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Nontraditional Risk Factors for Obesity in Modern Society

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Overweight and obesity, which have rapidly increased around the world in recent years, are significant health problems. They can lead to various morbidities, including cardiovascular diseases, cerebrovascular diseases, type 2 diabetes, some types of cancer, and even death. Obesity is caused by an energy imbalance due to excessive calorie intake and insufficient energy consumption, and genetic factors and individual behavioral problems are also known to be major contributing factors. However, these are insufficient to explain the surge in obesity that has occurred in recent decades. Recent studies have suggested that environmental factors arising from the process of socioeconomic development and modernization contribute to this phenomenon. These environmental factors include light pollution due to artificial lighting, air pollution, endocrine-disrupting chemicals, and reduced exposure to green spaces due to urbanization of residential areas. In this manuscript, the findings and mechanisms of these novel risk factors causing overweight and obesity are reviewed.

Key words: Obesity, Risk factors, Environmental pollution, Endocrine disruptors

INTRODUCTION

Overweight and obesity are among the most important health problems facing modern society worldwide. The World Health Organization (WHO) reported in 2016 that more than 1.9 billion adults (18 years and older) were overweight; of these, more than 650 million adults had obesity.[1] This figure means that 39% of adults were overweight and 13% obese. In fact, the worldwide prevalence of obesity nearly tripled between 1975 and 2016.[1] Similarly, the prevalence of obesity in Korea has increased by 6% (from 32.6% to 38.5%) in the last 10 years.[2] Currently, overweight and obesity are associated with more deaths than malnutrition and underweight in all parts of the world except for sub-Saharan Africa and Asia.[1]

Obesity has become a global health problem beyond individual health concerns because it is closely associated with the increased prevalence of chronic diseases, such as high blood pressure, dyslipidemia, coronary heart disease, stroke, type 2 diabetes, and some types of cancer.[3] Obesity appears as fat accumulation from high caloric intake and insufficient energy consumption, and many studies have shown that genetic factors and personal behavior play important roles as causes of obesity.[4-7] However, this is insufficient to fully explain the surge in overweight and obese populations in recent decades. Economic and social development and the urbanization of residential areas have brought about positive effects in modern society, such as convenience of living and affluent life, but detrimental results also exist. Accompanying negative effects include reduced physical activity, increased environmental pollution, com-

plex surroundings, and increased stress. Because studies have suggested that novel environmental factors in modern society may have caused the recent surge in obesity, these studies and their evidence are reviewed.

DISRUPTION OF CIRCADIAN RHYTHM AND LIGHT POLLUTION

Almost all living organisms have a self-regulating transcriptional-translational feedback loop that generates oscillations in a period of approximately 24 hours. This endogenous timekeeping mechanism is called a circadian clock.[6] The circadian clock controls many aspects of an organism's physiology and is affected by external stimuli, such as light, food, and temperature.[8,9] The main function of the circadian clock/rhythm is to maintain homeostasis by ensuring adaptive physiological responses to changing environments. For example, gene expression, transcription factors, signaling pathways, hormone secretion, energy metabolism, growth, and behavior are rhythmically regulated by the circadian system.[10,11] Therefore, disturbance of the circadian rhythm has a long-term effect on health and may be associated with the development of obesity in relation to lipid metabolism.[12] The main component of the circadian system in mammals is located in the suprachiasmatic nucleus (SCN) of the hypothalamus and consists of more than 20,000 neurons. The SCN interacts with peripheral circadian clocks, such as the heart, liver, stomach, adipose tissue, and pancreas.[13]

Various hormones, such as melatonin, leptin, and glucocorticoids, have a light-dark cycle and are involved in the regulation of feeding, lipid metabolism, and fat accumulation.[14,15] Melatonin is a pineal hormone synthesized at high levels during the night and at low levels during the day according to circadian patterns,[16] and its role in lipid metabolism has been widely reported. For example, in studies using mice, knockout of the melatonin receptor led to systemic insulin resistance, and these mice showed more fat mass, weight gain, and leptin resistance.[17,18] Leptin is mainly synthesized and secreted by white adipose tissue and peaks during the sleep phase in diurnal animals, such as humans, and during early to midnight in nocturnal animals, such as mice.[19] Leptin plays an important role in food intake, energy expenditure, lipid metabolism, and insulin sensitization,[20,21] and leptin resistance in obese people is as-

sociated with obesity and metabolic disease due to circadian dysfunction.[22] Glucocorticoids are regulated through the hypothalamus-pituitary-adrenal axis, and blood levels peak before the active phase (early morning) in humans.[23] Glucocorticoids are involved in lipid and glucose metabolism, and high concentrations of glucocorticoids are generally observed in obesity.[24]

Recently, artificial light at night (ALAN) has been suggested as an environmental factor that induces obesity. The invention of electricity enabled activities without distinction between day and night, resulting in positive effects, such as convenient life and social and economic development.[25] However, it has also caused exposure to ALAN, such as indoor lighting, road lighting, store signs, television screens, and smartphone and tablet devices used before bedtime or during sleeping. Because most organisms have developed endogenous circadian rhythms that are synchronized to the daily light/dark cycle, exposure to ALAN may disrupt the circadian rhythm and alter the secretion pattern of various hormones, leading to metabolic diseases, including obesity.[26]

Animal studies have provided evidence that exposure to artificial lighting can directly affect circadian rhythms, resulting in weight gain and obesity. Fonken et al.[27] exposed mice to complete darkness or dim light during the night and found that exposure to dim light at night altered circadian clock genes and protein rhythms, changed feeding behavior, and led to rapid and sustained body weight gain. There was no difference in total daily caloric intake between the two groups, but mice exposed to dim light at night consumed more food during the light period and less food during the dark period than mice housed on dark nights. Both the central clock rhythm (the amplitude of Per1 and Per2 rhythms was attenuated in the hypothalamus) and the peripheral clock rhythm (Rev-Erb expression was attenuated in the liver and adipose tissue) were altered in mice exposed to dim light at night. Similar results were found in human studies. An analysis using satellite images of nighttime illumination combined with country-level data on the prevalence of overweight and obesity showed that ALAN is a significant contributing factor to excessive body mass.[28] Zhang et al.[29] also showed that higher outdoor light at night, estimated from satellite imagery, is associated with higher odds (12% in men and 19% in women when the highest quintile group was compared with the lowest quintile group) of developing obesity over 10 years in non-obese American adults.

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Park et al.[30] investigated the relationship between ALAN exposure during sleeping and the prevalence and risk of obesity in women aged 35 to 74 years old recruited in 50 U.S. states and Puerto Rico from 2004 through 2009. ALAN was categorized as no light, small nightlight in the room, light outside the room, or light or television in the room. At baseline, having any ALAN exposure was positively associated with a higher prevalence of obesity and abdominal obesity. Furthermore, turning on the television or turning on the light in the room while sleeping was associated with a weight gain of 5 kg or more (relative risk [RR], 1.17; 95% confidence interval [CI], 1.08–1.27), body mass index (BMI) increase of 10% or more (RR, 1.13; 95% CI, 1.02–1.26), incident overweight (RR, 1.22; 95% CI, 1.06–1.40), and incident obesity (RR, 1.33; 95% CI, 1.13–1.57) compared to cases without ALAN exposure. These data suggest possible contribution of ALAN in the development or aggravation of obesity, and further studies on its precise mechanisms are warranted.

ENVIRONMENTAL POLLUTION AND PARTICULATE MATTER

Environmental pollution, which increases with industrialization, is reaching a level that threatens human health. In fact, it has been reported that 4.2 million people die per year as a result of exposure to fine particulate matter (PM).[31] PM is one of the major air pollutants. Particles with a diameter of 10 μm or less are classified into particulate matter (PM_{10}), and those with a diameter of less than 2.5 μm are classified into fine particulate matter ($PM_{2.5}$).[32] PM is known to contain various chemical components, such as nitrates, sulfates, and polycyclic aromatic hydrocarbons, as well as endotoxins, cell fragments, and various metal components.[33] $PM_{2.5}$ can enter cells more easily than PM_{10} due to its smaller size, and $PM_{2.5}$ entering the respiratory tract can therefore affect other tissues, such as the cardiovascular system and gastrointestinal system. The most commonly known mechanism of disease induction by PM is cytotoxicity caused by oxidative stress. PM entering the respiratory tract promotes the generation of active radicals, causing oxidative stress in lung tissue and activating intracellular stress signaling molecules, such as p53 and c-Jun N-terminal kinase (JNK), and transcription factors, such as nuclear factor kappa B (NF-κB) and activator pro-

tein 1 (AP-1). It also induces the expression of inflammatory cytokines, such as interleukin (IL)-1 and IL-6. These increased inflammatory cytokines promote cytotoxicity in tissues exposed to PM and induce various diseases.[34,35]

Recently, studies on the effect of $PM_{2.5}$ on metabolic diseases have emerged. Continuous exposure to PM is known to increase the local inflammatory response, hepatic endoplasmic reticulum stress, and insulin resistance.[36,37] In animal experiments, long-term exposure to $PM_{2.5}$ has been shown to activate the transcription factor NF-κB-related inflammatory protein complex, increase insulin resistance,[38] and induce macrophage infiltration and lipid deposition in white adipose tissue.[39] The hypothalamus maintains energy homeostasis by synthesizing nerves and regulating nutritional and hormonal signals. In particular, leptin receptor-expressing neurons in the hypothalamus nuclei are important for regulating food intake and energy expenditure, and leptin signaling through proopiomelanocortin (POMC) neurons promotes anorexigenic effects while increasing energy expenditure.[40,41] Toll-like receptor 4 (TLR4) contributes to insulin resistance and obesity, which activates signaling pathways of the inhibitor of NF-κB kinase subunit beta and NF-κB transcription factor. Thus, it increases the expression of proinflammatory genes.[42,43] Campolim et al.[44] investigated whether a reaction similar to the metabolic effect of a high-fat diet appeared when exposed to $PM_{2.5}$ in mice fed a chow diet. Compared to the filtered air group, the group exposed to $PM_{2.5}$ for 5 days had increased microglial density and expression of TLR4 and inhibitor-NF-κB-kinase-epsilon (Ikbkε); meanwhile, the amount of fat and food intake increased. In addition, in the group exposed to $PM_{2.5}$ for 12 weeks, decreased hypothalamic STAT3 phosphorylation and POMC expression were found, which were accompanied by increased food intake and low energy expenditure, leading to obesity along with increased leptin resistance and insulin resistance. In a rodent model, exposure to Beijing's highly polluted air was associated with more weight gain in pregnant rats and their offspring.[45]

Deschenes et al.[46] analyzed the relationship between air pollution and body weight in China using data from the China Health and Nutrition Survey. As a result of the analysis of 13,471 adults, when the average $PM_{2.5}$ concentration increased by 1 μg/m³ over the previous 12 months, the BMI increased by 0.27%, and there were increases in overweight and obesity rates by 0.82% and 0.27%, respec-

tively. A study consisting of 41,439 schoolchildren from China demonstrated that the obesity risk increased by 10% per 10 μg/m³ increase in $PM_{2.5}$ exposure.[47] A longitudinal study in overweight and obese Latino children investigated the association of exposure to nitrogen dioxide or $PM_{2.5}$ with adiposity, and concluded that both pollutants induced more rapid increases in BMI and central adiposity. A 4 μg/m³ difference in long-term $PM_{2.5}$ was associated with a 3 kg/m² higher BMI and a 2% higher body fat percentage at age 18 years.[48] Another Chinese study from a high pollution area showed that a 19 μg/m³ increase of PM_{10} was also associated with increased prevalence of overweight (8%) and obesity (12%), which were more apparent in women than in men.[49] However, a systematic review including 16 human studies suggested mixed results. Among a total of 66 reported associations between air pollution and weight status, 44% found a positive association, and 44% reported a null finding.[50] Therefore, well-designed prospective studies should be performed in various populations in the future.

ENDOCRINE-DISRUPTING CHEMICALS

Evidence suggests that interactions between environmental factors and genetic factors can lead to acquired obesity.[51,52] Endocrine-disrupting chemicals (EDC) are defined by the WHO as "exogenous chemicals or mixtures of chemicals that alter the function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, its progeny, or (sub)populations." Recent studies have shown that some of them are obesogenic by inducing altered epigenetic gene regulation.[53-55] EDC can occur naturally, such as plant estrogens, but they penetrate deeply into daily life in the form of synthetic compounds, such as pesticides, detergents, food packaging materials, internal coatings for metal cans, various plastic products, and thermal receipts. The human body is easily exposed to EDC through ingestion of contaminated water and food, inhalation, and skin contact. Even a small dose can have a strong effect and cause effects decades after exposure or even in descendants.[56]

EDC causes obesity and related metabolic diseases by binding to or interfering with hormone receptors, disrupting the homeostasis system in the body and the metabolism of lipid tissues with hormone receptors.[57,58] EDC is mostly lipophilic and can be stored in adipocytes for a long time. The number of adipocytes produced during early development is permanently established, and weight gain in adults occurs due to an increase in the size of existing adipocytes.[59] In addition, early lifetime EDC exposure affects epigenetic programming of obesity by activating or inhibiting nuclear receptors and the expression of target genes, creating a permanently increased number of adipocytes and altered metabolic set points. This increases the potential risk for obesity and metabolic diseases.[60,61]

Peroxisome proliferator-activated receptor-γ (PPARγ) is highly expressed in adipose tissue and is a key molecule that regulates adipogenesis. It regulates triglyceride accumulation, glucose metabolism, and insulin sensitivity in mature adipocytes as well as differentiation into adipocytes.[62] EDC acts as a ligand for PPARγ, mutating DNA methylation of PPARγ or its target genes.[63,64] Therefore, in a process that relies on binding to PPARγ with relative regulation of the PPARγ-inducing gene, mesenchymal stem cells can be preferentially introduced toward differentiation into adipocytes, potentially promoting the development of adipose tissue during early development. In addition to binding to PPARγ, EDC promotes provincial cell differentiation through a variety of regulatory pathways, including agonistic effects on estrogen, glucocorticoid, and aryl hydrocarbon receptors.[65,66] EDC, referred to as an obesogen, includes tributyltin, diethylstilboestrol, persistent organochlorine, bisphenol A (BPA), and phthalates. In particular, BPA and phthalate exposure can easily occur in daily life.[67,68]

BPA is a lipophilic molecule with estrogen activity that accumulates in adipose tissue and interferes with the adipose tissue differentiation mechanism. As a material for producing epoxy resin and polycarbonate plastic, it is used in baby bottles, the inside coat of cans, food containers, and dental treatment materials and the human body is easily exposed through oral ingestion.[69] Evidence suggests that exposure to BPA is associated with obesity in animal and human experiments. In animal experiments, Rubin et al.[70] found that Sprague-Dawley rats with perinatal exposure to BPA exhibited apparent weight gain immediately after birth and continued to gain weight until adulthood. In humans, BPA was shown to inhibit the release of adiponectin from adipose tissue, which is known to lower the likelihood of obesity-related diseases.[71] Carwile and Michels[72] analyzed the association between urinary BPA and BMI and waist circumference (WC) using data from the National Health and Nu-

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trition Examination Survey (NHANES) 2003–2006 and concluded that high BPA exposure is related to general and central obesity in adults.

Phthalates are used to increase the flexibility of plastic products; they are used in children's toys, food packing, medical devices, shampoos, and cosmetics. The human body is easily exposed to them through skin absorption, inhalation, or ingestion of contaminated materials.[73] Several *in vivo* and *in vitro* studies have shown that phthalates can promote obesity through anti-androgen effects, anti-thyroid hormone activity, and activation of PPARs.[74-77] Studies have also analyzed the cross-sectional relationship between phthalates and obesity in humans based on data from NHANES in the United States. Stahlhut et al.[78] demonstrated that urinary monoethyl phthalate (MEP), monobenzyl phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-oxohexyl) phthalate had positive correlations with WC in adult men. There was a positive correlation between female urinary MEP, monobutyl phthalate, MEHHP and BMI or WC.[79,80] A recent study based on the data of NHANES 2007–2010 found that high molecular weight phthalate was associated with an increased risk of obesity in adult men, while di(2-ethylhexyl) phthalate was associated with increased obesity in women.[81]

REDUCED GREEN SPACE

Urbanization of residential environments reduces the chances of human contact with green spaces, and accumulating evidence suggests that changes in the built environment may be related to obesity. In this regard, exposure to green spaces around residential areas (accessibility and availability of areas with vegetation, such as parks, gardens, and forests) has attracted more attention in recent years.[82,83] The exact mechanism for the association between green spaces and obesity is not yet known, but several hypotheses have been proposed regarding the pathophysiological pathway of obesity.[84,85] First, living close to green space increases opportunities and motivation for physical activity, and increases in physical activity can act as a strong protective factor against obesity.[86] Second, high levels of stress can lead to obesity.[84] Green spaces are known to alleviate exposure to harmful environments, such as noise and air pollution, and can help relieve stress, making them an environmental

resource for psychological recovery.[86] In addition, access to green spaces can provide opportunities for social interaction. Glonti et al.[87] suggested that high social bonding and cohesion are associated with a low risk of obesity.

Studies have shown that the presence of green spaces around residential areas has a positive effect on lowering obesity. A longitudinal study of people living in Finnish urban areas examined the relationship between the proximity of green spaces and BMI. Living at a distance exceeding 750 m compared to living at a distance less than 250 m from green spaces increased the incidence of overweight (odds ratio [OR], 1.50; 95% CI, 1.07–2.11). In addition, an analysis of people who moved during the study showed that the incidence of obesity increased (OR, 1.49; 95% CI, 1.08–2.06) when moving away from green spaces (from < 250 m to > 250 m).[88] Rundle et al.[89] surveyed 13,102 people in New York City and reported that a closer distance between large parks and residences was associated with a lower BMI (β, −1.69; 95% CI, −2.76 to −0.63), and Toftager et al.[90] reported that the incidence of obesity was higher in those living more than 1 km away from green spaces than in those living within 300 m (OR, 1.36; 95% CI, 1.08–1.71). However, research results on the relationship between the proximity of green spaces and BMI are not always consistent.[91] Luo et al.[91] reviewed epidemiological studies on green spaces and overweight/obesity published before January 2020 and conducted a meta-analysis on 57 studies in seven countries. They found that 55% of the studies reviewed reported an association between green space and lower odds of overweight/obesity in overall or subpopulations.

CONCLUSION

Recent studies have suggested that the surge in obesity prevalence may be due to novel environmental factors that occur in the process of developing into a modern society. This review focused on light pollution, air pollution, EDC, and reduced greenspace (Table 1, Fig. 1), but many more unknown nontraditional risk factors for obesity might exist. The exact mechanism by which these factors contribute to obesity has not yet been fully identified, and the associations are not always consistent. However, there is ample evidence to support the fact that the environmental factors described above are associated with an increased prevalence of obesi-

Table 1. Representative human studies on the effect of nontraditional risk factors of obesity

Study population	No. of participants	Exposure	Main finding	Reference
ALAN				
Non-obese American adults (age, 50–71 yr)	239,781	Outdoor light at night (by satellite imagery)	12% (Men) and 19% (women) higher odds of obesity in the highest quintile group	29
Women in US and Puerto Rico (age, 35–74 yr)	43,722	ALAN while sleeping	19% Increase in the risk of incident obesity by ALAN exposure while sleeping 17% Increase in the risk of gaining ≥ 5 kg and 13% increase in the risk of BMI increase ≥ 10% by sleeping with a television or a light on	30
PM				
Chinese adults (age, 18 yr or older)	13,741	$PM_{2.5}$	1 µg/m³ Increase of $PM_{2.5}$ in the past 12 months increases overweight and obesity rate by 0.82 and 0.27 percentage points, respectively	46
Overweight and obese Latino children (age, 8–15)	314	$PM_{2.5}$	4 µg/m³ Difference in long-term $PM_{2.5}$ was associated with a 3 kg/m² higher BMI and a 2% higher body fat percentage at age 18	48
Chinese adults (age, 18–74 yr)	24,845	PM_{10}	19 µg/m³ Increase of PM_{10} was associated with increased prevalence of overweight (8%) and obesity (12%)	49
Endocrine disrupting chemicals				
U.S. adults (age, 18–74 yr)	2,747	Bisphenol A	Higher odds of obesity (76%) and abdominal obesity (58%) in the highest quartile group	67
Women in US (age, 18 yr or older)	6,005	Phthalates	Positive association between BMI and MBP (OR, 1.13) or MEHP (OR, 1.12) Positive association between WC and MBP (OR, 1.13) Positive association between MEHP/MEHHP and BMI (OR, 1.21) or WC (OR, 1.20)	75
Reduced green space				
Employees in Finland	25,317	Distance to green space	Higher odds of overweight (OR, 1.50) in persons living > 750 m vs. < 250 m from a usable green area Higher odds of obesity (OR, 1.49) when moving away from the proximity of a green area (from < 250 m to > 250 m)	83
Danish adults (age, 16 yr or older)	21,832	Distance to green space	Higher odds of obesity (OR, 1.36) in persons living more than 1 km from green space than those living closer than 300 m	85

ALAN, artificial light at night; BMI, body mass index; PM, particulate matter; $PM_{2.5}$, particulate matter with a diameter of less than 2.5 µm; PM_{10}, particulate matter with a diameter of 10 µm or less; MBP, monobutyl phthalate; OR, odds ratio; MEHP, mono-2-ethylhexyl phthalate; WC, waist circumference; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate.
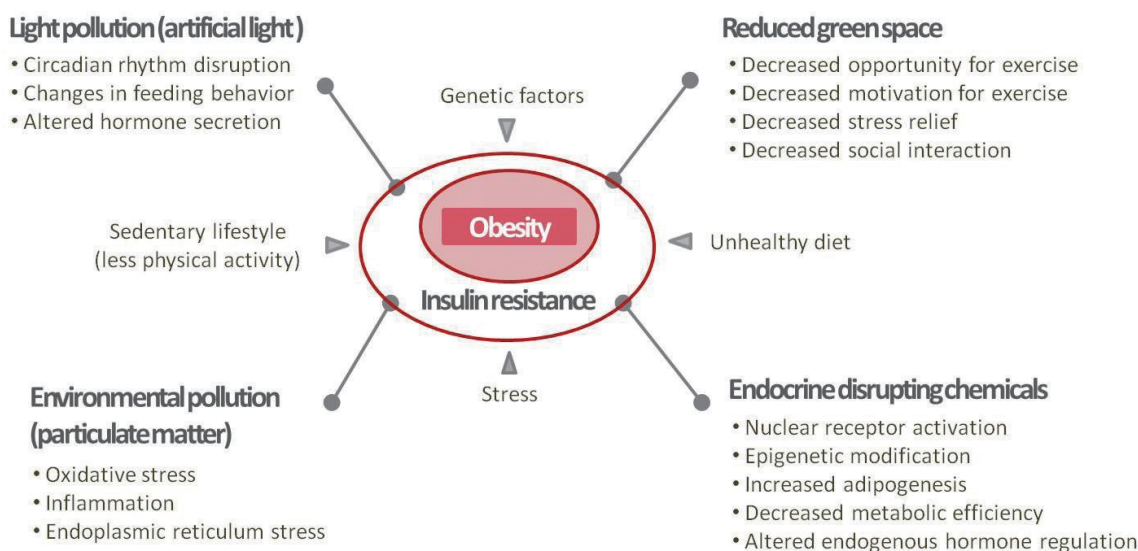

Figure 1. Nontraditional risk factors and their proposed mechanisms for obesity.

ty. Therefore, additional studies investigating the relationship and the mechanism of underrecognized risk factors for obesity should

be continued. This would be important for bending the curve of the obesity epidemic and finally reducing the personal and public

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medical and socioeconomic burden.

CONFLICTS OF INTEREST

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

Study concept and design: SHL; drafting of the manuscript: SJH; critical revision of the manuscript: SHL; obtained funding: SHL; study supervision: SHL.

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