciate that the relationship between development and adverse postnatal consequences operated over the full spectrum, rather than operating as a low-versus-normal birth weight dichotomy. However, available and subsequent datasets documented clear gradation in the relationship, strongly suggesting that foetal insults need not be severe for induction of increased disease risk (Hales *et al.*, 1991; Osmond *et al.*, 1993; Curhan *et al.*, 1996; Rich-Edwards *et al.*, 2005; Harder *et al.*, 2007). Birth weight came to gain undue importance as a proxy for foetal nourishment, leading to scepticism of the validity of DOHaD when data arose of a lack of association between birth weight and some disease markers (Paneth and Susser, 1995). Questions were also raised about its public health importance given the relatively low frequency of low birth weight in Western populations. Yet, importantly, human (Gale *et al.*, 2006; Drake *et al.*, 2012; Heijmans *et al.*, 2008) and animal (Nijland *et al.*, 2010) data have shown that disease susceptibility may be elevated in the absence of birth weight differences or other overt phenotypic outcomes. Furthermore, contrary to the model's assumptions of insulin resistance at birth, clinical data have shown that infants born small are in fact insulin sensitive at birth, and only display insulin resistance at about the age of three years (Mericq *et al.*, 2005). The absence of satisfactory mechanistic and theoretical frameworks by which to interpret the apparently conflicting observations thus remained a major impediment to the widespread acceptance of the DOHaD paradigm and its integration into clinical, medical, and public health domains (Gluckman and Buklijas, 2014).

Peter Gluckman, Mark Hanson, and Patrick Bateson, taking the Hales–Barker model as a starting point, provided further conceptual refinements based on the concept of *predictive adaptive responses* (PARs). PARs refer to a developing organism's capacity to assess the nature of cues to which it is currently exposed in order to predict its later life environment, and tune its phenotype accordingly, for delayed selective advantage (Bateson *et al.*, 2004; Gluckman *et al.*, 2005a, 2005b). Among the key attributes of this model was its differentiation between severe environmental influences that are developmentally disruptive (i.e. teratogenic), and more subtle cues of potentially evolutionarily adaptive value (Gluckman *et al.*, 2005b; Hanson and Gluckman, 2014). The latter invoke an organism's capacity for *developmental plasticity*, which refers to the adaptive responses to environmental cues that enable it to adjust its phenotypic development to match the current external environment. A key underlying principle is that organisms are more plastic in early development. Thus, exposure to exogenous influences in early life affects biological and behavioural development, leading to long-term consequences that become more apparent as the individual ages. The pervasiveness of this capacity throughout the animal kingdom implies that it has been evolutionarily conserved because it may be critical for maximizing survival and reproduction upon exposure to a range of physiologically and ecologically normative cues (Low *et al.*, 2012). As discussed later, there is increasing evidence that the molecular mechanisms underlying developmental plasticity include epigenetic changes that regulate gene expression from development through to maturity (Low *et al.*, 2014).

Another important attribute of the new model was that it further distinguished between responses that were potentially adaptive and induced by ecological cues such as alterations in maternal nutrition and maternal stress, and those associated with evolutionary novelty, which likely involved non-adaptive processes. The latter included cues such as maternal obesity, infant formula feeding, and gestational diabetes mellitus (GDM) (Ma *et al.*, 2013a). The model proposed that among exposures that are not outright teratogens or

representative of evolutionary novelty, those that are more severe may induce responses that have immediate phenotypic impact at the expense of longer-term trade-offs. An example is uterine infection-induced premature delivery, which promotes immediate foetal survival at the cost of greater morbidity or mortality in infancy. Cues that are less severe, such as variations in maternal diet and maternal stress, may elicit PARs that confer delayed adaptive advantage by tuning the individual's phenotype to best cope with the forecast postnatal environment (Gluckman *et al.*, 2005a; Bateson *et al.*, 2014). In this way, Darwinian fitness is enhanced even if no phenotypic consequences are outwardly observed. However, the corollary is that inaccurate transduction of cues, arising for example from placental insufficiency, erroneously signalling a low nutrient environment, or exposure to a postnatal environment different from that predicted *in utero*, then places the individual in a situation of *developmental mismatch* (Gluckman and Hanson, 2006a), which results in heightened risk of disease later in life. Despite the potentially deleterious effects of PARs, they are thought to have evolved and persisted through our evolutionary history owing to their value in maximizing survival to at least reproductive age. Being a fitness-enhancing strategy, no regard is paid to longer-term impact on health and longevity.

In its initial iteration, the PAR model encountered opposition primarily due to differing interpretations of the available empirical data in relation to maternal–foetal conflict theory; it was argued that protection of maternal fitness was the primary driver of foetal responses (Wells, 2007). This theoretical criticism has been thoroughly addressed (Bateson *et al.*, 2014; Hanson and Gluckman, 2014), and the model now emphasizes that adaptive advantage need only occur in childhood and early adolescence for Darwinian fitness to be promoted. Furthermore, the model explains some of the empirical data that were discrepant with the Hales–Barker model, such as the delayed appearance of insulin resistance until after infancy. An advantage of PARs is that they do not operate in the infant during the postnatal period of high maternal care and lactation, when the infant is somewhat protected from the actual macroenvironment, and when insulin resistance would impede fat deposition needed to buffer the infant brain at the evolved time of weaning (Kuzawa, 2010; Bateson *et al.*, 2014). Rather, insulin resistance only emerges upon cessation of the maternal supply of lipid-enriched milk, which in evolutionary terms signals a less secure nutritional environment. In the predicted nutritionally insecure post-weaning environment, the development of insulin resistance would, as Hales and Barker (2001) had proposed, become advantageous.

The operation of PARs has been experimentally supported by a number of animal studies. For example, rats whose mothers were undernourished during gestation become conditioned to develop obesity, insulin resistance, leptin resistance, hyperphagia (excessive appetite), and sedentary behaviour in adulthood (Vickers *et al.*, 2000). These physiological characteristics represent an integrated manifestation of an energy-conserving phenotype best adapted to a predicted low nutrient postnatal environment. Administering leptin, an anorexigenic hormone, to these offspring within the neonatal period appears to reverse PARs made *in utero* and abolishes phenotypic priming, restoring physiological settings to resemble those of pups born to adequately nourished mothers (Vickers *et al.*, 2005). PARs have also been reported in the silkworm (Sato *et al.*, 2014) and butterfly (van den Heuvel *et al.*, 2013). The meadow vole, a small rodent native to North America, provides an excellent ecological example. Maternal melatonin levels, mediated by day length, act as a cue to induce PARs in the foetus such that offspring are born with a thick fur coat in autumn in anticipation of impending cold, or with a thin coat in spring to cope with warmer temperatures (Lee and Zucker, 1988).

While it is more difficult to directly test PARs in humans, it has been shown that being born smaller is associated with less severe morbidity and rates of mortality when exposed to a very low plane of nutrition in childhood (Forrester *et al.*, 2012). This may reflect adoption of an energy-conserving metabolism prompted by *in utero* predictions of nutritional scarcity, and is the first direct demonstration of the PAR-induced promotion of fitness in humans. As discussed later, there is extensive evidence for developmental mismatch leading to NCDs at the public health level, particularly with respect to migration and socioeconomic advancement.

The role of epigenetics

A major hurdle faced by the DOHaD community was the lack of plausible biochemical explanations to account for the long latency between exposure to a cue which induced a response via developmental plasticity, and onset of adult disease much later in life. Early research, predominantly employing highly artificial models of maternal nutritional or stress manipulation, pointed towards conditioning of physiological systems including the neuro-endocrine-immune system and hypothalamic-pituitary-adrenal (HPA) axis (Plagemann, 2005), and structural alterations such as a reduction in nephron number (Dötsch *et al.*, 2009). Then the advent of the epigenomic era in the 2000s, facilitated by rapid advances in next-generation sequencing technology, began to reveal that epigenetic switches were responsive to external cues and could essentially function as a molecular interface between the genome and the environment. In a molecular context, epigenetic processes refer to the DNA sequence-independent mechanisms that establish and maintain patterns of gene expression that persist through mitosis (Gluckman *et al.*, 2009). These processes, which can sometimes be reversible and may be maintained by stochastic mechanisms, include methylation of specific nucleotides (in mammals, predominantly cytosine that is adjacent to guanine); post-translational modification of the histone proteins around which DNA is packed to form nucleosomes; and transcriptional modulation by noncoding RNAs.

Epigenetic mechanisms had long been known and studied, but mostly in the context of cell differentiation and oncology. It was the recognition that the epigenome is malleable to early environmental influences which persist, that then inspired a raft of studies investigating the epigenetic basis of DOHaD. This has been rigorously demonstrated in animal studies (Seki *et al.*, 2012). For example, in a maternal low-protein diet rat model, in which offspring are conditioned towards hypertension and lipid dysregulation, liver cells of offspring had lower promoter methylation at the gene-encoding PPARα, a transcription factor known to regulate lipid metabolism (Lillycrop *et al.*, 2005). The transcriptional impact of this change was reflected in higher PPARα expression levels. Importantly, maternal folic acid supplementation not only reversed the phenotypic effects of foetal unbalanced nutrition, but also normalized epigenetic regulation to control levels (Lillycrop *et al.*, 2005; Torrens *et al.*, 2006). The maternal hypocaloric diet rat model described earlier has reported greater promoter methylation at offspring hepatic *PPARα* promoter, an effect ablated by neonatal

leptin administration (Gluckman *et al.*, 2007). The bidirectional changes in methylation between the two maternal dietary manipulation models may reflect nuanced responses to different nutritional exposures. Nevertheless, the hormonal or dietary restoration of DNA methylation levels to those of controls, concomitant with phenotypic reversals, strongly supports the epigenetic basis of developmental conditioning. In baboons, mild undernourishment during gestation decreased promoter methylation levels at foetal hepatic *PCK1*, concomitant with elevated mRNA expression, suggesting downstream effects on intermediary metabolism (Nijland *et al.*, 2010).

In humans, initial evidence implicating early life-induced epigenetic dysregulation in disease risk came from studies of populations exposed to extraordinary circumstances. For example, a cohort of Dutch individuals whose mothers were exposed to a short but severe famine during pregnancy in the Second World War has been intensively studied. Comparisons with unexposed siblings revealed that prenatal famine exposure in early gestation is associated with increased risk of coronary heart disease, glucose intolerance, poorer lipid profile and, in female offspring, obesity (Roseboom *et al.*, 2006). These individuals, in about their sixth decade of life, showed differential methylation at multiple candidate genes such as *IGF2*, an imprinted gene involved in foetal growth (Heijmans *et al.*, 2008), and *LEP* and *APOC1*, both involved in lipid metabolism (Tobi *et al.*, 2009). The magnitude of changes was small; they may be real or an artefact of confounding variables that are hard to control in human studies, such as postnatal environmental effects or age-related epigenetic drift. Nevertheless it is interesting that such gene-specific methylation changes were identified against a background of relatively static global DNA methylation levels (Lumey *et al.*, 2012), the latter possibly reflecting a buffering effect within the epigenome. It is also remarkable that a relatively transient exposure may induce epigenetic changes that persist through to late adulthood and which are detectable in peripheral blood. A pilot study examining candidate gene methylation in blood from 40-year-old individuals has uncovered gene-specific correlations of current methylation levels with measures of neonatal anthropometry, current adiposity, and blood pressure, and exposure to a maternal low carbohydrate/high protein diet (Drake *et al.*, 2012). Notably, the effects observed in this and the Dutch famine studies were independent of birth weight.

In the first demonstration that epigenetic status at birth may be associated with later phenotypic variation of clinical relevance, Keith Godfrey and colleagues reported positive correlations between umbilical cord methylation levels in part of the *RXRA* gene and adiposity later in childhood (Godfrey *et al.*, 2011). RXRA is a crucial component of transcriptional regulation of adipogenesis and fat metabolism, underscoring the biological significance of these findings. This association, replicated in a second independent cohort, suggested that at least 25% of the variation had a developmental component, making this the first study to provide a quantitative estimate of early life contribution to a known human disease risk factor. Additionally, a lower proportion of dietary carbohydrate during early pregnancy, previously identified as a risk factor for higher neonatal adiposity (Godfrey *et al.*, 1997), was associated with higher *RXRA* methylation at birth. The detection of these effects in a cohort of uncomplicated pregnancies suggests an exquisite level of epigenetic sensitivity to apparently unremarkable cues operating early in pregnancy.

Other, mostly small sample-size studies, have linked birth weight (Gordon *et al.*, 2012; Zhao *et al.*, 2014) or aspects of maternal nutrition such as intake of the methyl donors folic acid and choline, or micronutrient supplementation, with epigenetic status of candidate genes at birth or in infancy (Hoyo *et al.*, 2011; Jiang *et al.*, 2012; Cooper *et al.*, 2012; Khulan *et al.*, 2012; Dominguez-Salas *et al.*, 2014), although the functional importance of these epigenetic changes for disease risk was not determined. A number of larger, longitudinal cohorts tracking individuals from before conception have recently been established (Soh *et al.*, 2014; Vuillermin *et al.*, 2015), providing a crucial tool for determining directions of causality and giving much needed insights into the effects of exposures within the normal range in normal populations, for greater applicability to the wider population. The fields of developmental epigenetics and epigenetic epidemiology are currently progressing with great vigour.

While much of the DOHaD work has centred on maternal undernutrition, in part as a result of the early focus on low birth weight, there is increasing appreciation that early life overnutrition—experienced via maternal overweight/obesity, excessive gestational weight gain, or GDM—also imposes increased risk of adiposity and metabolic disorders in offspring (Ma *et al.*, 2013b; Gademan *et al.*, 2014; Mitanchez *et al.*, 2014). Unlike maternal undernutrition and stress, which likely operate through adaptive mechanisms, extreme overnutrition—and maternal hyperglycaemia in particular—are proposed to present evolutionarily novel circumstances against which humans have evolved few protective mechanisms, and therefore could be expected to operate through different pathways (Ma *et al.*, 2013a; Hanson and Gluckman, 2014). Thus, in contrast to normative cues and undernutrition, both of which may induce plastic responses for potential adaptive benefit, the adverse consequences of extreme maternal overnutrition represent a pathophysiological (non-adaptive) pathway.

The influence of maternal overnutrition on the epigenome has been studied by analysing DNA methylation levels in placenta, cord blood, or umbilical cord samples. Small studies have detected a link between preconceptional BMI and methylation at the *PPARGC1A* promoter, which encodes a key regulator of gluconeogenesis (Gemma *et al.*, 2009), and a potential effect of maternal obesity, GDM, and pre-eclampsia on global methylation levels in the placenta (Nomura *et al.*, 2014). Genome-wide analyses have uncovered methylation differences in numerous genes in both placenta and cord blood samples from GDM pregnancies, many of which are involved in metabolic disease pathways including disorders of glucose metabolism (Ruchat *et al.*, 2013). GDM has further been associated with *MEST* hypomethylation in placenta and cord blood, an aberration that was similarly found in blood samples from morbidly obese adults (El Hajj *et al.*, 2012). However, of particular concern is that epigenetic changes are apparent even under milder levels of maternal hyperglycaemia (Desgagné *et al.*, 2014). Indeed, the relationship persists in a graded manner from normal through to high blood glucose levels (Bouchard *et al.*, 2010; Bouchard *et al.*, 2012), raising the possibility that even less severe maternal insulin resistance or clinically normal pregnancies may confer some level of risk. This accords with clinical observations that maternal hyperglycaemia and maternal BMI are associated in a continuous manner with risk of certain negative pregnancy outcomes including high birth weight, delivery by caesarean section, and high cord serum C-peptide, a proxy for neonatal hyperinsulinaemia (The