Developmental Exposure to Environmental Chemicals and Metabolic Changes in Children

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The incidence of childhood obesity, type 2 diabetes, and other forms of metabolic disease have been rising over the past several decades. Although diet and physical activity play important roles in these trends, other environmental factors also may contribute to this significant public health issue. In this article, we discuss the possibility that widespread exposure to endocrine-disrupting chemicals (EDCs) may contribute to the development of metabolic diseases in children. We summarize the epidemiological evidence on exposure to environmental chemicals during early development and metabolic outcomes in infants and children. Prenatal exposure to EDCs, particularly the persistent organic pollutant DDT and its metabolite DDE, may influence growth patterns during infancy and childhood. The altered growth patterns associated with EDCs vary according to exposure level, sex, exposure timing, pubertal status, and age at which growth is measured. Early exposure to air pollutants also is linked to impaired metabolism in infants and children. As a result of these and other studies, professional health provider societies have called for a reduction in environmental chemical exposures. We summarize the resources available to health care providers to counsel patients on how to reduce chemical exposures. We conclude with a discussion of environmental policies that address chemical exposures and ultimately aim to improve public health.

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Abbreviations: $\sum$, sum; ↑, positive association; ↔, no association; ↓, inverse association; 2,4-DCP, 2,4-dichlorophenol; 2,5-DCP, 2,5-dichlorophenol; 3,4-DHB, 3,4-dihydroxybenzoic acid; β-HCH, β-hexachlorocyclohexane; AAP, American Academy of Pediatrics; ACOG, American Congress of Obstetricians and Gynecologists; ADA, American Diabetes Association; AMA, American Medical Association; ANA, American Nurses Association; ANHE, Alliance of Nurses for Healthy Environments; APHA, American Public Health Association; ASRM, American Society of Reproductive Medicine; ATSDR, Agency for Toxic Substances & Disease Registry; BC, black carbon; BPA, bisphenol A; BPS, bisphenol S; BMI, body mass index; CAA, Clean Air Act; CB-153, 2,2′,4,4′,5,5′-hexachlorobiphenyl; CDC, Centers for Disease Control and Prevention; CEHN, Children's Environmental Health Network; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CHE, Collaborative on Health and the Environment; CO, carbon monoxide; DAP, dialkylphosphate; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DBP, dibutyl phthalate; DEHP, di(2-ethylhexyl) phthlate; DEP, diethyl phthalate; DES, diethylstilbestrol; DIBP, diisobutyl phthalate; DIDP, di-isodecyl phthalate; DINP, di-isononyl phthalate; DnBP, di-n-butyl phthalate; DOHaD, Developmental Origins of Health and Disease; EASD, European Association for the Study of Diabetes; EDC, endocrine-disrupting chemical; EPA, U.S. Environmental Protection Agency; EWG, Environmental Working Group; FDCA, Federal Food, Drug, and Cosmetic Act; FIFRA, Federal Insecticide, Fungicide, and Rodenticide Act; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HCB, hexachlorobenzene; HDL, high-density lipoprotein; IDF, International Diabetes Federation; IGF-1, insulin-like growth factor 1; LDL, low-density lipoprotein; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCiOP, mono-carboxyisooctyl phthalate; MCNP, di-2-ethylhexyl phthalate; MCOP, mono-carboxyisooctyl phthalate; MCPP, mono-(3-carboxypropyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-n-butyl phthalate; MMP, mono-methyl phthalate; MNP, mono-iso-nonyl phthalate; NO_2, nitrogen dioxide; NEEF, National Environmental Education Foundation; NHANES, National Health and Nutrition Examination Survey; NTP, National Toxicology Program; O_3, ozone; OBELIX, OBesogenic Endocrine-disrupting chemicals: LInking prenatal eXposure to the development of obesity later in life; PA, phthalic anhydride; PAH, polyaromatic hydrocarbon; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PCDD/Fs, polychlorinated dibenzo-*p*-dioxins, dibenzofurans; PEHSU, Pediatric Environmental Health Specialty Unit; pentaBDE, penta brominated diphenyl ethers; PFC, perfluorinated compound; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter (fine particulate matter); PM_{10}, particulate matter 10 μm or less in diameter; POP, persistent organic pollutant; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFOSA, perfluorooctane sulfonamide; PRHE, Program on Reproductive Health and the Environment; PSR, Physicians for Social Responsibility; PVC, polyvinylchloride; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; SMFM, Society for Maternal-Fetal Medicine; TBT, tributyltin; TEQ, toxic equivalent; TSCA, Toxic Substances Control Act of 1976; UCSF, University of California, San Francisco; UNEP, United Nations Environment Programme; WC, waist circumference; WHO, World Health Organization.

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Introduction

Metabolic disease includes any innate or acquired disorders, such as type 2 diabetes and obesity, which affects the body's ability to obtain or utilize energy from food.[1] Childhood metabolic problems are a significant public health concern. During the 1980s and 1990s, the number of U.S. children who were overweight or obese increased significantly.[2] As of 2011–2012, 8.1% of U.S. infants and toddlers had a high weight for length, and 31.8% of 2–19-year olds were either overweight or obese.[3] During 2000–2010, almost three-quarters of U.S. adolescents had at least one metabolic abnormality, and 1 in 10 had metabolic syndrome, a cluster of interrelated risk factors for diabetes and cardiovascular disease.[4] Between 2001 and 2009, the prevalence of type 2 diabetes in U.S. youth increased by 30.5%.[5] *Although diet and activity levels are clearly important, there is growing evidence that these factors alone cannot fully explain increasing rates of metabolic disease*. In this article, we discuss how widespread exposure to endocrine-disrupting chemicals (EDCs) may be linked to the development of metabolic diseases in children. We review epidemiological evidence on exposure to environmental chemicals during early development and metabolic outcomes in infants and children. We then summarize the resources available to health care providers to counsel patients on how to reduce environmental chemical exposures. We conclude with a discussion of environmental policy changes necessary to reduce chemical exposures and improve public health.

Widespread changes in the environment appear to have influenced metabolism in recent decades. For example, when comparing U.S. adults with the same caloric, macronutrient, and physical activity levels, those assessed in 2006 had a higher BMI than those assessed in 1988.[6] In other words, eating the same number of calories in 2006 as compared to 1988 resulted in a higher body mass index (BMI). Examples from the animal kingdom also provide clues to the contribution of environmental influences beyond energy intake and expenditure. Samples from over 20,000 animals from eight species show that average body weight has risen over the past decades in all species studied; the probability of this change occurring by chance is 1.2×10^{-7}.[7] Common environmental exposures may be affecting metabolism in human and animal populations in similar ways.

Metabolic Disease in Children

The accepted definitions of obesity, diabetes, and metabolic syndrome differ between adults and children. In adults, the U.S. Centers for Disease Control and Prevention (CDC) defines "overweight" as a BMI from 25 to 29.9, "obesity" as a BMI of 30 or higher, and "extreme obesity" as a BMI of 40 or higher.[8] In children and adolescents from age 2 to 19, the CDC defines "overweight" as a BMI between 85th and 95th percentiles for youth of the same age and sex; "obesity" as a BMI at or above the 95th percentile for youth of the same age and sex; and "extreme obesity" as a BMI at or above 120% of the 95th percentile for youth of the same age and sex.[9] The American Diabetes Association (ADA) defines type 2 diabetes as the type associated with insulin resistance (not autoimmune), and relative (not absolute) insulin deficiency.[10] Health organizations have agreed on a harmonized definition of "metabolic syndrome" as three of five clinical findings: elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure, and elevated fasting blood glucose.[11] The International Diabetes Federation (IDF) proposed guidelines for diagnosing metabolic syndrome in children and adolescents. These guidelines state that in children younger than 10 years, metabolic syndrome cannot be diagnosed, while youth aged 16 years and older can be diagnosed using adult criteria.[12]

In recent years, there is encouraging evidence that the increasing trends of pediatric metabolic disorders may be leveling off or even declining. For example, the prevalence of obesity among 2–5-year old U.S. children decreased significantly from 13.9% in 2003–2004 to 8.4% by 2011–2012.[3] Data from nine countries show that childhood overweight and obesity may have plateaued.[13] Yet despite the recent decrease in the number of obese preschoolers, the overall prevalence of metabolic diseases in children remains troubling.

Another continuing concern is that metabolic problems are appearing earlier in life. Although there is not yet a standard definition of "infant obesity," researchers have found that even infants under 6 months of age have become proportionately heavier since the 1980s.[14] An alarming case study of a 3-year old from Texas with type 2 diabetes—perhaps the youngest ever reported—was presented at the 2015 annual meeting of the European Association for the Study of Diabetes (EASD).[15] Metabolic diseases in children tend to continue into