INVITED REVIEW

Chemical and non-chemical stressors affecting childhood obesity: a systematic scoping review

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Childhood obesity in the United States has doubled over the last three decades and currently affects 17% of children and adolescents. While much research has focused on individual behaviors impacting obesity, little research has emphasized the complex interactions of numerous chemical and non-chemical stressors found in a child's environment and how these interactions affect a child's health and well-being. The objectives of this systematic scoping review were to (1) identify potential chemical stressors in the context of non-chemical stressors that impact childhood obesity; and, (2) summarize our observations for chemical and non-chemical stressors in regards to child-specific environments within a community setting. A review was conducted to identify chemical and non-chemical stressors related to childhood obesity for the childhood life stages ranging from prenatal to adolescence. Stressors were identified and grouped into domains: individual behaviors, family/household behaviors, community stressors, and chemical exposures. Stressors were related to the child and the child's everyday environments and used to characterize child health and well-being. This review suggests that the interactions of chemical and non-chemical stressors are important for understanding a child's overall health and well-being. By considering these relationships, the exposure science research community can better design and implement strategies to reduce childhood obesity.

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INTRODUCTION

Obesity is a worldwide problem affecting both affluent and less affluent countries. According to the World Health Organization (WHO), obesity has nearly doubled since 1980 and, as of 2008, there were 40 million (6%) preschool-aged children worldwide classified as overweight.¹ De Onis et al.² estimated that by 2020 the percentage is expected to increase to 9.1%, resulting in approximately 60 million preschool-aged children who are overweight or obese. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that childhood obesity affects 17% of all children and adolescents, a rate which has tripled from one generation ago.^{3–5}

The United Nations (UN) recognizes that reducing obesity requires urgent global action and has responded with policies and procedures that require the involvement of stakeholders from many sectors (such as health, education, nutrition, policy, agriculture, industry and trade, finance) to combat this epidemic.¹ The UN realizes that childhood obesity will only be resolved with a combination of interventions catering to the specific needs of the geographic area and population receiving the intervention. These interventions have been implemented as part of programs already in place to improve health and well-being.¹

Obesity and being overweight result when the body accumulates fat over time above what are considered normal adiposity levels. It is increasingly recognized that obesity is a complex issue

that results from the interactions of many factors, including but not limited to genetic, metabolic, behavioral, and environmental. Much research has been undertaken to study the link between any one individual factor and obesity.^{6–14} For example, metabolic risk factors such as diabetes have been shown to be linked to obesity, and there is growing research exploring the associations between chemical exposures and diabetes.^{15,16} However, the inter-relationships between stressors are not well understood. Generally, the obesity epidemic is thought to be a result of chronic energy imbalance between calories consumed and calories expended.^{17–23} In addition to physical activity and caloric intake, other non-chemical stressors that may influence weight include personal habits (e.g., smoking); psychosocial stress (e.g., parental divorce, domestic violence, exercising poor judgement, depression); access to health care; and/or aspects of the built and natural environments.^{24–27} There is also increasing evidence that obesogens (i.e., chemical stressors) may influence obesity by affecting metabolic activities in the body. Finally, genetic predisposition plays a large role, accounting for >40% of the population variation in body mass index (BMI), suggesting that genes factor into how the body captures, stores, and uses energy from food consumption.²⁸ Some health effects resulting from exposures to chemical and non-chemical stressors during the prenatal period are considered to have lifelong impacts, suggesting that reduced exposures to obesogens and non-chemical stressors may need to begin early in life to serve as a preventive measure.²⁹

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Figure 1. Flowchart showing how studies were included in this literature review.

The goal of this systematic scoping review is to examine recent evidence from the peer-reviewed literature about the role of chemicals as obesogens in human populations and the inter-relationships between chemical and non-chemical stressors in impacting childhood obesity. The specific objectives are to (1) identify potential chemical stressors in the context of non-chemical stressors that impact childhood obesity and (2) summarize our observations for the chemical and non-chemical stressors in regards to child-specific environments (i.e., where a child lives, learns, and plays) in a community setting. A better understanding of the cumulative exposures that children experience may inform improved approaches to manage and reduce the incidence of childhood obesity.

METHODS

This literature review focused on a holistic analysis of childhood obesity by considering myriad influencing factors, including individual behaviors; social determinants; the natural environment; the built environment; and potential exposures to environmental chemicals. We examined multiple stressors for childhood lifestyles guided in part by EPA's age grouping guidance.³⁰

Stressors are defined as any physical, chemical, or biological entity that can induce an adverse response. Chemical stressors are exogenous environmental compounds which change or damage living organisms or ecosystems.^{31–33} Non-chemical stressors are factors found in the built, natural, and social environments such as noise, temperature, humidity, stress from the built environment, social factors, and lack of health care.^{24,26,33}

Using PubMed and Google Scholar, we identified relevant literature articles using several search strings (Figure 1—Step 1). More information on the search strings (including specific stressor terms) can be found in the Supplementary Information. Oftentimes published articles led to additional relevant articles or books. All references were first screened by title to determine relevance. For each stressor identified, if the childhood data were

not available, we included *in vitro/in vivo* studies to support the limited epidemiological findings.

Selected articles were published between January 2004 and July 2014, written in English, and addressed the topic of childhood obesity and chemical and or non-chemical stressors (Figure 1—Step 2). Abstracts were then reviewed (Figure 1—Step 3), and duplicate articles, concept papers, any study that excluded data collection and analysis, any study focused on obesity in adults, and any study focused predominantly on diabetes and asthma were removed from further consideration, reducing the number of manuscripts for full review to 723 (Figure 1—Step 4). Full text copies of manuscripts were obtained and evaluated based on the following criteria:

- (1) Focus on children ranging in age from prenatal to 18 years
- (2) Type of study (e.g., longitudinal, retrospective, prospective, cross-sectional)
- (3) Available data (with supporting information (e.g., methods) to assess relevance and data quality).

In the end, 234 articles were included in this review (Figure 1—Step 5). When available, review papers were selected for well-studied stressors (e.g., activity, diet, socioeconomic status, prenatal exposures, environmental tobacco smoke). Citations were managed with EndNote X7.

This manuscript is organized into the following sections: individual and family/household behaviors, community stressors, and chemical exposures to align with the Sustainable and Healthy Communities research program (<https://www.epa.gov/research>).

RESULTS

Individual Behaviors

A summary of papers included in this review can be found in Supplementary Tables S1–S4. Individual behaviors include: diet, activity level, and sleep. Because the relationships between diet,

activity level, and sleep, and childhood obesity are well studied, we only provide brief summaries of these important factors here. More information can be found in the Supplementary Information.

Diet

Many research efforts have studied the relationship between dietary factors and childhood obesity including diet during developmental periods (including maternal diet during prenatal development), parental influence, food advertisements, and neighborhood food (e.g., fast-food restaurants, convenience stores, and small food stores), sweetened beverages, high-fructose corn syrup, processed foods, junk food, and meal frequency. Inconsistencies indicate that increased energy intake alone may not be the leading cause of childhood obesity. More details on associations between diet and childhood obesity can be found in the Supplementary Information.

Activity Level

Research has examined activity levels and obesity in children including aspects of a child's built environment, socioeconomic status, gender, race, social support, technology, and home environment. Evidence in the literature suggests that activity level alone may not explain childhood obesity. More details on associations between activity level and childhood obesity can be found in the Supplementary Information.

Sleep

Sleep plays an important role in all aspects of a child's life including overall health. However, inconsistencies indicate that sleep alone may not explain childhood obesity. More details on the relationship between sleep and childhood overweight/obesity can be found in the Supplementary Information.

Family and Social Stressors

Family and social stressors include socioeconomic status (SES), psychosocial stress, maltreatment (Supplementary information), and prenatal and postnatal exposures that children cannot avoid on their own (e.g., maternal smoking, secondhand smoke exposure (SHS), illicit substance use (Supplementary Information)).

Socioeconomic Status (SES)

SES is a combined measure of economic and social position as it relates to others based on race/ethnicity, income, education, and occupation. Studies report conflicting results when examining levels of SES and obesity. Lower SES neighborhoods are at a higher risk for childhood obesity since they often have limited access to healthy food options and facilities for activity as compared to middle and upper SES neighborhoods.^{34,35} Aitsi-Selmi *et al.*³⁶ found that higher SES Brazilian girls had lower adiposity as adults, but the opposite was found for boys. Another study of Brazilian children who were followed until age 15 years found that higher SES children were more likely to be overweight and obese than lower SES children.³⁷

Studies of children in the United States, Canada, and Europe have shown that children from higher SES families are more physically active, eat healthier food options, and participate in more organized recreational activities as compared to lower SES families.^{38,39} Studies examining SES have shown an association with low SES, increased childhood obesity and greater adiposity.^{34,40–44} Data collected in a German health interview of 13,450 obese/overweight children found that obesity was strongly related to both low SES and parental obesity.⁴⁵ Similarly, low SES backgrounds in conjunction with high amounts of television viewing put children at a higher risk for being overweight.^{46,47}

Other aspects of SES have also been examined. Morrissey *et al.*⁴⁸ examined the association between maternal work and children's BMI. They found that maternal employment has a cumulative influence associated with increases in the child's BMI, especially for those children in the sixth grade, as compared to younger children.⁴⁸ Chen and Escarce⁴⁹ found that children were more likely to be obese by the fifth grade if they lived in a single parent household, did not have any siblings, or both.

Studies examining race/ethnicity related to weight and SES have found varied results. For example, African-American children have a prevalence of being overweight when compared to Caucasian children.^{50,51} Whitaker and Orzol⁵² found that race/ethnicity and other SES indicators did not explain the higher rates of obesity in Hispanic children when compared to Caucasian or African American children. Other studies reported in the literature have shown similar conflicting results.^{53–55}

Psychosocial Stress

Psychosocial stress has been identified as a possible factor contributing to childhood obesity. Psychosocial stress may result from a child's school, family, or other interpersonal environments they encounter daily. It is hypothesized that these psychosocial stressors lead to metabolic changes that increase cortisol and catecholamine levels, leading to behavioral changes like emotional eating, inactivity, and disruption of sleep. The relationship between obesity and various psychosocial stressors is not consistent.

Parental stress could potentially preprogram the fetus resulting in childhood obesity as a potential outcome.^{56,57} A Danish National Birth cohort of 37,764 women and children examined associations between anxiety, depression, and stress of the mother during pregnancy and the child's rate of being overweight at age 7 years. The results indicated maternal stress during pregnancy did not appear to influence a child's weight at age 7 years.⁵⁶ Another study by Van Dijk *et al.*⁵⁷ found that increased cortisol production and work strain while the mother was pregnant may not have pre-programmable obesity and adiposity effects on children at age 5 years.

Conversely, a Danish study found that children whose mothers were stressed during 6 to 0 months before birth due to bereavement of someone close had increased BMI values as compared to children whose mothers did not report a death during their pregnancy. The increased BMI values, however, were not significant until the age of 10 years and beyond, suggesting that early-life exposures to stress may have effects later on in childhood.⁵⁸

Other parental stressors that influence BMI levels in children include violence, serious life events, food or housing insecurity, maternal depression or substance abuse, and paternal incarceration.^{59–67} For many studies, SES was a controlled variable in order to determine associations with other psychosocial stressors, but an article by Garasky *et al.*⁶⁸ found that financial strain was positively associated with children being overweight or obese.

Besides familial stress, childhood depression has been associated with obesity. Blaine *et al.*⁶⁹ found that children who were depressed were two and a half times more likely to be obese than children who were not depressed. Similar associations were found in other studies examining children with depression, anxiety, stress, unhealthy peer relationships alone or in combination.^{65,70–73}

Prenatal Exposure

Research evaluating childhood obesity also examines how the child responds to shared environmental stressors between mother and child. Parental obesity is associated with infant and early childhood weight gain.^{10,74,75} Studies have shown an association

with a mother's weight gain during pregnancy and a child's increased risk of being obese later in life.^{74–76} To determine whether a mother's weight gain during pregnancy was the cause and not the infant's surrounding environment, two studies examined the mother and father's BMI values and their relationship to the child's BMI value and found that the association between maternal BMI and child BMI was statistically similar to the paternal BMI and child BMI, suggesting that increased adiposity could be more related to the postnatal environment and not a maternal effect.^{10,77}

Secondhand Smoke Exposure (SHS)

The role of prenatal cigarette smoke exposure and childhood obesity has long been a focus of many adverse health outcomes including obesity. These studies found an association between maternal prenatal smoking and childhood obesity even after accounting for various confounding factors.^{12,16,76,78–91} Although there is a compelling link between prenatal smoking and childhood obesity, it is not always clear-cut for both genders and all maternal smoking levels.^{86,87} One study followed children from 2 to 10 years of age and found that males whose mothers smoked during pregnancy had a lower BMI at age 2 years than those born to non-smoking mothers or had partners who smoked. The study further indicated that female offspring had a slightly higher BMI and this was not attenuated by adjusting for confounders.⁹²

Other studies not only looked at the mother's smoking status during pregnancy, but also the association with paternal smoking both during and after pregnancy. Weak paternal associations were found by Leary et al.⁸⁸ suggesting confounding by social factors rather than a direct effect from maternal smoking. Another study examined the role of parental smoking and childhood obesity and found an association from paternal smoking when the child was 6 years old. They further examined the paternal association as a confounder, but it only partially explained the effect of maternal smoking and childhood obesity, suggesting that paternal smoking might be a factor for obesogenic outcomes.⁹³

Community Stressors

Community stressors include the built and natural environments and neighborhood food outlets in a child's environment.

Built Environment

The built environment (BE) represents all infrastructure found in a community, including but not limited to roads, sidewalks, parks, trails, recreational facilities, neighborhood surroundings, playgrounds, buildings, and homes. These neighborhood characteristics can promote physical activity by increased active transport to work, school, and food sources.^{33,35,38,94} Much research pertaining to the BE is focused on the importance of community level factors in explaining dietary choices or physical activity, and links to various health outcomes, including obesity. Studies examining aspects of the BE found that property disorder, nuisances, violent and total crime were all associated with increased weight, while factors such as housing damage, vacancy, bars on doors/windows, and warning signs had no association with childhood obesity.^{95,96}

Researchers have used various approaches to examine associations between BE factors and childhood obesity.^{95–108} Evidence in the literature shows that improvements to the BE (e.g., places to exercise, green space, sidewalks, recreational areas, neighborhood safety, food access and healthier food options) will increase physical activity, potentially resulting in a decrease in obesity.^{94,97,98,109} Decreased activity levels have been found when these services are difficult to access.^{103,104,110} Lower activity levels due to a poorly structured and unsafe BE are associated with an

increase in obesity.⁹⁹ Rahman et al.³⁵ examined the decline in how children actively get to school by analyzing available data from the U.S. Department of Transportation. The analysis indicated a rapid decline in the percentage of children who walk or bike to school (42% in 1969 to 13% in 2001). In a 2009 survey, 84% of children either rode the bus or commuted in cars, largely due to a lack of neighborhood sidewalks and concerns about distance and traffic safety.³⁵

Daycares and schools can potentially affect children's health and well-being. Studies have indicated a higher BMI for children who received care from a center-/family-based facility or by a relative/nanny.^{101,105} Although these studies found a correlation with care outside the home and increased BMI, no clear underlying causal linkages were identified. It was suggested that there may be a need for interventions to promote awareness of activity levels and better nutrition.¹⁰¹ On the other hand, since children spend a lot of their time in school, they obtain physical activity by participating in teams, lessons, and gym class, suggesting that neighborhood physical characteristics such as traffic, density, and land use may be less relevant.¹⁰⁰

Neighborhood Food Outlets

Many food outlets readily accessible to children have poor dietary choices (e.g., fast-food restaurants, convenience stores, small food stores) with high fat, large portion sizes, and sugary drink options.^{111–113} Research shows that children who have easy access to poor quality food outlets tend to have a higher BMI and the potential to become overweight/obese when compared to children who do not have easy access to these food outlet types.¹⁰⁷ In addition, the built environment plays a critical role in how adolescents perceive distances and safety to these various food outlets. Studies show that these types of stores, when in close proximity to neighborhoods or schools, increased the likelihood of purchases made at these food outlet types.^{107,111–114} Sanchez et al.¹¹¹ indicated that minorities, specifically in neighborhoods that are predominantly Hispanic and African American, have a higher prevalence of obesity related to neighborhood food choices, and that 1/3 of all U.S. public middle and high schools have at least one fast food or convenience store within walking distance. In 2011, Leung et al.¹¹⁴ suggested that residents with more produce vendors or farmers markets nearby had a lower risk of being overweight/obese. On the other hand, Shier et al.¹¹⁵ found no consistent evidence to support the idea that more grocery stores lowered youth BMI or that greater exposure to fast-food restaurants, convenience stores, and small food stores increased BMI.

Natural Environment

The natural environment refers to parks, trails, and green spaces that provide opportunities for physical activity. Aspects of the natural environment are often considered within BE research studies, where they examine accessibility to recreational facilities and schools.^{33,94,97,102,116,117}

The literature indicates that greenness has many beneficial factors when it comes to influencing childhood obesity and activity levels. In a study that followed 9–10 year olds for 8 years, increased green space was significantly associated with lower BMI z-scores, suggesting that greener neighborhoods led to higher activity levels or more time spent outside.¹¹⁶ This correlation between increased proximity to large amounts of green space and reduced BMI levels remained consistent throughout other studies.^{97,102,118} Other studies examining activity levels and green space found that children living closer to parks and green spaces were more likely to be active and more creative than those who lived further away.^{119,120} While Potestio et al.¹²¹ found similar results with reduced risk of childhood obesity, once they incorporated other factors, the effect was reduced to non-

significant, suggesting that findings may differ depending on the type of urban environment being studied.

A review article by McCurdy *et al.*¹²² provides more examples of how nature and outdoor activity can improve a child's health. Studies included in their review suggested that for every additional hour spent outdoors, physical activity increased and the prevalence of children being overweight dropped.¹²² Increasing urbanization and population density can potentially reduce the green space available for active recreation, leaving school environments as the only available play areas, but if they are made of asphalt, they can only be used for certain types of activities. This limitation can be resolved with school playgrounds that maintain a greener landscape (trees, gardens, trails) that may stimulate activity.¹²³

Environmental Chemical Stressors

An obesogen is an environmental pollutant that inappropriately stimulates the development of adipose tissue, stores fat in existing cells, disrupts the energy balance controlling systems, alters tissue sensitivity to some neurotransmitters, or disturbs the activity of the autonomous nervous system.^{124,125} This term was coined in 2006 by Bruce Blumberg when he discovered that tin-based compounds given to pregnant laboratory mice predisposed offspring to weight gain.²⁹ This finding suggested that humans who have been exposed to certain types of chemicals during sensitive windows of development may be pre-programmed to store increased amounts of fat, resulting in a lifelong struggle to maintain a healthy weight and exacerbating the deleterious effects of poor diet and inadequate exercise.^{126,127} Endocrine disrupting chemicals interfere with the body's endocrine system and may adversely affect the metabolic system in humans by targeting the nuclear hormone proliferator-activated receptor gamma (PPAR γ). The number of environmental chemicals that may activate peroxisome PPAR γ is unknown, but much research indicates that activating PPAR γ is an important pathway for adipogenesis and obesity.^{128–132}

Although correlations between obesogens and obesity have been found in animal studies, there is a knowledge gap regarding how obesogens affect children's health. To overcome this gap, researchers use retrospective cross-sectional analyses to examine relationships, in addition to epidemiological studies specifically examining obesogens. Various chemicals have been studied, including flame retardants, polychlorinated biphenyls (PCBs), perfluorinated compounds (PFCs), bisphenol A, phthalates, pesticides and their degradation products, metals, and mixtures of air pollutants (Supplementary Table S4). However, the research community does not agree on whether chemicals should be considered obesogens. In the following sections, we explore the evidence surrounding these chemicals. For metals, bisphenol A, phthalates, and mixtures of air pollution, the evidence suggests linkages between exposures to these chemical classes and obesity; hence these chemical classes are described in the manuscript. For the others, the evidence is less clear, and those are described in the Supplementary Information.

Metals

Organotins, a suspected obesogenic chemical class, are the active ingredients in fungicides, miticides, wood preservatives, and heat stabilizers in polyolefin plastics, among many other uses.^{126,133,134} Organotins are considered ubiquitous and human exposure may occur from ingestion of drinking water and foods and direct contact with house dust.^{126,134,135} Although there is compelling evidence to suggest that organotins may be contributing to the obesity epidemic, there is a data gap concerning their effects on humans.^{126,134}

Toxic metals may contribute to obesity by potentially interfering with aspects of metabolism by substituting for essential metals

and micronutrients or by causing oxidative stress.¹³⁶ Toxic metals such as lead, cadmium, cobalt, antimony, barium, molybdenum, thallium, tungsten, and cesium have been examined for their role in causing obesity. Various studies have examined how metals may cause obesity during the early life course (prenatal exposure during pregnancy to early life stage environmental exposures) through ingestion or inhalation of low levels in air or secondhand smoke.^{136–138}

One study examined the association between BMI, waist circumference (WC) and toxic metals, adjusting for age, ethnicity, and gender, using participants aged 6–60 years from the National Health and Nutrition Examination Survey (NHANES). Of the nine metals examined (barium, cadmium, cobalt, cesium, molybdenum, lead, antimony, thallium, tungsten), for children aged 6–18 years, BMI and WC were negatively associated with cobalt and lead exposures and positively associated with barium exposures. The other metals had no significant associations with children's weight or WC.¹³⁶ In 2011, Afeiche *et al.*¹³⁷ examined prenatal lead exposures and the weight of children from the age of 0–5 years and found that maternal bone lead concentrations were associated with lower weight among female children but not male children. Another study found a negative association between maternal cadmium exposure and birth weight for girls and little evidence of any effect for boys, suggesting that gender could be a factor for susceptibility.¹³⁸ The inconsistent associations between metal exposure and weight suggest further research is needed.

Persistent Organic Pollutants

Persistent organic pollutants, including various flame retardants, PCBs, and PFCs, have been linked to childhood obesity in some research. These manmade compounds have been or are used in numerous products including many found in a child's environment. In addition, exposures may occur as a result of the compounds' distributions in food, water, air, and other environmental media. Because the results reported in the literature are inconsistent, these chemicals are further discussed in the Supplementary Information.

Biologically Non-persistent Pollutants

Bisphenol A (BPA), a monomer component of polycarbonate plastics, can be found in canned foods, food and beverage containers, and other consumer products.^{6,8,127} Research indicates that BPA has estrogenic properties, can interfere with endocrine signaling pathways, and may affect energy balance and glucose homeostasis.^{8,127,139}

BPA was measured in spot urine samples collected from pregnant women and children at ages 5 and 9 years as part of the CHAMACOS study. Results indicated that prenatal urinary BPA concentrations were negatively associated with BMI at 9 years of age in girls but not boys. Urinary BPA concentrations measured at 9 years of age were positively associated with BMI, WC, fat mass, and overweight/obesity in both boys and girls.¹⁴⁰ Contrary to these findings, in a different cohort, Yamano *et al.*¹⁴¹ found that after a five year follow-up, urinary BPA measurements had no association with BMI. Similar results were seen in other cross-sectional studies where older children had higher BPA concentrations that correlated to an increased risk of being overweight/obese, specifically in females.^{142,143} A cross-sectional study examining NHANES data (2003–2008) found that urinary BPA concentrations were significantly associated with obesity in children and adolescents after controlling for several cofactors.⁶ Another study using the NHANES data reported that non-Hispanic white boys were more likely to be overweight/obese, independent of other major risk factors, as a result of exposure to BPA.¹⁴⁴ To support these associations, more research is needed using longitudinal studies to confirm the findings observed in the available cross-sectional studies.^{6,142–144}

In 2008 (^{ref. 145}) and 2010 (^{ref. 150}), Hatch et al. examined the associations between various urinary phthalate metabolites and BMI values and WC from NHANES. For adolescent girls, they found that BMI values and WC increased with increases in urinary monoethyl phthalate (MEP) concentrations, but were inversely related to increases in urinary mono(2-ethylhexyl)phthalate (MEHP) concentrations. They found no associations between BMI, WC, and phthalate metabolites measured for children aged 6 to 11 years.^{145,150} Trasande et al.¹⁵¹ performed stratified and whole-sample cross-sectional analyses for NHANES children aged 6–19 years (2003–2008) and found that low molecular weight phthalate metabolites were associated with increases in obesity in non-Hispanic black children.¹⁵¹ Other studies have reported similar results in spite of weak statistical evidence that phthalates increase a child's weight.^{152–154} While most phthalate research has

Air pollution (such as PAHs, ozone, PM_{2.5} and PM₁₀, carbon monoxide (CO), nitrogen oxides (NO_x)) has been linked to various

adverse health outcomes such as asthma, cardiovascular disease, inflammatory responses, neurocognitive difficulties, and obesity.^{160,161} These adverse health outcomes may affect a child's ability to engage in physical activities, which may impact his/her weight.¹⁶² Prenatal air pollution exposures (PAHs, NO_x, CO, PM) associated with birthweight have found either no associations or low birthweight, except for one report by Rundle *et al.*, where prenatal exposures to PAHs were associated with obesity at age 7 years.^{160,161,163–170} Jerrett *et al.*^{162,171} examined the relationship between BMI levels in children and traffic density, air pollutants, and proximity of roadways to residential areas. In both studies, exposure to air pollutants resulted in increased BMI levels.

DISCUSSION

Obesity is a critical health issue affecting millions of children worldwide, with the number of overweight or obese pre-school aged children projected to increase to approximately 60 million by 2020 (ref. 2). This review illustrates the myriad plausible contributors to childhood obesity. Literature discussing various chemical and non-chemical stressors associated with childhood obesity was collected and categorized into individual, family, community, or chemical exposures from the total environment where children live, learn, and play. When studies of chemical and non-chemical stressors were compared, inconclusive or contradictory results were sometimes observed, suggesting that obesity is a complex problem and the scientific community is far from finding evidence to support a single stressor responsible for childhood obesity.^{172,173}

The vast majority of obesity research focuses on non-chemical stressors such as SES, diet, the built environment, and activity. Figure 2 illustrates that 67% of the articles in this literature review focused on non-chemical stressors and, in general, reported a causal link between one non-chemical stressor of interest and obesity. Some studies do account for non-chemical stressor confounders, but lack data on chemical exposures that occur within a particular environment. For instance, parental smoking status is measured in many studies of non-chemical stressors as a surrogate for chemical exposure. While exposure to the chemicals in cigarette smoke is important, they are certainly not the only chemical agents to which children are exposed across their life stages.

Over the last decade, much research has considered the role of obesogens in affecting childhood obesity. A common theme is that obesogens are ubiquitous, man-made chemicals with multiple routes of exposure, acting on the same metabolic pathways, suggesting the importance of cumulative exposures. Much of the research conducted for chemical responses employs animal studies, where outcomes and trans-generational responses can be observed in a relatively short period of time.^{127,147,148,174–176} Based on the selection scheme detailed in this paper's methodology, only 33% of the studies included in the literature review considered environmental chemical exposures that were not a consequence of prenatal cigarette smoke exposure or physician-prescribed medications. The most common chemical exposures included perfluorinated compounds, phthalates, and outdoor air pollution. As with much of the non-chemical stressor research, many of the chemical exposure studies included covariates such as SES, nutrition, and activity.

Research on chemical stressors as factors in childhood obesity is relatively new and new methods and technologies are being created to support this novel research. There are vast numbers of chemicals to which children are exposed in their total environment and the lack of information in the literature would suggest more research needs to focus on environmental exposures and childhood obesity. The literature focused on chemical exposures and obesity outcomes is limited, and often involves cross-sectional studies that are not necessarily designed to answer questions on

cause and effect. Positive associations between exposures and obesity across all chemical and non-chemical stressors is difficult to observe due to inconsistencies in data collection, duration of exposure time, age at outcome measurement, study types, logistical challenges of early life exposures and measurements of similar stressors (diet, activity).

A few studies included more than one potential confounder and though they were able to capture a more complete picture of the exposure scenarios, the studies were cross-sectional by design.¹⁵¹ Complex cohort studies like CHAMACOS, the German Ulm Birth Cohort, and the Danish National Birth Cohort have used a more comprehensive approach, incorporating both chemical and non-chemical stressors such as diet, activity, television watching, SES, secondhand smoke, and maternal and infant weights. While this mix of chemical and non-chemical stressors is more indicative of real-world exposures, these studies examined chemical exposure only *in utero* or from cord blood—not continuously through the follow-up years.^{158,177–179}

Finding cumulative, multiplicative, and possibly antagonistic effects among the myriad stressors is daunting, but it is important whether we want to explore the argument that multiple stressors are at play in childhood obesity. It is important for researchers to obtain accurate and complete measurements to fill the data gaps so that we can better understand the onset of obesity and potential opportunities to evaluate interventions relevant to child-specific environments. Examining relationships among stressors may also determine which stressors could be easily modified by interventions to reduce obesogenic behaviors and exposures. Many stressors are interconnected, and their effects should be examined while accounting for multiple covariates, confounders, and effect modifiers.

To encourage integrated transdisciplinary thinking and hypothesis generation, researchers from diverse fields (such as medicine, genetics, behavioral and environmental sciences) need to work together. They should also join with those in economics, marketing, communications, and policy, alongside industry partners, urban planners, community leaders, and transportation designers to produce environments that are conducive to children's health and well-being.¹⁸⁰ Designing research to encompass all stressors related to obesity will be costly and logistically challenging, but robust prospective longitudinal and translational studies can begin to bridge existing knowledge gaps, and possibly find subtle causalities.

Many studies use cross-sectional designs because they are more cost effective, can take a snapshot of different population groups at a single point in time, and generate large amounts of data. However, these types of studies lack definite conclusions regarding cause and effect.^{46,117,140,181–184} On the other hand, while longitudinal studies follow children for a period of time, these types of studies may be limited by the use of retrospective data, parent-based reporting, limited measurements of other covariates, imperfect or missing measurements of confounders, gaps in data reporting, or selection bias.^{165,185,186} Cross-comparison studies may prove difficult due to varying study designs and ages of the children. This situation is especially likely for measurements made during adolescence, when the onset of puberty can modify responses.

If we hope to combat childhood obesity, large longitudinal cohort studies that begin in the prenatal period will be essential to understand the complex interrelationships between the myriad chemical and non-chemical stressors.¹⁸⁷ Studies like the perinatal prospective longitudinal study at Duke University, the Newborn Epigenetic Study (NEST), and the CHAMACOS study are representative of the types of longitudinal cohort studies needed to examine the effects of environmental exposures and nutrition, both *in utero* and during childhood.^{167,188}

Researchers suggest that childhood obesity may be an early adaptive response to epigenetic mechanisms that guide gene

expression involved with energy balance through DNA methylation.¹⁸⁹ Ongoing studies suggest that nutrition during pregnancy may affect the health status of children and may be passed down through generations. These epigenetic changes are thought to be explained by modifications in chemical markers that attach to susceptible loci in DNA.^{188,189} Determination of these epigenetic pathways acting on genes and proteins and how they may encode could eventually lead to prevention and treatment options.¹⁹⁰ When researchers propose this type of analysis, it will still be important to consider non-chemical stressors along with chemical agents to better understand epigenetic mechanisms that regulate metabolic states, and to determine if and when those factors incur changes leading to obesity.

This systematic review suggests that childhood obesity is multifactorial, where the interrelationships between chemical and non-chemical stressors may have an effect on a child's health and well-being. An integrative approach needs to be implemented to examine the child from a holistic point of view. To accomplish this, researchers need to take into account the well-being of the child through various lifestages, from early child development through adolescence. Tulve et al.³³ has designed a conceptual framework where a child's health and well-being is influenced by all the components of the built, natural, and social environments. A child's holistic health extends beyond a child's physical and mental health to include emotions, learning and development, physical safety, relationships, and material well-being. Children's health and well-being are ultimately the product of inherent factors (e.g., race, gender, genetics), as well as their activities and behaviors. However, as shown in this paper, health and well-being may be influenced by the interrelationships of chemical and non-chemical stressors found in the real-world environment where children live, learn, and play.

Limitations

A literature review of this magnitude is a tremendous undertaking, and while we strove to be systematic in our review, there is still the possibility that we missed relevant articles. For this review, the literature search was limited to PubMed and Google Scholar and covered the time period of January 2004 to July 2014. Only peer-reviewed literature was included in this review. Since our focus was on chemical and non-chemical stressors and the interrelationship of these stressors in impacting child health and well-being (i.e., obesity), we did not include research published in non-life science fields (such as economics or political science).

Due to the vast number of stressors encountered in the literature, it was important to organize the stressors for easier reference. We recognize that other organizational methods could have been used to present the information but found separating them into four major categories that coincide with the conceptual framework outlined in Tulve et al.³³ allowed for clear organization and focus to present the information. A holistic understanding of childhood obesity begins with the individual child and their behaviors/habits formed as a result of their surroundings. The second section contained family and social stressors that impact and influence children's behaviors or exposures to which the child had no control. The third section incorporated the built and natural environments in the community, thereby encompassing their total environment. The final section incorporated all the environmental chemicals to which children may potentially be exposed.

CONCLUSIONS

This comprehensive review of the childhood obesity literature set out to examine the interrelationships between chemical and non-chemical stressors which may play a role in childhood obesity. This

review shows how numerous chemical and non-chemical stressors are linked to childhood obesity, but does not claim to have exhausted the list of plausible contributors that are yet to be discovered or are in the early stages of being linked to the obesity epidemic. This review provides information on the complexities and possible interactions between chemical and non-chemical stressors in a child's environment and how these impact childhood obesity. By better understanding the interactions of chemical and non-chemical stressors contributing to childhood overweight and obesity, we can begin to inform community decision makers on how to promote healthy, child-specific environments and provide solutions to improve overall community health and well-being.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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