

Review

Rosana E. Norman*, David O. Carpenter, James Scott, Marie Noel Brune^a and Peter D. Sly

Environmental exposures: an underrecognized contribution to noncommunicable diseases

Abstract: Previous attempts to determine the degree to which exposure to environmental factors contribute to noncommunicable diseases (NCDs) have been very conservative and have significantly underestimated the actual contribution of the environment for at least two reasons. Firstly, most previous reports have excluded the contribution of lifestyle behavioral risk factors, but these usually involve significant exposure to environmental chemicals that increase risk of disease. Secondly, early life exposure to chemical contaminants is now clearly associated with an elevated risk of several diseases later in life, but these connections are often difficult to discern. This is especially true for asthma and neurodevelopmental conditions, but there is also a major contribution to the development of obesity and chronic diseases. Most cancers are caused by environmental exposures in genetically susceptible individuals. In addition, new information shows significant associations between cardiovascular diseases and diabetes and exposure to environmental chemicals present in air, food, and water. These relationships likely reflect the combination of epigenetic effects and gene induction. Environmental factors contribute significantly more to NCDs than previous reports have suggested. Prevention needs to shift focus from individual responsibility to societal responsibility and an understanding that effective prevention of NCDs ultimately relies on improved environmental management to reduce exposure to modifiable risks.

Keywords: burden of disease; children; environment; exposure; noncommunicable diseases.

^aAn author is a staff member of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of the World Health Organization.

*Corresponding author: **Dr. Rosana E. Norman**, Children's Health and Environment Program, Queensland Children's Medical Research Institute, The University of Queensland, Herston, Queensland, Australia; and School of Population Health, The University of Queensland, Herston, Queensland, Australia, Phone: +61-7-3346-4619, Fax: +61-7-3365-5442, E-mail: r.norman@sph.uq.edu.au

David O. Carpenter: Children's Health and Environment Program, Queensland Children's Medical Research Institute, The University

of Queensland, Herston, Queensland, Australia; and Institute for Health and the Environment, University at Albany, Rensselaer, NY, USA

James Scott: Children's Health and Environment Program, Queensland Children's Medical Research Institute, The University of Queensland, Herston, Queensland, Australia; and Metro North Mental Health, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia; and The University of Queensland Centre for Clinical Research, Herston, Queensland, Australia

Marie Noel Brune: Public Health and Environment, World Health Organization, Geneva, Switzerland

Peter D. Sly: Children's Health and Environment Program, Queensland Children's Medical Research Institute, The University of Queensland, Herston, Queensland, Australia

Introduction

Quantifying the disease burden caused by the environment has been difficult given the relative lack of evidence on causal links between environmental exposures and health outcomes as well as lack of reliable data on population levels of exposure (1). Nevertheless, several reports have attempted to determine what proportion of the global burden of disease is attributable to environmental factors (1–7). In the World Health Organization's (WHO) Comparative Risk Assessment, environmental risk factors accounted for approximately 9.6% of the total global disease burden for 2000 (2). Building on this analysis, Prüss-Üstün et al. then published estimates of the environmental disease burden for 2002, which also involved surveys of expert opinion with large uncertainty around these estimates. About 24% of the global disease burden and an estimated 23% of all deaths were attributable to environmental factors. For children 0–14 years old, the proportion of deaths attributed to the environment was as high as 36% (4). The authors also reported the fraction of disease that could be attributed to the environment for 85 diseases. These estimates provided an overview of opportunities for prevention through healthier environments with a focus on health gains that could be achieved through environmental interventions. The WHO Environmental Burden of Disease series also provides practical guidance to estimate the burden from selected risks at country level (8) and a country-by-country analysis of

the health impact of environmental factors (9). Several national-level estimates of environmental burden of disease have also been conducted (10–12). The problem is that these analyses are, by their nature, conservative and, for the most part, have dealt with exposures from only limited sources with estimates based on traditional well-established environmental risk factors like unsafe water, sanitation and hygiene, indoor and outdoor air pollution, lead exposure, and occupational exposures.

In a more recent analysis, 8.3% of deaths were attributable to chemical exposures including indoor and outdoor air pollutants, second-hand smoke, lead, arsenic in drinking water, chemicals in occupational exposures, and acute poisonings due to pesticides and other chemicals (6). Notably, this analysis did not consider exposure to chemicals in food, personal care products or other household items, or the effects of prenatal exposure leading to diseases later in life.

The aim of this review is to revisit the question of how environmental exposures contribute to disease, drawing on new information and using a broader definition of what constitutes an “environmental disease”. The focus is on noncommunicable diseases (NCD), including diseases that either present or have their origins in childhood. Thinking needs to change in these areas to make progress in reducing the burden due to such disorders. The need for a change in thinking is highlighted by a recent commentary written on behalf of the Lancet NCD action group in which a call for action was made to the United Nations (UN) high-level meeting on NCDs to stimulate a coordinated global response to major NCDs including heart disease, stroke, cancer, diabetes, and chronic respiratory diseases (13). These authors highlight key risk factors that cause NCDs, namely, tobacco use, including second-hand smoke, diets high in fats, salt, and sugar, environments that prevent physical activity, and alcohol consumption. In addition, they include the intermediate risk factors like obesity, increased blood pressure, and glucose, and cholesterol concentrations. However, the issue of low-dose chronic exposure to a variety of environmental exposures, including chemical toxicants, was lacking.

The so-called lifestyle behavioral risk factors have traditionally been excluded from consideration when determining environmental contributions to disease (4) and are often considered to involve an element of choice and individual responsibility. However, diet is not only a function of individual behavior – it is also a function of the social and economic environment and national and international food production policies. Lifestyle factors vary greatly with socioeconomic status, which is a major consideration in population health. It is also important

to recognize that for children, exposure to lifestyle risk factors like diet and tobacco smoke are not lifestyle choices but rather environmental exposures imposed on them by others. There is no question that diet, habits, and exercise influence susceptibility to disease. However, these sources of exposure should not be excluded from the category of environmentally induced diseases. Clearly, smoking and excessive alcohol consumption involve exposure to chemical agents known to increase risk of developing cancer as well as cardiovascular and liver disease. However, as detailed below, exposure to certain chemicals, primarily through diet, has also been linked to risk of cancer, type 2 diabetes, hypertension, cardiovascular disease, and obesity. These diseases have not generally been considered to be “environmental” in the past, although about 8%–10% of cardiovascular disease has been attributed to environmental causes through consideration of only air pollution and occupation (7).

Furthermore, we know much more about gene-environment interactions today and understand that genetic susceptibility is an essential factor for the development of many chronic diseases. An environmental exposure is often responsible for triggering disease in susceptible individuals. There is emerging evidence that the origins of many adult diseases are found during fetal development and early childhood (14). These early life experiences and exposures can affect adult mental and physical health either by cumulative damage over time or by the biologic embedding of adversities during sensitive developmental periods (15). However, due to the long lag between exposure and outcome, these connections are sometimes difficult to establish. NCDs should be recognized as largely “environmental diseases” and doing so will allow the environmental contributions to NCDs to be appropriately recognized.

Definition of environment and environmental disease

The environment has been defined as all that which is external to the human host and can be divided into physical, biologic, social, or cultural, all of which can influence the health status of populations (16). As such, the environmental causes of disease would include all factors other than genetic factors – in other words, the classic dichotomy between nature and nurture. Smith et al. (7) argued that these broad definitions of environmental factors are not useful and that the inclusion of lifestyle or behavioral risk factors as “environmental” would overwhelm the more conventionally understood environmental factors.

However, in our view, excluding major lifestyle risk factors results in a gross underestimation of the role of environmental exposures in inducing and/or progressing NCDs. Lifestyle and behavior are determined largely by the environment, and in turn, lifestyle and socioeconomic status influence environmental exposures.

Socially corrosive forces such as inequalities, stigma, discrimination, and exclusion have deleterious effects on health and well-being and can also lead to other social problems like crime and violence. Violence, which can be physical, sexual, or emotional or involve deprivation or neglect, can also have adverse impacts on mental and physical health (17). Inclusion of social factors as environmental causes of disease is justified because such factors are modifiable through effective education, policy, and legislation and because environmental exposures may contribute to the social risk factors (18). Environmental diseases should be defined as all diseases caused by physical, chemical, biologic, behavioral, cultural, social, and economic factors external to a person, excluding only diseases caused solely by genetics.

The role of environmental factors in disease initiation, progression, and/or prognosis

Most chronic NCDs appear to arise from environmental exposures acting within a framework of genetic susceptibility, often within a developmental context. The last several years have seen an enormous growth in our understanding of gene-environment interactions, yet these interactions are not generally considered when determining the extent of environmentally induced disease. Many chemical contaminants alter the expression of various genes, often genes regulating so many different cellular functions that it is not possible to trace the exact pathway leading from exposure to a particular disease. For example, 2,3,7,8-dibenzo-*p*-dioxin upregulates at least 114 genes and downregulates another 196 genes (19). In addition, single-nucleotide polymorphisms can greatly alter disease susceptibility secondary to environmental exposures. For example, the impact of prenatal exposure to organophosphates on cognitive development is enhanced in children born to mothers who carry the *PON1* *Q₁₉₂R* *QR/RR* genotype (20). Similarly, reduced responses to tetanus and diphtheria vaccination in children carrying the *IL-4RA* *Q551R* genotype are only seen if they are also exposed to environmental tobacco smoke (21).

The emerging field of epigenetics, where gene expression and/or function is altered by environmental exposures without altering the basic deoxyribonucleic acid (DNA) structure, is providing both new information and new challenges in interpreting the role of environmental exposures in NCD causation. Asthma is one disease where epigenetics is thought to play a substantial role, with clear evidence in animal models of DNA methylation via a diet rich in folate, a source of methyl donors, altering the response to environmental allergens (22) to produce an “asthma phenotype” in mice not normally susceptible. The situation is less clear in humans, although data from appropriately designed studies are lacking (23). Although detailed pathways between exposure to chemicals that are associated with increases in risks of cancer, diabetes, heart disease, asthma, or altered immune regulation may not be clear, the lack of a detailed mechanistic pathway should not be a barrier to identification of the disease being at least in part “environmental”.

Environmental exposures, including social determinants of health, may contribute to disease initiation, disease progression, and disease prognosis. Diseases will take different courses depending on the environmental conditions. Social determinants of health act as modifiers of the environmental determinants, and wealthier people can often better protect themselves against environmental risks. Exposure is a social, demographic, and economic process, and there is a myriad of ways in which socioeconomic and demographic factors influence exposures, individual susceptibility, and health outcomes (1). In addition, early life exposure to chemical contaminants is now clearly associated with elevated risk of several diseases later in life. In the next section, we summarize the evidence of associations between NCDs (diabetes and cardiovascular disease) and their intermediate risk factors (obesity and hypertension) and exposure to environmental chemicals present in air, food, and water likely reflecting a combination of epigenetic effects and gene induction.

Environmental contributions to major NCDs

Cancer

Most cancers are caused by exposure to chemical carcinogens or radiation, not by inherited genetic factors. Based on Scandinavian twin studies, the environment plays a principal role in the causation of sporadic cancer, whereas

genetics in the absence of an environmental exposure makes a relatively minor contribution (24). Even for those cancers where genetic factors play a larger role (colorectal, breast, and prostate cancers), it is likely that gene-environment interactions are critical, and at the population level, the increase in the risk of cancer among close relatives of persons with cancer is generally moderate (24). In addition to the traditional environmental risk factors like indoor and outdoor air pollution, and tobacco smoke, other exposures are also likely to pose a risk. The International Agency for Research on Cancer (25) lists 109 agents as known, 65 as probable, and 275 as possible human carcinogens. Many of these are in our air, food, and water.

Asthma

There is an increasing understanding that asthma develops from complex interactions between environmental exposures and a number of underlying genetic predispositions (26–28). Exposures during fetal development or in early postnatal life are especially important, and the consequences of these exposures are determined, at least in part, by the stage of development of the respiratory and immune systems when the exposures occur (29). Early life risk factors for asthma include exposures that have adverse impacts on lung growth and immune development and increase the risk of lower respiratory infections and allergic sensitization in early life (30–32).

Environmental factors that have been associated with asthma in childhood include respiratory viral infections (33, 34), aeroallergens (30), environmental tobacco smoke (35), and inflammatory stimuli associated with ambient air pollution (36, 37) and indoor air pollution (38). Domestic exposure to formaldehyde in early life significantly increases the risk of asthma (39). Ecologic data also suggest a link between exposure to organic chemicals such as polychlorinated biphenyls (PCBs) and admission to hospital for respiratory infections and asthma (40). Indeed, there is strong evidence that environmental factors are largely responsible for triggering exacerbations of asthma.

Neurodevelopmental conditions in children

Child abuse, neglect, and bullying are important environmental factors that increase the risk of mental illness in children (41–43). Cognitive function is also a consequence of genetic influences moderated by exposure to environmental chemicals like lead, PCBs, methyl mercury, and environmental tobacco smoke. Attention deficit hyperactivity disorder

(ADHD), autism, learning disabilities, and other neurodevelopmental disorders result from environmental exposures in presumably genetically susceptible individuals.

Violent and aggressive behavior have been reported to be increased by early life exposures to a variety of environmental chemicals that reduce the ability of a person to deal with frustration (44). Lead, a known neurotoxicant, is associated with IQ loss and behavioral problems, including decreased academic performance, sociobehavioral problems consistent with ADHD, learning difficulties, oppositional/conduct disorders, and in some studies, delinquency (45). Over the past 3 decades, blood lead levels declined dramatically in North America and Europe following the removal of lead from gasoline, paints, and other consumer products. The reduction in violent crime seen in the 1990s has been attributed in part to reduced lead exposure in early life (18).

Posttraumatic stress disorders have also been linked to natural disasters such as floods, earthquakes, and fires, which could also be prevented by environmental measures.

Type 2 diabetes, cardiovascular disease, and hypertension

Epidemiologic studies have shown an increased risk of type 2 diabetes after exposure to persistent organic pollutants (POPs) including dioxins, PCBs, organochlorine pesticides (46–48), arsenic (49), and bisphenol A (50). Strong dose-response relations between serum concentrations of six selected POPs and the prevalence of diabetes persisted after adjustment for other traditional risk factors, including body mass index (47).

Cardiovascular diseases including ischemic heart disease and stroke are leading causes of death and disability in the developed world. These diseases are not usually considered to be “environmental”, although tobacco smoke, lead exposure, and outdoor air pollution are known risk factors (4). However, recent evidence demonstrates strong associations between risk of cardiovascular diseases (51–53), hypertension (54), and stroke (55) and exposure to POPs.

Obesity

Obesity prevalence is rising dramatically in adults and children around the world. There is no doubt that overnutrition and lack of exercise are important environmental factors impacting on obesity. However, the view that these

two risk factors alone explain the entirety of the obesity epidemic is far too simplistic. There is considerable evidence that the obesity risk may begin during pregnancy and early childhood (56) and that the obesity epidemic is at least in part due to chemical exposures, especially during these vulnerable windows of development (57).

Although risk factors like excess caloric intake, decreased exercise, genetics, and the built environment are active areas of research into the causes of obesity, the obesogen hypothesis postulates that prenatal and perinatal chemical exposure, particularly to endocrine-disrupting chemicals (EDCs), contributes to the risk of obesity (58–60). EDCs are environmental chemicals with hormone-like activity that can disrupt the programming of endocrine-signaling pathways during development and cause disruption of the energy storage-energy balance endocrine system. Developmental exposure to a large number of EDCs, including tributyltin chloride, bisphenol A, organochlorine compounds, organophosphate pesticides, air pollution, lead, diethylstilbestrol, perfluorooctanoic acid, monosodium glutamate, and nicotine, can lead to increased weight gain later in life in animals (59, 61). An association between *in utero* exposures to several POPs and subsequent increased weight gain in the first few years of life has also been observed in infants and children (59, 62, 63). There is also strong epidemiologic evidence that smoking during pregnancy is associated with increased weight gain in infants (64, 65). There is a strong relationship among obesity, type 2 diabetes, and the metabolic syndrome (66), and many chemicals that cause obesity in animal models result in altered glucose tolerance via insulin resistance.

Conclusion

Despite the adoption of a political declaration on the prevention and control of NCDs in the UN in 2011, NCDs continue to increase. Effective action requires an understanding of the magnitude of the problem as well as the full spectrum of its causes and underlying mechanisms. The contribution of environmental exposures to the development of NCDs has been underestimated in previous

assessments. There is a need to build on the conceptual framework outlined in this review to quantify the full environmental contribution to NCD. However, the full impact of the environment cannot yet be fully appreciated because of the difficulty in quantifying the effects of early life exposure on later development of disease, the difficulties of exposure assessment, and incomplete understanding of gene-environment interactions. Considerable research efforts will be required to provide the appropriate data. In particular, large birth cohort studies are needed, allowing prospective measurement of the environmental effects of chemicals including biomonitoring data and biomarkers of past exposure to determine the most vulnerable period or critical window of exposure for health effects. The first step would involve existing birth cohorts collaborating so that environmental risk factors for both common and low prevalence outcomes can be identified. This will enable a better understanding of potential exposure-response relationships, enable the assessment of specific chemicals in more detail, and also improve the understanding of potential mechanisms of action and gene-environment interactions. However, a change in thinking will also be required. The prevention of NCDs needs to shift focus from individual responsibility to societal responsibility because behavioral change can only take place through changes in the environment. Effective prevention of NCDs ultimately relies on improved environmental management to reduce exposure to modifiable risks.

Author contributions

R.E.N., D.O.C., and P.D.S. conceived the article and all authors contributed to writing and editing the article.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors declare they have no actual or potential competing financial interests.

Financial disclosure: No external funding was used to produce this manuscript.

Received December 9, 2012; accepted March 14, 2013

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