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RESEARCH ARTICLE

OBESOGEN CONSUMPTION AS A SILENT RISK FACTOR FOR CHILDHOOD OBESITY

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ABSTRACT

Childhood and adolescent rates of obesity and overweight are continuing to increase in much of the world. Most of them begin as early as the ages of 5 and 6 years, or during adolescence. Obesity is indeed a major public health concern due to its huge negative impact on the society at large which is well supported by evidence-based literatures. Risk factors such as diet composition, excess caloric intake, decreased exercise, genetics, and the built environment are active areas of etiologic research. Current evidence proposes that the systemic responses to exposure to environmental factors could potentially increase the risk of excess weight. The effects of exposure to these chemicals known as obesogens are of crucial importance during developmental phases of life. By considering the adverse trans-generational effects of obesogen chemicals on human health, the global obesity epidemic should be considered as a multifactorial complex disorder necessitating the emphasis of public health interventions for environmental protection.

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INTRODUCTION

Obesity is a public health concern because of its association with a number of medical complications that lead to both increased morbidity and mortality. Studies have shown that children between the ages of 10 to13 who are overweight has an 80 percent chance of becoming obese adults unless they adopt and maintain healthier range of body weights (A. Janesick, and Blumberg 2012). Several studies have also shown that childhood obesity will continue towards adolescence and adulthood obesity (Li, and Hooker 2010). Considerable advances have been made to treat obesity either through diet, exercise and behavioral modifications. However, despite this progress, prevalence of obesity has risen sharply over the last decade. The current trend in developed countries is the enormous cost of high technology and tertiary healthcare needed to diagnose and manage the high incidence of obesity-related complications. Similar demands in Malaysia will impose a huge burden on the human and economic resources of the country and are liable to disturb priorities in the healthcare or other sectors. This article will present the prevalence of childhood obesity, interaction of obesogen and childhood obesity, source of obesogen in environment and pathophysiology of causation.

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Prevalence of obesity among children globally: In 2005 to 2006, Health Behavior School-aged Children survey by Currie (2008) was carried out in 36 countries and this survey has found that the prevalence of overweight and obese among adolescence was 5-25%. The prevalence of overweight is higher among the boys (16%) compared to girls (12%) (Merrill, and Birnbaum 2011). Another author reported, more than half of all United States adolescents are overweight in which 19% were obese (Cupul-Uicab *et al*. 2013). Similar findings from the National Health and Nutritional Examination Survey (NHANES) carried out in the United States, also showed an alarming prevalence of overweight and obesity even among younger children. The most Recent NHANES 2011-2012 data recorded prevalence of obesity of 16.9% in youth and 34.9% in adults (A. S. Janesick, Shioda and Blumberg 2014). WHO estimated that there were 40 million or 6.0% of world population of preschool children who were overweight (World Health Organization 2010). Looking at the global trend of obesity among children it is projected that the prevalence will continue to become worse. In 2010, WHO ranked Malaysia as the sixth country in Asia with the highest prevalence of obesity. WHO data showed 60.0% Malaysians were overweight. What is more worrying is that 38.0% of them were children. There was an increase in obesity in Malaysia i.e. 6.6% for the children aged 7 and 13.9% for the children aged 10 years old (World Health Organization 2010).

Obesogen and Childhood Obesity: As in adults, several factors have been shown to be associated with the development

of childhood obesity, including nutrition, physical activity, sleep, socioeconomic status, parental obesity, birth weight and genetics. The most common complications are type II diabetes, hypertension, dyslipidemia, cardiovascular disease (CVD), gallstones and cholecystitis, respiratory dysfunction and certain cancers (Sabramani *et al*. 2015). These diseases represent far too great a burden for policy-makers, healthcare providers and researchers to ignore. Although the increasing prevalence of obesity is usually attributed to changes in diet, physical activity, and underlying genetic susceptibility, the possibility that environmental chemicals could influence obesity is relatively underexplored. Early life exposure to environmental chemicals is beginning to be examined as a contributing cause of the obesity epidemic. One view is that the interaction between genetics and the modern environment work to intensify an individual's propensity towards developing obesity, acting via early metabolic programming that occurs in the womb. Another is that the environment plays a different role in obesity is via exposure to chemicals in the environment, whether due to exposure in the womb, or a lifetime of exposure. One of them is through ingestion of chemicals called obesogens. Some of these chemicals either from dietary, pharmaceutical or industrial compounds may predispose people to obesity through altering and disrupting normal bodily metabolic processes (Kelishadi, Poursafa and Jamshidi 2013).

Source of Obesogen: An obesogen has been defined as "an exogenous substance that causes adverse health effects in an intact organism, and/or its progeny, consequent to changes in endocrine function" (Darbre 2017). Another author, defined obesogen as "chemicals that inappropriately alter lipid homeostasis and fat storage, metabolic set points, energy balance, or the regulation of appetite and satiety to promote fat accumulation and obesity". Obesogens are also known as endocrine disrupters (Kabir, Rahman and Rahman 2015). Some of these compounds are present in nature (e.g. plant phytoestrogens), but the majority are synthetic chemicals which have been released by human activities into the environment without any prior knowledge of their effects on ecosystems or human health. The human population is now ubiquitously exposed to such chemicals in daily life, in indoor as well as outdoor environments, through their use in pesticides/ herbicides, industrial and household products, plastics, detergents, flame retardants and as ingredients of personal care products. Intake to the human body may be oral, inhalation or dermal absorption (Vollmer, and Mobley 2013).

Examples of obesogens

- Tributyltin (TBT) is an environmental contaminant from its use as a biocide in antifouling paints applied to the hulls of ships, and it has been reported to cause to masculine female fish. TBT can inhibit aromatase, which is the enzyme responsible for the conversion of testosterone into estrogens (Cupul-Uicab *et al*. 2013).
- Diethylstilbestrol (DES) is a synthetic non-steroidal oestrogen that was first synthesized in 1938 and then prescribed to several million women between 1940 and 1971 to prevent threatened miscarriage in the first trimester, before untoward side effects stopped further prescription. It has also been used to enhance fertility in farm animals used for meat supply (Merrill, and Birnbaum 2011).
- Persistent organic pollutants (POPs) are stable man-made compounds that do not readily degrade and tend to persist in the environment and bio accumulate. Many are lipophilic and therefore become stored in fatty tissues, passing up the food chain in animal fat. From use as an insecticide, both dichlorodiphenyltrichloroethane (DDT) and its breakdown product dichlorodiphenyldichloroethylene (DDE) remain widely present in human adipose tissue and are endocrine disrupters (Valvi *et al*. 2014). Polychlorinated biphenyls (PCBs) are industrial POPs which are also widely measurable in human adipose tissue and have been shown to be endocrine disrupters (Darbre 2017).
- Bisphenol A and phthalates are used in the manufacture of plastics. Bisphenol A (BPA) is used for its cross-linking properties in the manufacture of polycarbonate plastics and epoxy resins, which are now ubiquitous in consumer products such as water bottles, linings of water pipes, coatings on food and beverage cans, thermal paper and dental sealants. It is listed as a high production volume chemical by the Organization for Economic Cooperation and Development (OECD). It can leach out from plastic containers and has endocrine-disrupting properties. Phthalates are esters of phthalic acid and are used mainly as plasticizers to increase the flexibility, transparency and durability of plastic materials. They are found in many consumer products including adhesives, paints, packaging, children's toys, electronics, flooring, medical equipment, personal care products, air fresheners, food products, pharmaceuticals and textiles. Many of the phthalates are also listed by the OECD in their 2004 list of high production volume chemicals and possess endocrine-disrupting properties (Valvi *et al*. 2013).
- Polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls are widely used as flame retardants. They are now detectable in human tissues and have endocrine-disrupting properties through interference in thyroid function (Erkin-Cakmak *et al*. 2015).
- 4-Nonylphenol is one of the long-chain alkyl phenols used as a surfactant in industrial and domestic applications worldwide which is listed as a high production chemical by the OECD and is an endocrine disrupter due to its estrogenic activity.
- Parabens (alkyl esters of p-hydroxybenzoic acid) are used as antimicrobial agents for the preservation of personal care products, foods, pharmaceutical products and paper products. They are widely present in human tissues including breast tissue and have estrogenic properties (A. S. Janesick *et al*. 2014).
- Phytoestrogens are produced naturally by plants and as such are ingested by humans in the diet in edible plant material. Isoflavones such as genistein and daidzein are found in soybeans, legumes, lentils and chickpeas. Phytoestrogens are so named for their estrogenic activity. On the general assumption that naturally occurring compounds are more beneficial than synthetic compounds, phytoestrogens have been embraced much more positively by society than the synthetic xenoestrogens, and as such, potential benefits tend to have been overemphasized compared with adverse effects, such as those potentially related to obesity (Valvi *et al*. 2014).

Pathophysiology of Obesogen in Children: When organs and tissues are developing, they are particularly at risk to toxic insult. This was first observed decades ago in the case of lead and other metals which could harm neurological development as a result of *in utero* and childhood exposures. This concept also applies to agents that alter metabolic homeostasis during development, which can lead to obesity, diabetes, and metabolic syndrome. In particular, exposure to toxicants during the organogenesis of tissues involved in metabolic homeostasis, e.g. adipose, liver, skeletal muscle, pancreas and brain, may play an important pathophysiological role in the development of childhood obesity (Kabir *et al*. 2015). Whereas much of organogenesis occurs prenatally, adipose, skeletal muscle, pancreas, and brain continue to develop postnatally. It remains possible that fetal adaptations to toxic metabolic insults restrict the scope of adaptive responses to a toxic postnatal environment. If this were the case, one could envision DOHAD (Developmental Origins of Human Adult Disease) similar to the multistage carcinogenesis hypothesis, where risk of obesity results from multiple toxic insults that temporally span the various stages in which metabolic tissues are developing (Merrill, and Birnbaum 2011).

Other pathways of action of these obesogens are

- **Obesogens acting on sex steroid receptors:** Estrogens in the adult are protective against abdominal obesity and metabolic disease whereas perinatal oestrogen exposure has the opposite effect. Foetal or neonatal oestrogen exposure can have the opposite effect and lead to obesity later in life. Dichlorodiphenyl-dichloroethylene (DDE), the major metabolite of the pesticide DDT, is both an oestrogen receptor activator and an anti-androgen (Buckley *et al*. 2016). Mother who lived along the Lake Michigan shoreline where they were exposed to high levels of DDT, were more likely to have a child that exhibited elevated BMI in adulthood. More recently, new studies showed that prenatal exposure to DDE was associated with rapid weight gain in human infants and elevated BMI later in infancy. Whilst some obesogens may act directly through cellular steroid receptors, while other obesogens may act less directly by stimulating oestrogen synthesis. Adipose tissue is known to be a site of oestrogen synthesis, and the cytoplasm of adipocytes contains the cytochrome P450 enzyme aromatase which converts testosterone to oestrogens. Several EDCs are now known to be able to influence intracellular aromatase activity and could therefore act indirectly to raise the intracellular levels of oestrogen in adipocytes with a consequent increase in obesity (A. S. Janesick *et al*. 2014).

- **Obesogens and glucocorticoid metabolism:** In addition to the sex steroid receptors, disruption of another nuclear hormone receptor regulated signaling pathway, the glucocorticoid receptor, is known to contribute to obesity (Darbre 2017). Obesity is linked to a general increase of positive feedback within the hypothalamic pituitary-adrenocortical (HPA) axis, leading to an over secretion of cortisol from the adrenal gland. Therefore, excess glucocorticoid levels in adipose depots are likely to stimulate local adipogenesis (A. Janesick, and Blumberg 2012).

Conclusion

The current evidence proposes that the systemic responses to exposure to environmental factors, notably during developmental phases of life, could potentially increase the risk of excess weight in children. By taking into account the current knowledge on the adverse trans-generational effects of obesogen chemicals on human health, the global childhood obesity epidemic should be considered as a multifactorial complex disorder necessitating the emphasis of public health interventions for environmental protection.

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Glossary of Abbreviations

BPA	bisphenol A
CVD	cardiovascular disease
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DES	diethylstilbestrol
DOHAD	
HPA	hypothalamic pituitary-adrenocortical
NHANES	
OECD	Organization for Economic Cooperation and Development
POPs	persistent organic pollutants
PBDEs	polybrominated diphenyl ethers
PCBs	polychlorinated biphenyls
TBT	tributyltin
WHO	World Health Organization

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