

# Modern environmental and lifestyle risk factors, oxidative stress, perturbed epigenetic processes, and increasing incidence of neurodevelopmental, neurodegenerative and neurological disorders

Császár N<sup>1,2</sup>, Kapócs G<sup>3,4</sup>, Erdöfi-Szabó A<sup>5</sup> and Bókkon I<sup>2,6\*</sup>

<sup>1</sup>National University of Public Services, Budapest, Hungary.

<sup>2</sup>Psychosomatic Outpatient Clinics, Budapest, Hungary.

<sup>3</sup>Buda Family Centred Mental Health Centre, Department of Psychiatry and Psychiatric Rehabilitation, Saint John Hospital, Budapest, Hungary.

<sup>4</sup>Institute for Behavioral Sciences, Semmelweis University, Budapest, Hungary.

<sup>5</sup>BioLabor Biophysical- and Laboratories Services Ltd., Budapest, Hungary.

<sup>6</sup>Vision Research Institute, Neuroscience and Consciousness Research Department, Lowell, MA, USA.

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## ABSTRACT

Our goal is not to describe a single harmful environmental or lifestyle risk factor in great detail, as most scientific articles do. In contrast, we aim to point out that human beings are continuously and simultaneously exposed to countless kinds of harmful environmental and lifestyle risk factors. First, we briefly review and evaluate several environmental, technological, and lifestyle risk factors. We point out that each of these can be associated with perturbed oxidative and epigenetic processes, and the onset of various diseases, including neurodevelopmental, neurodegenerative, and neurological disorders, with a worldwide increasing prevalence. In addition, disturbed epigenetic changes by modern technological innovations and lifestyle risk factors can be inheritable to offspring and subsequent generations. Furthermore, disturbed epigenetic changes may also accumulate in the genome. Finally, diverse environmental and lifestyle risk factors may enhance vulnerability and decrease the resilience of modern humans.

**Keywords:** Modern environmental and lifestyle risk factors, oxidative stress, perturbed epigenetic processes, neurodevelopmental, neurodegenerative and neurological disorders.

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\*Corresponding author. E-mail: bokkoni@yahoo.com. Fax: +36 30 208 57 26.

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## INTRODUCTION

New technologies, lifestyle changes, urbanization, innovations in chemical, biological and physical technology made our lives more comfortable. At the same time, more and more scientific studies revealed that these environmental, technological, and lifestyle risk factors (like plastics, artificial electromagnetic environment, endocrine-disrupting chemicals, addictive drugs, hospital birth with separation of mothers and their newborns, internet, novel ingredients like preservatives, artificial flavors and sweeteners, hormonal contraceptives, etc.) can also have significant adverse effects. Moreover, the developing nervous system of the

fetus and young children is particularly vulnerable to exposure to risk factors like modern environmental, lifestyle and social stressors (Bölte et al., 2019; Guzylack-Piriou et al., 2021; Perlroth and Castelo Branco, 2017; Ross et al., 2015).

In addition, in reality, humans are incessant and simultaneously exposed to numerous modern environmental and lifestyle risk factors that can be associated with the onset of various diseases. Furthermore, physical harmful risk factors of the environment cannot be separated from lifestyle or sociological risk factors considering the occurrence of

various disorders (Lederbogen et al., 2013). There is probably a direct causal relationship between the environmental and lifestyle risk factors and the onset/development of diverse diseases.

In the next sections, we briefly evaluate several important risk factors of the modern human environment, originating from innovations in chemical, biological and physical technology, as well as modern, urbanized lifestyle. We point out that each of these risk factors can be associated with oxidative stress\* and various perturbed epigenetic\*\* processes. We should consider that the brain is highly susceptible to oxidative stress due to its high oxygen consumption and lipid-rich content (Salim, 2017). We also show that evaluated risk factors are also associated with one or more neurodevelopmental, neurodegenerative, and neurological disorders. It is probable that these disturbed epigenetic changes may accumulate in the genome, and are inheritable to offspring and subsequent generations (Takeshima and Ushijima, 2019). These risk factors may enhance vulnerability and decrease the resilience of modern human beings (Gottschalk, et al., 2020; Dudley et al., 2011; Zannas and West, 2014).

Our aim is not to review a single harmful environmental or lifestyle risk factor in greater detail, as most scientific studies do. In contrast, we aim to point out that human beings are continuously and simultaneously exposed to numerous kinds of harmful environmental and lifestyle risk factors.

## AIR POLLUTION

Air pollution results from a complex mixture of thousands of pollutants, including particulate matter (PM) and trace gases (SO<sub>2</sub>, NO<sub>2</sub>, CO and O<sub>3</sub>) produced via diverse industrial, commercial, and individual processes (Mao et al., 2018). PM is not a single toxicant but a mixture of carbon, crustal elements, heavy metals, polycyclic aromatic hydrocarbons (PAHs), and inorganic ions (Gao et al., 2018). Microscopic pollutants in the air can penetrate our respiratory and circulatory systems, damaging our lungs, heart, and brain. Particle pollution (also termed particulate matter or PM) is a mixture of solids and liquid droplets floating in the air. The size of the particles determines the level of particle penetration into the respiratory system or bloodstream. PM with a diameter between 2.5 and 10 µm (PM<sub>2.5</sub> and PM<sub>10</sub>) can penetrate the bronchi. PM with a diameter less than 2.5 µm can reach the alveoli and can enter the bloodstream (Philip et al., 2014; Ferrari et al., 2019).

The lack of visible smog is no indication that the air is healthy. According to World Health Organization (WHO, 2018), the harmful effects produced by air pollution are responsible for about 8 million premature deaths every year. Urban populations are especially exposed to air pollution.

Current studies have revealed that outdoor air pollution will be the major environmental cause of premature death over the next few decades (Khomenko et al., 2021; Cariolet et al., 2018). Traffic-related air pollution (TRAP), among them particulate matter (PM), black carbon (BC), ozone (O<sub>3</sub>), nitrogen oxides (NO<sub>x</sub>), and polyaromatic hydrocarbons (PAHs) have been associated with perturbed DNA methylation, histone modifications, and Non-coding RNA expression (Rider and Carlsten, 2019; Kupsco et al., 2020). Air pollution has harmful effects on human health associated with cardiovascular diseases, metabolic disorders, lung diseases (including asthma and chronic obstructive pulmonary disease (COPD)), female infertility, cancers, Alzheimer's disease, among others (Boda et al., 2019; Kim et al., 2018; Reyes-Caballero et al., 2019; Conforti et al., 2018; Calderón-Garcidueñas et al., 2020). Mental disorders are also associated with exposure to air pollutions (Buoli et al., 2018; Lee et al., 2019; Bernardini et al., 2019). It was revealed that long-term exposure to PM<sub>2.5</sub> and short-term exposure to PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, CO significantly increased the risk of depression (Zeng et al., 2019). According to WHO (2020): "Depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease."

The central nervous system (CNS) of a growing fetus during pregnancy and young children are especially sensitive and vulnerable to exposure to air pollutions. Chronic exposure to PM during pregnancy is associated not only with various birth complications such as pre-term birth, low birth weight, spontaneous abortion, childhood asthma but with neurodevelopmental impairment and neurological disorders, among them (Saha et al., 2018).

Increasing evidence suggests that neuroinflammation and cerebral oxidative stress can be key factors in the pathogenesis of air pollution-induced cerebrovascular and neurological disorders (Hahad et al., 2020). Furthermore, air pollution, particularly PM<sub>2.5</sub> and NO<sub>x</sub>, is known to affect the CNS, causing systemic inflammation, neuroinflammation, and oxidative stress (Kim et al., 2020). Zhou et al. (2019) revealed that prenatal air pollutant exposure leads to oxidative stress in newborns. It was also proposed that air pollutants disturb the mitochondrial processes via reactive oxygen species (ROS) that can initiate redox-sensitive signaling mechanisms and cause irreversible epigenetic changes (Shukla et al., 2019). Thus, air pollution produced irreversible epigenetic modifications (epimutations) that may be intergenerationally and/or transgenerationally transmitted (Ferrari et al., 2019).

## HEAVY METALS

In the last decades, abundant studies presented evidence that most intracellular and extracellular signal processes are directly or indirectly linked to redox-

regulated reactions (see in \*Footnote).

Although heavy metals are natural constituents of the earth's crust, these metals are one of the most hazardous groups of biological important pollutants. In the last decades the rapid pace of industrialization and urbanization worldwide increased anthropogenic activities (i.e. mining and agricultural activities, industrial activities, traffic and energy production, chemical industry, etc.) that caused pollution of air, water, and soils that threaten plant, animal, and human health, as well as the quality of the environment (Ali et al., 2019; Vareda et al., 2019; Srivastava, et al., 2017).

There is no exact definition of heavy metal, but they can be defined as metallic elements that have a relatively high density compared to water (Banfalvi, 2011). Any toxic metal may be considered a heavy metal, irrespective of its atomic mass or density (Singh et al., 2011). Some heavy metals at low concentrations - such as cobalt (Co), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), and zinc (Zn) - are essential inorganic nutrients for normal physiological processes of plants and animals, since they are co-factors for numerous enzymes and proteins (Jaishankar et al., 2014; Singh et al., 2011). However, high concentrations of these metals can be toxic to organisms. Heavy metals can enter the human body through food, water, air, or absorption through the skin. Various toxic heavy metals - like lead, mercury, cadmium, arsenic and nickel, aluminum, etc. - are present in many cosmetics (color cosmetics, face and body care products, hair cosmetics, herbal cosmetics, etc.), and can act directly on the skin or be absorbed through the skin, pass into our blood, accumulate in our body and could produce toxic effects in various organs (Borowska and Brzóška, 2015).

The harmful effects of heavy metals are mainly due to the perturbation of redox processes that lead to oxidative stress. Namely, heavy metals can induce ROS production, which leads to lipid peroxidation, thus impairing membranes, proteins, DNA. Redox-active metals, like Fe or Cu can generate ROS directly. However, several heavy metals (e.g. Pb, Cd, Ni, AL, Mn, and Zn) cannot produce ROS directly, so these generate ROS by indirect processes, such as via stimulation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, displacing essential cations from specific binding sites of enzymes (Jaishankar et al., 2014; Wu et al., 2016). Pb can be toxic by the depletion of antioxidants, but the Cd indirectly generates ROS by replacing iron and copper (Wu et al., 2014). Heavy metals may also perturb various metabolic processes through the production of reactive oxygen species causing oxidative damage and health-related adverse effects (Fu and Xi, 2020; Valko et al., 2016).

It could be important that in the real environment the living systems usually interact with a mixture of heavy metals. However, metal mixtures can produce higher toxicities compared to the individual metal exposition by

synergistic, antagonistic or additive processes (Karri et al., 2018; Wu et al., 2016).

Heavy metals can pass the blood-brain barrier and retain themselves for a longer period of time in it (Gilani et al., 2015). It was proposed, that heavy metals may be associated with neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease and Alzheimer's disease (AD) via oxidative stress, mitochondrial dysfunctions, perturbed protein turnover, and brain inflammation (Monnet-Tschudi et al., 2006; Jomova et al., 2010; Cicero et al., 2017). The adverse effect of heavy metals can also be associated with neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation (Gorini et al., 2014). Cognitive functions can also be perturbed by heavy metals (Karri et al., 2016).

Toxic metals could perturb Deoxyribonucleic acid (DNA) methylation, histone modification, and non-coding RNA expression (Ryu et al., 2015; Fragou et al., 2011). Metals can activate or silence transcription via epigenetic processes. Prenatal exposure to arsenic (As) and lead (Pb) produces epigenetic changes via DNA methylation that may result in the later development of disease (Nye et al., 2014). Heavy metal exposure like arsenic, cadmium, chromium, lead, mercury, and nickel are also associated with cancer, genetic and epigenetic factors (Koedrih et al., 2013).

Aluminum (Al) is one of the most commonly found elements in the Earth's crust. The human population nowadays is exposed to aluminum (Al) not only through diet but by antacids, vaccine adjuvants, and antiperspirants. But several studies have found that Al is harmful to health. The toxicity of aluminum is controversial because Al toxicity is complex and depends on its chemical and physical forms, the characteristics of the local environment, especially pH, relative solubility in water, etc. (Willhite et al., 2014; Mold et al., 2020; Łukasz et al., 2020).

Al is a metalloestrogen (inorganic xeno-estrogens, which affects gene expression of human cells responding to estrogen) and estrogen is a risk factor for breast cancer (Darbre, 2016). ADRB2 5'-UTR methylation is a biomarker of asthma severity (adrenoceptor beta 2, (ADRB2), 5' untranslated region (5'UTR)). Nafea et al. (2020) found an association between high blood aluminum concentration and high blood ADRB2 5'-UTR methylation level. Al<sup>3+</sup> produced cellular damage and reduced proliferation and migration in neural progenitor cells (NPCs) (Reichert et al., 2019). It was also suggested that aluminum exposure may be associated with Autism-spectrum disorder and Alzheimer's disease (Mold et al., 2018; Mirza et al., 2017).

## PESTICIDES

Pesticides are diverse chemicals like insecticides, herbicides, fungicides, rodenticides, etc. (Mostafalou and

Abdollahi, 2017) that are intended to kill unwanted insects, plants, molds, and rodents. There is numerous evidence that pesticides produce various human chronic diseases affecting the nervous, reproductive, renal, cardiovascular, and respiratory systems, among them (Mostafalou and Abdollahi, 2012). Pesticides can enter the body through different routes such as direct contact with chemicals, ingestion (particularly fruits and vegetables, or contaminated water), or inhalation of polluted air. Many pesticides have been identified as endocrine disruptors (synthetic chemicals that mimic the actions of natural hormones due to structural similarity (Mnif et al., 2011) that cause harm to people, especially to fetuses and children. Metabolic pathways of fetuses (prenatal) and children (peri- and postnatal) are immature and thus, their ability to metabolize and excrete toxic chemicals is different from adults (Fernandez et al., 2011; Landrigan and Goldman, 2011).

Several toxic effects of pesticides can be produced by oxidative stress. Namely, pesticides can alter cellular redox equilibria by the accumulation of reactive oxygen species (ROS), lipid peroxidation, DNA damage, and impairment of antioxidant enzyme functions (Čermak et al., 2018; Banerjee et al., 2001; Abdollahi et al., 2004; Ledda et al., 2021; Limón-Pacheco and Gonsebatt, 2009).

Prenatal exposure to organophosphate pesticides produced negative effects on child mental development (González-Alzaga et al., 2014). Pesticides can reduce birth weights, disturb cognitive development, and induce higher rates of cancer (Guidice et al., 2017; Whyatt et al., 2004; Van-Maele-Fabry et al., 2010). Pesticide exposure during pregnancy is associated with neurodevelopmental disorders like autism spectrum disorders (ASD) or developmental delay (DD) (Shelton et al., 2014). It seems that Parkinson- and Alzheimer-diseases, asthma, various autoimmune diseases and reproductive disorders can also be associated with pesticide exposure (Mostafalou and Abdollahi, 2013).

Various pesticides perturb the gene expression via non-coding Ribonucleic acids (RNAs), histone deacetylases and DNA methylation patterns suggesting their role in epigenetics (Sabarwal et al., 2018). Pesticides may cause cancer via epigenetic mechanisms by modification of gene promoter DNA methylation levels (Zhang et al., 2012). Occupational exposure to pesticides is associated with differential DNA methylation (regarding lung diseases) (van der Plaats et al., 2018). Vinclozolin or DDT exposure can produce transgenerational epigenetic dysregulation (i.e. perturbed expression of long noncoding RNAs (lncRNAs) and small noncoding RNAs (sncRNAs)) in ovarian granulosa cells that could promote the development of diseases such as Ovarian Insufficiency (POI) and Polycystic Ovarian Syndrome (PCOS)) (Nilsson et al., 2018). Paraquat (a toxic herbicide, primarily for weed and grass control) inhibited the proliferation of human neural stem cells via reduced

DNA methylation by suppressing the protein expression and transcription of DNA methyl transferase (DNMTs) (Huang et al., 2019).

## PLASTIC POLLUTION

Bisphenols (ubiquitous endocrine-disrupting chemicals) are extensively used in the manufacture of polycarbonate plastics, epoxy resins, and thermal paper. Approximately 8 million tons of Bisphenol A (BPA) are produced worldwide annually, and about 100 tons could be released into the atmosphere within one year (Vandenberg et al., 2010). Bisphenols are released from these materials depending on temperature and pH and migrate into food, air, skin, saliva, and blood (Acconcia et al., 2015). Thus, most people are exposed almost continuously to bisphenols directly by oral and topical routes, and indirectly via environmental pollution and the food chain.

Bisphenols (Bisphenol A, 4,4'-dihydroxy-2,2-diphenylpropane, (BPA)) and its analogs as Bisphenol B (BPB), Bisphenol C (BPC), Bisphenol S (BPS), Bisphenol F (BPF) and Bisphenol AF (BPAF)) have similar or even more toxic effects compared to BPA (Ullah et al., 2019). BPA can be detected in most people's serum and urine (Fredericket al., 2014). Bisphenols could bind to androgen-, estrogen-, progesterone-, thyroid hormone-, and arylhydrocarbon-receptors and through disrupting their normal functions, cause abnormal regulation within various systems in the body like endocrine, reproductive, respiratory, and nervous systems (Acconcia et al., 2015). Bisphenol analogues have endocrine disruption, cytotoxicity, genotoxicity, reproductive toxicity, dioxin-like, and neurotoxicity effects (Chen et al., 2016). Since bisphenols can migrate into food stored, in materials containing them, the packaged foods and drinks are the major sources of harmful exposure to bisphenols (Adeyi and Babalola, 2019). BPA produces oxidative stress, mitochondrial dysfunctions, inflammatory responses, and apoptosis (Wang et al., 2019; Yang et al., 2009; Xin et al., 2014; Kabuto et al., 2004; Meli et al., 2020). BPA induces necrosis, apoptosis and genotoxicity in a concentration-dependent manner. The toxic effect of BPA probably could be generated via oxidative stress-associated mitochondrial apoptotic pathway (Huang et al., 2018).

Studies have revealed that bisphenol toxicity is associated with obesity, impaired lipid and glucose homeostasis, Type 2 Diabetes Mellitus, cardiovascular diseases, cytokines and chemokines, among others (Mirmira et al., 2014; Han et al., 2016; Menget al., 2018; Chen et al., 2018). Bisphenol toxicity is also linked to reproductive abnormalities such as premature puberty, ovarian dysfunction, implantation failure, abnormal sperm function, fertilization failure, sex hormone abnormality, premature birth, and lower birth weight (Kim et al., 2019).

The studies also found that gestational and childhood Bisphenol A exposure was associated with ASD, ADHD, anxiety, and depression in children (Perera et al., 2016; Stein et al., 2015; Xu et al., 2015). It is especially noteworthy that BPA is not metabolized well in children with ASD (Stein et al., 2015).

According to several investigations, BPA can have significant toxicity in the reproductive system via its estrogenic and anti-androgenic effects, especially in males, but the mechanisms are still unclear (Ferguson et al., 2014; Cariati et al., 2019; Hong et al., 2016; Scinicariello et al., 2016; Caporossi and Papaleo, 2015; Nakamura et al., 2010). Prenatal and peripubertal exposure to phthalates or BPA is associated with increased SHBG (Sex Hormone Binding Globulin) levels and decreased testosterone levels (Ferguson et al., 2014). SHBG is produced mainly in the liver, which transports testosterone, dihydrotestosterone (DHT), and estradiol in the blood as biologically inactive forms. Toxic estrogenic and anti-androgenic effects of BPA on the vertebrate brain and reproductive organs may perturb the development of sex-specific neurodevelopmental mechanisms, physiology and behavior (Inadera, 2015; Frye et al., 2012).

Since BPA can bind to estradiol-receptors (estrogen receptor alpha (ER $\alpha$ ) and estrogen receptor beta (ER $\beta$ )) with an approximate 104 -fold lower affinity than estradiol (E2), these developmental effects of BPA cannot be explained by its mere estrogenic activity (Hiroi et al., 1999). Recently it was revealed, that in utero exposure to BPA decreased methylation of *Hoxa10* (Homeobox A10 is a protein-coding gene that is directly involved in the embryogenesis of the uterus) (Bromer et al., 2010). In experiments by Jorgensen et al. (2016) pregnant mice were exposed to an environmentally relevant dose of BPA that produced changes in the global expression and methylation pattern of uterine genes and special hypomethylation of ER $\alpha$  binding genes in mice.

Shoaff et al. (2019) revealed that exposure to antiandrogenic phthalates during adolescence produced maladaptive behaviors, like externalizing behavior, developmental social disorders (DSD) behaviors, and decrements in adaptive skills. Witchey et al. (2019) found that prenatal exposure of juvenile rats to BPA could abolish sex differences in oxytocin receptor (OTR) expression in three hypothalamic regions and that male OTR expression may be more susceptible. DNA methylation of *Bdnf* (encoding BDNF, a brain-derived neurotrophic factor is a member of the neurotrophin family of growth factors), *Fkbp5* (encoding FKBP5, binding protein that is involved in the regulation of neuroendocrine stress mechanisms), and *Grin2b* (encoding NR2 subunit of the N-methyl-d-aspartate (NMDA) glutamate receptor) genes are involved in brain development and function. Alavian-Ghavanini et al. (2018) found that developmental BPA exposure reduced methylation levels in *Grin2b* in females, but not in males

in the rat hippocampus. In humans, the authors found a sexual dimorphic link where prenatal BPA exposure was associated with higher methylation levels of *GRIN2B* gene methylation in 7-year old girls, but not in boys of the same age. The observed opposite associations between BPA exposure and *Grin2b* methylation in humans compared to rats may reflect differences between species (Faulk et al., 2016). There is increasing evidence that endocrine-disrupting chemicals (EDCs), like bisphenol A (BPA) and genistein (GEN), can be harmful to the brain and behavior. These harmful effects are associated with perturbed epigenetic processes including DNA methylation, histone modifications, and non-coding RNAs (Martini et al., 2020; Butler et al., 2020).

However, there is increasing evidence that numerous and diverse chemical substances have epigenetic toxicity (Marczylo et al., 2016; Ideta-Otsuka et al., 2017). Epigenetic toxicity means a chemical substance can produce harmful effects on living organisms, though affecting epigenomes, which may explain the long-term effects of chemical substances and the predisposition to various diseases due to environmental factors including chemicals. It seems that in utero exposure to BPA (or to diverse chemical substances) could produce permanent epigenetic changes in exposed offspring. In addition, perturbed epigenetic processes by environmental endocrine disruptors may also be transgenerationally inherited (Brieno-Enrriquez et al., 2015; Krishnan et al., 2019; Skinner et al., 2011; Wolstenholme et al., 2012, 2013; Fan et al., 2018).

## ARTIFICIAL SWEETENERS

Sugar substitutes (artificial sweeteners or non-nutritive sweeteners, NNS) are food additives that have been widely used in our modern diet: in baking, soft drinks, candy, canned food, powdered drink mixes, jams, pudding, dairy products, and jellies, etc. According to the Food and Drug Administration (FDA), the five main artificial sweeteners are aspartame, neotame, saccharin, acesulfame potassium, and sucralose (Neacsu and Madar, 2014). Although artificial sweeteners were developed to reduce insulin resistance and obesity, there is increasing evidence that these compounds can contribute to various diseases. NNS is associated with chronic inflammation, metabolic syndrome, obesity, type 2 diabetes, gut microbiota perturbation, glucose intolerance, increased risk of hypertension, cardiovascular disease, among others (Pearlman et al., 2017; Bian et al., 2017; Kim et al., 2016; Fowler, 2016). NNS can perturb the energy balance, metabolic hormone secretion, and cognitive processes that may be mediated by activation of sweet taste receptors in oral and extraoral tissues (e.g. intestine, pancreatic  $\beta$  cells, and brain), and alterations of the gut microbiome (Burke and

Small, 2015; Rother et al., 2018). Zhu et al. (2017) found associations between intrauterine exposure to artificially sweetened beverages (ASBs) and birth size and risk of overweight/obesity at 7 years in offspring. Aspartame was found in over 6,000 food items, and millions of American adults and children consume aspartame each day. Aspartame is associated with adverse neurobehavioral health outcomes, like anxiety and depression (Choudhary and Lee, 2018; Lindseth et al., 2014; Guo et al., 2014).

NNS is also associated with perturbed redox regulations. Aspartame exposure produces increased ROS generation and lipid peroxidation, reduced glutathione (GSH) concentration, increased superoxide dismutase activity (SOD) and glutathione peroxidase levels (GPx), increased catalase activity (CAT), and reduced glutathione reductase (GR) activity (Iyyaswamy and Rathinasamy, 2012; Ashok et al., 2017). The long term aspartame exposure can modify the brain's antioxidant status and induce mitochondrial-mediated activation of apoptosis in the brain (Ashok and Sheeladevi, 2014). Specifically, in Ashok and Sheeladevi's (2014) experiments the gene and protein expression of pro-apoptotic Bax presented a conspicuous increase while the anti-apoptotic Bcl-2 decreased noticeably indicating the aspartame could be harmful at a cellular level in the rat brain. Iyyaswamy et al. (2018) found that aspartame metabolites could be a contributing factor for the development of oxidative stress in the brain.

Various mechanisms were proposed for the adverse effects of NNS like the stimulation of intestinal sugar absorption, disruption of the ability of sweet taste to signal caloric consequences, increased appetite, impaired glycemic or insulin responses (Fowler, 2016). NNS uncouples sweet taste and caloric consequences, thus, misleading the sweet taste receptors (STRs), which can disrupt an organism's ability to predict the metabolic consequences of sweet taste. STRs are expressed throughout the body, not only in taste buds but also in pancreatic islet cells, bladder, gastrointestinal tract (mainly expressed in entero-endocrine cells), brain, bone and adipose tissues (Laffitte et al., 2014; Park et al., 2019). So, misleading the STRs and the gut microbiota may play a central role in the development of various diseases caused by NNS.

Trillions of microbes in the human gut take an active part in most physiological and pathophysiological processes that affect host health throughout the life cycle (Zhuang et al., 2019). More and more studies have revealed that artificial sweeteners are harmful to the intestinal bacterial ecosystem (Wanf et al., 2018; Suez et al., 2015; Bian et al., 2017; Frankenfeld et al. 2015). The major adverse effects of artificial sweeteners may be produced via perturbation of the gut microbiota and fecal metabolite profiles. For example, Chi et al. (2018) has reported that neotame consumption dramatically increased the concentrations of multiple fatty acids, lipids,

and cholesterol in the feces in mice. In contrast, neotame decreased malic acid and glyceric acid (Chi et al., 2018). Mice exposed for 11 weeks to high doses of commercial formulations of saccharin, sucralose or aspartame produced glucose intolerance by perturbation of the gut microbiota (Suez et al., 2014, 2015).

The gut-brain axis is a continuous bidirectional communication system between the brain and the gut. This bidirectional communication involves several afferent and efferent pathways such as the vagus nerve and the hypothalamic-pituitary-adrenal (HPA) axis that is essential in the maintenance of homeostasis (Carabotti et al., 2015). Disruption of the normal microbiota causes dysbiosis (shift in the microbiota composition) that impairs the crosstalk between the gut-brain axis and changes in microbial metabolites, which could lead to numerous intestinal and extra-intestinal disorders, including those of the CNS (Lynch and Pedersen, 2016).

Short-chain fatty acids (SCFAs, acetate, propionate and butyrate) are produced by the gut microbiota during the fermentation of partially- and non-digestible polysaccharides. SCFAs possess neuroactive properties that may play a key role in microbiota-gut-brain crosstalk (Silva et al., 2020). SCFAs may change BBB integrity, can cross into the CNS and, modulate the levels of neurotransmitters and neurotrophic factors (Silva et al., 2020).

Thus, the adverse effects of artificial sweeteners may be produced by misleading the sweet taste receptors and changed microbial metabolites. The changed microbial metabolites (like SCFAs) may induce perturbed metabolic and epigenetic changes in host tissues as a response to the artificial sweeteners (Silva et al., 2020; Miro-Blanch et al., 2019; Collison et al., 2013).

## HORMONAL CONTRACEPTION

Currently, about 842 million women of reproductive age in developing countries use contraceptive methods (WHO, 2020). There are three main formulations of hormonal contraception that can be administered orally, by injections, subcutaneous implants, and by intrauterine devices. These hormonal contraceptions include: monophasic combination pills (they contain equal amounts of the hormones estrogen and progestin for an entire month's cycle); multiphasic combination pills have varying amounts of estrogen and progestin (this type of pill follows the changing hormone levels during a woman's menstrual cycle more closely); progestin-only pills (it does not contain estrogen, and it may not have as many side effects) (Egarter, 2020; Van Vliet et al., 2006).

Oral contraceptives (OCs) can perturb the pituitary-ovarian axis and the hypothalamus-pituitary-adrenal axis (Willis et al., 2006; Kirschbaum et al., 1999). OCs can also perturb carbohydrate and lipid metabolism (Krauss and Burkman, 1992). OCs increase the risk of



cardiovascular diseases, in particular the risk of venous thromboembolism, myocardial infarction, and stroke (Kaminski et al., 2013). Haarala et al. (2009) revealed that combined oral contraceptives (COCs) can alter the metabolic determinants and genetic regulation of C-reactive protein (CRP) which is a predictor of cardiovascular diseases.

Although the exact mechanisms of the harmful effects of oral contraceptives are unknown, various studies suggested that OCs may increase oxidative stress via lipid peroxidation and overproduction of ROS that could increase the risk of thromboembolic events and vascular complications (Kowalska et al., 2018; Kowalska and Milnerowicz, 2016; Chen and Kotani, 2012; De Groot et al., 2009; Pincemail et al., 2007; Norris and Bonnar, 1997).

In addition, animal studies revealed that hormonal contraceptives influence neurohormones, neurotransmitters, neuropeptides, and emotional, cognitive, social and sexual behaviors. So, it was suggested that the brain can be an essential target of hormonal contraceptives (Porcu et al., 2019). Sex hormones act through steroid receptors and perform important effects on various neurotransmitters, like GABA, serotonin, dopamine, and glutamate (Del Río et al., 2018). Oral contraceptives modulate social-emotional behavior and brain function (Montoya et al., 2017). Sex hormones and their metabolites influence brain areas that control mood, behavior, and cognitive abilities. According to recent studies by Skovlund et al. (2016, 2018), hormonal contraception, mainly among adolescents, is associated with a higher rate of subsequent use of antidepressants and a first diagnosis of depression, subsequent suicide attempt, and suicide. Anderl et al. (2020) found a long-term association between adolescent OC use and depression risk in adulthood regardless of current OC use. The greater effect of OC use (exogenous hormones) during adolescence could be elucidated that this is a sensitive period of neuronal plasticity (Vigil et al., 2016). It seems that exogenous hormones could produce adverse changes in neurons and neuro-architecture, and structural and functional changes in the developing brain during adolescence (López Moratalla et al., 2011).

Based on the above-mentioned studies the widespread use of oral contraceptives could be seen as an environmental risk factor. Sexual hormone receptors work as transcription factors (Ascenzi et al., 2006). Moradi Sarabi et al. (2017) investigated the possible effects of OCs on cancer susceptibility by determining the methylation status of serum DNA. They found that OCs can affect the genome-wide status of methylation and promoter methylation of tumor suppressor genes as adenomatous polyposis coli (APC1) and estrogen receptor  $\alpha$  (ESR1). Monocyte-derived macrophages (MDMs) express estrogen and androgen receptors (Murphy et al., 2009). Campesi et al. (2012) found that OCs modified estrogen receptor  $\alpha$  and estrogen receptor

$\beta$  levels, and estrogen receptor  $\beta$  activity, but androgen receptor expression was unchanged in healthy adult women. The authors also found that OCs could cause changes in hematological and plasmatic markers, modifying hormonal levels, endothelial function, inflammation index and redox-related mechanisms that have effects on macrophage function.

Maternal exposure to hormonal contraceptives may be a risk factor via hormonal, epigenetic and transgenerational processes that increase the prevalence of autism spectrum disorder (ASD) (Strifert, 2014, 2015; Donhauser, 2020). Recently, Zou et al. (2017) demonstrated that prenatal exposure of levonorgestrel (LNG) alone or a combined LNG/ ethinyl estradiol (EE) treatment produced significant estrogen receptor  $\beta$  (ER $\beta$ ) suppression in the amygdala with autism-like behavior in the offspring of rats. The authors also revealed that ER $\beta$  suppression in the amygdala induced decreased expression of superoxide dismutase (SOD2) and estrogen-related receptor  $\alpha$  (ERR $\alpha$ ), thus subsequently produced damage in amygdala tissue via oxidative processes and dysfunction of mitochondria and fatty acid metabolism. These effects eventually contribute to autism-like behavior in offspring. In addition, Xie et al. (2018) reported, that exposing pregnant dams to clinically relevant doses of progestins caused decreased ER $\beta$  expression in the amygdala in offspring, with autism-like behavior. The authors proposed that prenatal progestin exposure may counteract the neuroprotective effect of estrogen and emphasized, that prenatal progestin exposure is a strong risk factor for autism-like behavior.

Based on the above-mentioned studies, we should consider that hormonal contraceptives, acting as endocrine disruptors, could cause adverse effects by different mechanisms at much lower doses than overt toxicity since hormones can have effects at very small doses (parts per billion ranges). In addition, as endogenous hormones are already present in our body in biologically active concentrations, any further exposure to exogenous hormonally active substances could interfere with receptors for hormonally assisted processes and perturb the proper functioning of the endocrine system (Rogan and Ragan, 2003; Timm et al., 2005).

## PREGNANCY IN ADVANCED MATERNAL AGE

In developed countries, childbirth is becoming more and more protracted in the last decades. Advanced maternal age (AMA) is a significant risk regarding pregnancy (Lampinen et al., 2009). During pregnancy, women over 35 years of age have increased risk for various diseases, like gestational diabetes, placenta praevia, pre-eclampsia, miscarriage and pregnancy-induced hypertension, Caesarean sections, maternal overweight or obesity pregnancy complications and adverse fetal outcomes, congenital anomaly, spontaneous abortion,

perinatal mortality, among others (Shan et al., 2018; Lampinen et al., 2009). In addition, AMA presents an increased prevalence of postpartum depression and these women are more worried about the baby, compared with younger women (Muraca and Joseph, 2014; Zasloff et al., 2007).

Human ovarian aging starts at the age of 30 and the number and quality of oocytes continuously decline (Broekmans et al., 2009), resulting in reduced fertility (Cimadomo et al., 2018). In addition, human oocyte chromosome aneuploidy (aneuploidy is the presence of an abnormal number of chromosomes in a cell) increases with age. Several cases of infertility are attributable to aneuploidy, other important contributing factors are mitochondrial dysfunctions and abnormal gene expressions (Reyes et al., 2017).

Advanced maternal age is linked to perturbed redox homeostasis and unregulated free radical production (Turpin et al., 2015; Odame Anto et al., 2018). It is currently accepted that mitochondrial dysfunctions play key roles in aging and age-related diseases (Rottenberg and Hoek, 2021; Haas, 2019; Pella et al., 2020). Maternal ageing is associated with mitochondrial dysfunction resulting in decreased oxidative phosphorylation and ATP production (Simsek-Duran et al., 2013).

Mitochondria are the most numerous organelles in the oocyte. However, in older oocytes, there is mitochondrial DNA damage, abnormal mitochondrial gene expression, and decreased mitochondrial membrane potential (Harvey, 2019; May-Panloup et al., 2016; Keefe et al., 1995; Mihalas et al., 2017). Mitochondria, particularly important for fertilization and early development, play key roles in cellular life, such as redox homeostasis, ATP-production, thermogenesis, free radical creation,  $Ca^{2+}$  homeostasis, cell growth, apoptosis, various cell signaling, iron metabolism, steroidogenesis, etc. (Dumollard et al., 2007a, b; Harvey, 2019).

There is a considerable difference in gene expression profiles between younger and older metaphase II stage (MII) human oocytes (Zhang et al., 2020). The global transcriptional activity in the oocytes may be considerably dysregulated with increased oocyte age. In addition, there is a higher incidence of chronic medical conditions among older women. Finally, it should also consider that older mothers (i.e. AMA, women over 35 years of age, compared with younger mothers), could have experienced more environmental and psychosocial stress events, that could be passed on to the offspring via an epigenetic manner.

## URBANIZATION

In the 20th century, the continuing worldwide movement of populations from rural to urban regions has fundamentally changed our lives. More than 50 percent of the global population now lives in cities. The association

between diseases and urbanization is a complex and context-specific phenomenon. Although cities have both various benefits and different health risks, cities have a serious impact on our mental health. Beil and Hanes (2013) investigated the effects of four distinct urban environments (i.e. very natural; mostly natural; mostly built and very built) by physiological and psychological stress measures. They revealed that the exposure to natural settings relative to built settings presented greater benefit measured by pre-to-post changes in salivary amylase and self-reported stress. Lederbogen et al. (2011) revealed that social stress-induced amygdala activity was specifically related to city dwelling. The incidence of mood and anxiety disorders, depression and schizophrenia, and other non-affective psychoses are more prevalent in urban compared areas to rural ones (Costa ESilva and Steffen, 2019; Heinz and Deserno, 2013). Haddad et al. (2015) proposed that early-life urbanicity (psychosocial stress) may produce anatomical and functional changes in the brain that increase the risk for schizophrenia. The urban built environment and physical environment involve higher rates of pollution (air, water), road traffic noise, population density, more physical threats (accidents, violence), among them, compared to rural regions (Gruebner et al., 2017; Melis et al., 2015). Areas with high population densities are characterized by higher rates of criminality, mortality, social isolation, air pollution and noise (Peen et al., 2010). Constant exposure to noise could produce various negative health effects such as sleep disturbance, cardiovascular effects, learning impairment, heart diseases, and depressed mood, among others (Leijssen et al., 2019; Wang et al., 2018; de Kluizenaar et al., 2009). Air pollution exposure is particularly critical in urban areas since these are population centers and hot spots for emissions. For example, short-term exposure to diesel exhaust fumes increases the cardiovascular risk of subjects (Tousoulis et al., 2020). The urban environment can discourage physical activity and favor less-healthy dietary choices by fast-food outlets or reducing access to fresh products (Mackenbach et al., 2014). Social stress was recognized as one of the most powerful causes for the development of mental disorders. Socioeconomic factors like poverty, low income, material deprivation, low level of education, and occupation are also essential determinants of health in urban populations (Ompad et al., 2007). However, in urban populations, social stress as a risk factor for mental disorders also includes social-economic status, environmental pollutants, infrastructure and economic issues (Lederbogen et al., 2013). Namely, physical risk factors of the environment cannot be separated from sociological risk factors considering the occurrence of mental disorders.

In an urban setting, social stress, psychological stress, air pollution, traffic noise, population density, physical threats (accidents, violence) each can be associated with oxidative stress (Hahad et al., 2019;



Sánchez-Rodríguez et al., 2006; Leni et al., 2020; Gruebner et al., 2017; Salmón et al., 2018; Isaksson, 2015).

There is mounting evidence that epigenetic processes have an important function in the pathophysiology of posttraumatic stress disorder (PTSD) and other stress-related disorders (Morrison et al., 2019). DNA methylation is one epigenetic mark that has been studied in PTSD. In addition, environmental factors play a key role in developing PTSD. Social exposures (for example, low socioeconomic status, unemployment, failing social network support, etc.) can manipulate DNA methylation that enhances stress sensitivity and reactivity, which can increase the risk of PTSD (Uddin et al., 2013). Galea et al. (2011) suggested that perturbations in DNA methylation may be one possible mechanism through which features of the urban environment contribute to psychopathology. In an urban environment, traffic-related air pollution (TRAP) - especially particulate matter (PM) - is associated with a variety of health effects, including quality of sperm, female reproductive mechanisms, cardiovascular and respiratory diseases, mental disorders, and cancer (Ferrari et al., 2019). However, air pollution has been associated with perturbation of DNA methylation (Ferrari et al., 2019).

## MOTHER-INFANT SEPARATION IN HOSPITALS

In the 20th century maternal separation (MS) from her infant shortly after birth has become a routine and unique procedure to humans in hospitals. Women conventionally gave birth at home and the crib was kept next to the mother's bed. The mother and her newborn have an emotional and physiological need to be together at the moment of birth as well as in the first hours and following days and weeks (Crenshaw, 2019). Although, there is a debate about whether planned home birth is as safe as planned hospital birth (Grünebaum et al., 2015), the risk of perinatal or neonatal mortality is not different when birth was intended at home or in hospital (Hutton et al., 2019; Zielinski et al., 2015).

In rats, experimental MS caused increased anxiety and depression, social deficits, impaired adult neurogenesis, dysregulated hypothalamic-pituitary-adrenal (HPA) axis, abnormal behaviours, perturbed cognitive and cortical functions, increased amygdala activity (Diehl et al. 2014; Janetsian-Fritz et al., 2018; Wu et al., 2014; Daniels et al., 2009), perturbation of serotonergic, noradrenergic, and dopaminergic neurotransmitter systems (Arborelius and Eklund, 2007), among others.

Various studies were also performed on primates to reveal the adverse effects of early MS. For example, MS produced increased serum cortisol level, dysfunction of the hypothalamic-pituitary-adrenal axis, distress behaviours, depression-like behavioural, dysfunction of the neurobiology of emotion and behaviour, decreased CNS serotonin turnover (Shannon et al., 2005; Pryce et

al., 2004; Parker and Maestriperi, 2011; Laudenslager et al., 1995; Feng et al., 2011).

Early MS studies cannot be conducted ethically in humans. Thus, human investigations on the adverse effects of early MS usually focus on the first 1-2 hours or early postpartum days of the infant. Namely, infants' skin-to-skin interaction with their mothers and its effects on breastfeeding, cortisol levels, reduction of the pain, infant's crying and sleeping, infants' physiological, emotional, and cognitive regulation, among others (Császár and Bókkon, 2017).

MD is also associated with perturbed redox mechanisms (Spivey et al., 2011; Hendricks et al., 2012). Prenatal stress and longer periods of maternal separation can produce depression-like and anxiety-related behavioural alterations that are associated with alterations in redox balance and reduced mitochondrial biogenesis (Rappeneau et al., 2020). In Marković et al.'s (2017) experiments, early maternal deprivation produced long-term redox alterations in the brain of rats. MD decreased levels of GSH in all investigated brain structures as the cortex, hippocampus, thalamus, and caudate nucleus. Lipid peroxidation increased in the cortex and thalamus. Cytochrome C oxidase activity was unchanged in all investigated structures, although complex I activity was increased in all structures except the cortex. In addition, the activity of SOD increased in the cortex and hippocampus in MD rats. The authors found an increased expression of membrane NOX2 subunits in the cortex and hippocampus and decreased expression of both membrane and cytosolic subunits in the caudate nucleus. Malcon et al. (2020) found that MS induces long-term alterations in oxidative stress and increased anxiety-like behaviors in Balb/cJ mice.

MS (or deprivation) was linked to disturbed epigenetic mechanisms that could be transmitted to offspring or next generations (Franklin et al., 2011). For example, MS is linked to epigenetic changes in the brain-derived neurotrophic factor (BDNF) gene in the rat hippocampus (Seo et al., 2016; Park et al., 2018); modulation of oxytocin receptor gene (OXTR) in rhesus macaque hippocampal samples (Baker et al., 2017); increased expression of oestrogen receptor- $\alpha$  (ER $\alpha$ ) in the medial preoptic area (MPOA) (Champagne et al., 2003); changes in DNA methylation, histone acetylation, and NR3C1 glucocorticoid receptor expression (McGowan et al. 2011; Park et al., 2017); reduced expression of serotonin receptor (5HT1A) in the dorsal raphe (Franklin et al., 2010), among others.

## RADIOFREQUENCY POLLUTION

## ELECTROMAGNETIC

### Radiofrequency electromagnetic radiation

Radiofrequency (RF) electromagnetic radiation (EMR) is non-ionizing electromagnetic radiation, which includes

radio waves and microwaves, and lies in the frequency range about between 3 kilohertz (kHz) to 300 gigahertz (GHz). The most common sources of radiofrequency radiation are radios, televisions, radars, satellites, wireless cellular telephones, microwave ovens, computers, and wireless networks (Wi-Fi) (Bortkiewicz, 2019). Extremely-Low-Frequency Electromagnetic field (ELFEMF) is also non-ionizing radiation in the frequency range between 0-3000 Hz. The most common sources of the exposure of the public to ELF EMF originated from 50 Hz/60 Hz electric and magnetic fields from high-voltage electric power transmission lines, secondary distribution lines, electrical installations and power grids.

Electricity became an indispensable part of our daily life that has made our lives incredibly easier. However, with the increasing use of electricity, we also had to face its potential adverse effects on human health, since power lines, electrical wiring, and every type of electrical equipment produces electromagnetic radiation (Kocaman et al., 2018).

The proposed mechanisms that are responsible for the adverse effects of artificial nonionizing electromagnetic radiations include: increased reactive oxygen species (ROS); changes in levels of blood antioxidants; perturbation of intracellular calcium and nitric oxide signal processes; increased lipid peroxidation; increased proteolytic activity; inhibited cell proliferation and differentiation; altered cell morphology and cytoskeletal organization; facilitated vesicle endocytosis and synaptic plasticity in a calcium-dependent manner; gene expression alterations and DNA damage via epigenetic and genetic mechanisms, among others (Kivrak et al., 2017; Pall, 2015; Alkis et al., 2019; Sun et al., 2016; Eleuteri et al., 2009; Falone et al., 2007; Lacy-Hulbert et al., 1998; Sulpizio et al., 2011; Cho et al., 2012; Löscher et al., 1998; An et al., 2015).

The adverse effects of artificial non-ionizing radiofrequency electromagnetic radiations are associated with cancers, neuropsychiatric effects including stress, depression, anxiety, and behavioral problems, among others (Bortkiewicz, 2019; Pall, 2016, 2018; Henz et al., 2018; Višnjić et al., 2018; Sudan et al., 2016). During pregnancy, maternal cell phone use may be associated with an increased risk for behavioral problems, particularly hyperactivity/inattention and emotional problems in the offspring (Birks et al., 2017).

Radiofrequency electromagnetic exposure is considered genotoxic, but the energy transferred into the cells is not strong enough to produce direct damage to DNA. According to Sage and Burgio (2017), "Epigenetic changes, rather than genetic changes in DNA, may underlie many or even most of the biological effects of non-thermal EMFs." Studies support the pathogenetic importance of perturbed epigenetic changes (like altered microRNA, histone modification, DNA methylation, chromatin remodeling) produced by EMFs (Liu et al., 2015; Manser et al., 2017; Goodman et al., 2009; Dasdag

et al., 2015; Sage et al., 2018; Vijayalaxmi and Prihoda, 2009).

### ***Mobile phone and microwave radiation***

The above-mentioned harmful effects of radiofrequency electromagnetic radiation on biological systems, the use of mobile phones spreading all over the world, has caused another challenge. In the last two decades, artificial microwave radiation (MWR) and the enormous increase in the number of mobile phone users could have more important adverse effects. Nowadays, a new addiction has been emerging, the so-called cell-phone addiction (mobile phone devices are now commonly referred to as "smartphones," as these have greater functionality and numerous gratifications above traditional phones) (De-Sola Gutiérrez et al., 2016; Amiri et al., 2020). People spend their time more likely on social media, playing games, do business emails, academic searches, finding answers to questions, etc. However, this excessive use of cell phones is associated with anxiety, stress, depression (Shoukat, 2019; Pall, 2016). The excessive and problematic use of cell phones is also associated with personality changes, such as extraversion, neuroticism, impulsivity, self-esteem, self-identity, and self-image problems (De-Sola Gutiérrez et al., 2015). The mobile phone's excessive usage could produce headaches, sleep disturbances, fatigue, impaired cognitive functions (Wilmer et al., 2017; Wang et al., 2017; Oviedo-Trespalacios et al., 2019; Liu et al., 2019). In addition, people can develop so-called "electrohypersensitivity" or "microwave illness", which is one of several syndromes commonly categorized as "idiopathic environmental intolerance" (Belpomme et al., 2018). Fetuses, babies, and younger children are especially vulnerable to environmental electromagnetic fields (EMF) because they have smaller head sizes and thickness of the skull, and their brain tissues absorb more MWR than the adults (Morgana et al., 2014).

The main effect of mobile phone radiation likely is to disrupt redox regulatory signal processes (Durdik et al., 2019; Singh et al., 2020; Desai et al., 2009). But the cellular target of mobile phone microwave radiation is still controversial, though one of the supposed effects is that microwave radiation stimulates plasma membrane NADH oxidase that produces free radicals and oxidative stress (Friedman et al., 2007). However, NADH oxidase plays numerous essential roles in cellular regulatory processes (Breitenbach et al., 2018).

RF-EMFs have adverse effects on cognition and produce neurobehavioral decrements, mainly in children and adolescents (Belpomme et al., 2018). In utero RF-EMF exposure from mobile phones produces alterations in neurodevelopment and behavior in offspring (Aldad et al., 2012; Zhang et al., 2015).

The latest version of mobile networking technology was

4G (fourth generation, 1900-2100 MHz), and the next version is called 5G (fifth generation, 3500 MHz) (McClelland and Jaboin, 2018). 5G further increases the strength of artificial microwave radiation and its possible harmful effects on biological systems. According to Kostoff et al. (2020), "The studies on wireless radiation health effects reported in the literature should be viewed as extremely conservative, substantially underestimating the adverse impacts of this new technology." According to Belpomme et al. (2018), "Exposure to low frequency and radiofrequency electromagnetic fields at low intensities poses a significant health hazard that has not been adequately addressed by national and international organizations such as the World Health Organization."

### **DIGITAL TECHNOLOGY, VIRTUAL REALITY, AND VIDEO GAMING**

Technology has been making our lives more secure, comfortable, and entertaining, although we lose out on chances to practice coping with uncertainty, inconvenience, and boredom. On-screen communication is very different from the world of face-to-face communication and puts us into a virtual world. However, there is increasing evidence that using devices of the digital world, like smartphones, tablets, gaming consoles, and televisions increases the prevalence of psychosomatic problems, anxiety, aggression, loneliness and decreases the level of psychological well-being (Twenge and Campbell, 2018). Children and especially adolescents are particularly vulnerable to the harmful effects of smartphones, tablets, and video gaming (Twenge et al., 2018). Of course, there are many benefits of onscreen technology as well. For example, major demographic changes, such as aging and living alone have taken place in recent decades, and digital technology could reduce the isolation of these people (Anttila et al., 2020). Digital technologies, like helping travel, work, shopping, entertainment, communication, students to learn, recall and retain information are just some of the areas. Nevertheless, digital virtual reality takes children and adolescents into a seeming lonely world where nothing needs to be done, and as they grow up, they may pass on their behavior patterns to their offspring.

Today, there are more than two billion users of video gaming worldwide (Newzoo, 2017). Internet gaming addiction (IGA) is worldwide one of the most serious public health issues among adolescents. The association between screen use and mental health is very complex and different types of screen time may produce different effects. Children and adolescents who spent more time using screen media, presented lower psychological wellbeing, poor emotion regulation, inability to finish tasks, lower curiosity, and more difficulty making friends compared to low users (Twenge and Campbell, 2018;

Rosen et al., 2014). In a cohort study, Khouja et al. (2019) investigated associations between screen time measured at 16 years and anxiety and depression at 18. They revealed associations between longer screen time - mainly computer users - and a small increased risk of anxiety and depression.

In 2013, the American Psychiatric Association (APA) defined Internet Gaming Disorder (IGD) in the DSM-5. In the DSM-5 IGD classification has taken into consideration that it has many features in common with addictive disorders, such as diminished control over gaming, spending excessive amounts of time playing games, while schoolwork and interpersonal activities are neglected, and deception of family members regarding its extent (Petry et al., 2015). But there is a lack of full consensus about the diagnostic criteria, hence in 2017, the World Health Organization (WHO) 11th Revision of the International Classification of Diseases (ICD) the gaming disorder was identified as a new disorder (van den Brink, 2017).

However, several studies supported the view, that problematic video gaming is related to low self-esteem, low self-efficacy, anxiety, aggression, depression, maladaptive coping strategies, negative affectivity, poor school performance, loneliness (Tortolero et al., 2014; Anderson et al., 2008; Greitemeyer and Mügge, 2014; Anderson et al., 2017; Cudo et al., 2019). According to Blasi et al. (2019), "problematic players are likely to escape online games as a maladaptive coping strategy for dealing with adverse emotional experiences."

Studies suggested that anxiety, aggression, and depression are associated with increased oxidative stress (Coccaro et al., 2016; van Velzen et al., 2017; Black et al., 2015). Thus, one of the possible important mechanisms of video gaming-induced anxiety, aggression, and depression could be perturbed redox signal mechanisms.

Psychometric studies suggested self-concept deficits to play a key role in the pathogenesis of the IGD (Dieter et al., 2015). For example, Leménager et al. (2014) investigated the neurobiological processes in addicted Multiplayer Online Role-Playing Games (MMORPG) players by functional Magnetic Resonance Imaging (fMRI) while evaluating their own and their personal avatar's body image (physical self-concept). Addicts presented an extended negative body image and lesser gender identity levels, having decreased bilateral brain activations in the angular gyrus (AG) and the middle occipital gyrus during self-perception. Moreover, addicted gamers identified themselves easier with their avatar, than with their real self.

In addition, males play video games more often than females, so males are more vulnerable than females in developing IGD (Dong et al., 2018). Moreover, several antecedent factors (risk factors) have been identified regarding gaming addiction, such as social phobia, ADHD, ASD, depression, high impulsivity, conduct problems, and instability in the parental relationship,

among others (Saunders et al., 2017).

Epidemiological studies have reported varying incidence rates of IGD in adolescents across countries from 0.8 to 26.7% (Kuss et al., 2014). Individual differences in internet use could be due to varying degrees of genetic and environmental factors (Long et al., 2016). It is known that neurobehavioral phenotypes are epigenetically directed by non-coding RNAs (ncRNAs) like microRNAs (miRNAs) (Kocerha et al., 2015). Circulating miRNAs was proposed to serve as biomarkers for various neuropsychiatric disorders (Kichukova et al., 2015). Lee et al. (2018) investigated IGD-associated miRNA markers by observing differentially expressed plasma miRNAs between the IGD and control groups. They found that miRNAs are involved in various neuropsychiatric disorders and investigated if dysregulation of these miRNAs could be associated with the pathophysiology of IGD. Three IGD-associated miRNAs were found and the authors proposed that dysregulation of these miRNAs may be associated with the pathophysiology of IGD. Vink et al. (2016) studied the heritability of compulsive internet use in a Caucasian sample. They collected data using the Internet Use Scale (CIUS) in 5247 monozygotic (MZ) and dizygotic (DZ) adolescent twins and found a moderate heritability without sex differences, in accordance with heritability investigations of addictive behavior (Distel et al., 2011; Geels et al., 2012). However, we should take more seriously the dangerous effects of digital virtual reality (Anderson and Rainie, 2018).

## SUMMARY AND CONCLUSIONS

The prevalence of neurodevelopmental, neuropsychiatric and neurodegenerative diseases has substantially increased over the last decades, although the etiology of these diseases is multifactorial and still uncertain (NHS, 2018; Erkinen et al., 2018; Alabaf et al., 2019; Arora et al., 2018; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; Heemels, 2016; Gitler et al., 2017; Carballal Mariño et al., 2018). The incidence of neurodegenerative disorders is increasing that only partly due to the extension of life span. Most mental illnesses in adults have their onset during childhood or adolescence. There is increasing evidence that diverse environmental exposures during the sensitive neurodevelopmental periods, like fetal development and early life could be important risk factors, thus predisposing the individual to the development of mental diseases later in life (Grova et al., 2019).

In addition, the ASD, ADHD, anxiety, depression, Alzheimer's and Parkinson's diseases could be inherited with varying degrees in which the epigenetic processes may play important roles (Gudmundsson et al., 2019; Sandin et al., 2017; Kwok, 2010; Marques and Outeiro, 2013; Harari and Cruchaga, 2016; Fetahu et al., 2019;

Zheng et al., 2016). Moreover, in the last two decades, numerous studies revealed that epigenetics is fundamental to neurodevelopment, as well as in various neurodegenerative and neurological disorders (Starr, 2019; Hwang et al., 2017; Gangisetty et al., 2016; Bókkon and Mallick, 2016; Jakovcevski and Akbarian, 2012). Thus, epigenetic mechanisms could strengthen the links between neurodevelopmental disorders and neurodegenerative diseases (Starr, 2019). The studies also found that epigenetics is the key link in the integration of the genetic and environmental risk factors in complex human diseases (Marsit, 2015; Canas et al., 2016; Babenko et al., 2012). According to Cavalli and Heard (2019), "Gene × environment interactions determine how individuals with the same or different genotypes will respond to environmental variation." Further, it has been revealed that the stress-response genes via epigenetic processes may influence the psychological susceptibility or resilience to environmental stressors (Zannas and West, 2014).

While we are considering the occurrence of mental disorders, the physical risk factors of the environment cannot be separated from the socio-economic risk factors (Ompad et al., 2007; Lederbogen et al., 2013). Social exposures (e.g. low socioeconomic status, unemployment, lack of social network support, maternal and/or material deprivation, low education, etc.) could lead to changes in DNA methylation, which through enhancing stress sensitivity and reactivity can increase the risk of PTSD (Uddin et al., 2013).

As we could see in our paper, all selected and briefly reviewed environmental, innovation, and lifestyle risk factors are associated with disturbed redox regulations and oxidative stress (Table 1), perturbed epigenetic regulations (Table 2), and various neurodevelopmental, neuropsychiatric or neurodegenerative diseases (Table 3). It is possible that one of the main adverse effects of modern environmental, innovation, and lifestyle risk factors due to the perturbed redox regulations. However, redox regulations have key roles in the regulation of epigenetic mechanisms (Sundar et al., 2013; Mikhed et al., 2015; García-Giménez et al., 2014, 2017, 2019; García-Guede et al., 2020; Pérez-Torres et al., 2020; Leisegang et al., 2018; Cyr and Domann, 2011; Gámez-Valero et al., 2020). So, these perturbed redox regulations (oxidative stress) can bother epigenetic processes that could eventually lead to the emergence of various diseases, including neurodevelopmental, neuropsychiatric, and neurodegenerative diseases.

In addition, in reality, people are constantly exposed to countless different modern environmental, innovation, lifestyle and psychosocial risk factors simultaneously and day by day. Multiple exposures at multiple life stages could be additive and/or cumulative. These risk factors could even individually perturb redox regulations and epigenetic regulations that are associated with the onset of various diseases, including neurodevelopmental,

**Table 1.** Risk factors associated with oxidative stress.

<b>Risk factors</b>	<b>Selected references: Risk factor associated with oxidative stress</b>
Air pollution	Hahad et al., 2020; Kimet et al., 2020; Shukla et al., 2019; Zhou et al., 2019
Heavy metals	Jaishankar et al., 2014; Wu et al., 2016; Fu and Xi, 2020; Jomova et al., 2010; Valko et al., 2016
Pesticides	Čermak et al., 2018; Banerjee et al., 2001; Abdollahi et al., 2004; Ledda et al., 2021; Limón-Pacheco and Gonsebatt, 2009
Plastic pollution	Huanget al., 2018; Wang et al., 2019; Yang et al., 2009; Xin et al., 2014; Kabuto et al., 2004; Meli et al., 2020
Artificial sweeteners	Iyyaswamy and Rathinasamy, 2012; Ashok et al., 2017 Ashok and Sheeladevi, 2014 Iyaswamy et al., 2018
Hormonal contraception	Kowalska et al., 2018; Kowalska and Milnerowicz, 2016; Chen and Kotani, 2012; De Groote et al., 2009; Pincemail et al., 2007; Norris and Bonnar, 1997
Pregnancy in advanced maternal age	Turpin et al., 2015; Odame Anto et al., 2018; Pella et al., 2020 Simsek-Duran et al., 2013 Mihalas et al., 2017
Urbanization	Hahad et al., 2019; Sánchez-Rodríguez et al., 2006; Leni et al., 2020; Gruebner et al., 2017; Salmón et al., 2018; Isaksson, 2015
Mother-infant separation in hospitals	Spivey et al., 2011; Hendricks et al., 2012 Rappeneau et al., 2020 Marković et al., 2017 Malcon et al., 2020
Radiofrequency electromagnetic pollution	Durdik et al., 2019; Singh et al., 2020; Desai et al., 2009; Friedman et al., 2007; Breitenbach et al., 2018; Kivrak et al., 2017; Alkis et al., 2019; Nazıroğlu and Akman, 2014
Digital technology, virtual reality, and video gaming	One of the possible important mechanisms of video gaming induced anxiety, aggression, and depression could be perturbed redox signal mechanisms. (Coccaro et al., 2016; van Velzen et al., 2017; Black et al., 2015).

**Table 2.** Risk factors associated with perturbed epigenetic regulations.

<b>Risk factors</b>	<b>Selected references: Risk factor associated with perturbed epigenetic regulations</b>
Air pollution	(Rider and Carlsten, 2019; Kupsco et al., 2020; Ferrari et al., 2019)
Heavy metals	(Ryu et al., 2015; Fragou et al., 2011; Nye et al., 2014; Koedrith et al., 2013; Nafea et al., 2020)
Pesticides	(Mnif et al., 2011; Sabarwal et al., 2018; Nilsson et al., 2018)
Plastic pollution	(Bromer et al., 2010; Shoaff et al. 2019; Alavian-Ghavanini et al., 2018; Martini et al., 2020; Butler et al., 2020)
Artificial sweeteners	(Silva et al., 2020; Miro-Blanch et al., 2019; Collison et al., 2013; Ashok and Sheeladevi, 2014)
Hormonal contraception	(Moradi Sarabi et al. 2017; Campesi et al. 2012; Zou et al. 2017; Xie et al. 2018)
Pregnancy in advanced maternal age	(Reyes et al., 2017; Zhang et al., 2020; Harvey, 2019)
Urbanization	(Toyokawa et al., 2012; Galea et al. 2011 Ferrari et al., 2019)
Mother-infant separation in hospitals	(Franklin et al., 2011; McGowan et al. 2011; Park et al., 2018; Champagne et al., 2003; Baker et al., 2017)
Radiofrequency electromagnetic pollution	(Liu et al., 2015; Manser et al., 2017; Goodman et al., 2009; Dasdag et al., 2015; Sage et al., 2018; Vijayalaxmi and Prihoda, 2009)
Digital technology, virtual reality, and video gaming	(Lee et al., 2016; Vink et al., 2016; Bromer et al., 2010; Shoaff et al. 2019)

**Table 3.** Risk factor associated with neurodevelopmental, neuropsychiatric, and neurodegenerative diseases.

<b>Risk factors</b>	<b>Selected references:</b>	<b>Risk factor associated with</b>
<b>neurodevelopmental, neuropsychiatric, and neurodegenerative diseases</b>		
Air pollution	(Saha et al., 2018; Zeng et al., 2019; Bernardini et al., 2019; Calderón-Garcidueñas et al., 2020)	
Heavy metals	(Karri et al., 2016; Monnet-Tschudi et al., 2006; Jomova et al., 2010; Cicero et al., 2017; Mold et al., 2018; Mirza et al., 2017)	
Pesticides	(Shelton et al., 2014; González-Alzaga et al., 2014)	
Plastic pollution	(Perera et al., 2016; Stein et al., 2015; Xu et al., 2015; Acconcia et al., 2015; Chen et al., 2016)	
Artificial sweeteners	(Choudhary and Lee 2018; Lindseth et al., 2014; Lynch and Pedersen, 2016; Silva et al., 2020)	
Hormonal contraception	(Porcu et al., 2019; Skovlund et al. 2016, 2018; Anderl et al., 2020; Strifert, 2014, 2015; Donhauser, 2020; Zou et al., 2017)	
Pregnancy in advanced maternal age	(Muraca and Joseph, 2014; Zasloff et al., 2007; Shan et al., 2018; Lampinen et al., 2009)	
Urbanization	(Lederbogen et al., 2013; Galea et al. 2011; Leijssen et al., 2019)	
Mother-infant separation in hospitals	(Császár and Bókkon, 2017; Shannon et al., 2005; Pryce et al., 2005; Parker and Maestripieri, 2011; Laudenslager et al., 1995; Feng et al., 2011; Janetsian-Fritz et al., 2018)	
Radiofrequency electromagnetic pollution	(Shoukat, 2019; Aldad et al., 2012; Zhang et al., 2015; Belpomme et al. 2018; Pall, 2016; 2018; Henz et al., 2018; Višnjić et al., 2018; Sudan et al., 2016)	
Digital technology, virtual reality, and video gaming	(Tortolero et al., 2014; Lee et al., 2016; Twenge and Campbell, 2018; Khouja et al., 2019)	

neurodegenerative, and neurological disorders, with a worldwide increasing prevalence. We should consider that epigenetic modifications, like DNA methylation, histone modifications, ncRNAs, etc., are not separated mechanisms. In contrast, these epigenetic modifications converge and interact to control gene expression throughout mammalian development at multiple levels (Marczylo et al., 2016).

Of course, there are numerous further modern environmental and lifestyle risk factors that were not mentioned in our paper, because it would be impossible. For example: I: hormones and antibiotics in livestock animals (Andersson and Skakkebaek, 1999; Jeong et al., 2010; Malekinejad and Rezaabakhsh, 2015; Brinkman et al., 2010; Nachman and Smith, 2015; Stephany, 2010; Tang et al., 2017); II: genetically modified organisms (GMOs) (Doerfler, 2019, 2016, 2011; Weber et al., 2015; Zhang et al., 2016); III: there are more than 70,000 diverse synthetic chemicals in the global market, and numerous others are emitted as by-products of their production or disposal (WIT's World Ecology Report, 1997); IV: short-term and long-term health effects of caesarean section (Sandall et al., 2018; Souza et al.,

2010; Keag et al., 2018; Schlinzig et al., 2009; Almgren et al., 2014); V: antibiotic treatments with serious side effects, that occur primarily through disruption of intestinal microbiota (dysbiosis) and via the gut-brain axis may produce diverse psychological disturbances and neuropsychiatric diseases (Raymond et al., 2016; Scriven et al., 2018; Skonieczna-Żydecka et al., 2018; Cox and Blazer, 2015; Szóke et al., 2020; Devaux and Raoult, 2018; Lurie et al., 2015). These factors may also perturb redox and epigenetic regulations that can also be associated with the onset of various diseases, including neurodevelopmental, neurodegenerative, and neurological disorders.

Based on the briefly reviewed artificial chemical, biological, physical compounds, as well as modern lifestyle and psychosocial factors in our paper we could come to the following conclusions:

- Humans are simultaneously and continuously exposed to numerous modern environmental and lifestyle risk factors.
- Each of reviewed risk factors can be associated with various perturbed redox regulations (oxidative stress).

- These perturbed redox regulations (oxidative stress) can bother epigenetic regulations and as a result, perturbed epigenetic processes disrupt normal cellular signal mechanisms.
- Disturbed epigenetic regulations could eventually lead to the emergence of various diseases, including neurodevelopmental, neuropsychiatric, and neurodegenerative diseases.
- The brain is highly susceptible to oxidative stress due to its high oxygen consumption and lipid-rich content. Therefore, the brain can be particularly sensitive to numerous modern environmental and lifestyle risk factors
- Since human is simultaneously and continuously exposed to many diverse modern environmental and lifestyle risk factors, they can simultaneously disrupt numerous redox and epigenetic regulations, which could significantly enhance vulnerability and decrease the resilience.
- The human biological and nervous system cannot adapt to numerous modern environmental and lifestyle risk factors that can promote the development of various diseases, including neurodevelopmental, neurodegenerative, and neurological disorders.
- Perturbed epigenetic regulations by modern environmental and lifestyle risk factors may accumulate in the epigenome during our lives and could be inheritable to offspring and subsequent generations. This inheritance of perturbed epigenetic can also enhance vulnerability and decrease the resilience in the human population.

#### \*Footnote

Most intracellular and extracellular signal pathways are directly or indirectly linked to redox-regulated processes. Numerous studies demonstrated that reactive oxygen species (ROS), including hydrogen peroxide ( $H_2O_2$ ), superoxide anion ( $O_2^{\bullet-}$ ), hydroxyl radical ( $HO\bullet$ ), and singlet oxygen ( $^1O_2$ ) - and reactive nitrogen species (RNS) including nitric oxide ( $NO\bullet$ ) and peroxynitrite anion ( $ONOO^-$ ), among them, are fundamental signalling molecules for cells (Dröge et al., 2002; Valko et al., 2007). Reactive species and their derivatives are required for apoptosis, cell cycle, cell growth, cellular migration, autophagy and inflammatory processes, microcirculation, regulation of the blood-brain barrier, gene expression and DNA repair, epigenetic regulation, cell adhesion, chemotaxis, protein-protein interactions and enzymatic functions,  $Ca_2+$  and redox homeostasis, immune processes, production of cytokines, transcription factors, mitochondrial functions, regulation of cytoskeletal dynamics both within and between cells (Dröge et al., 2002; Terzi et al., 2020; Bókkon, 2012; Bókkon and Antal, 2011; Egea et al., 2017; Nordziede et al., 2018; García-Giménez et al., 2019; Mullen et al., 2020). ROS, RNS and their derivatives also act as signalling

molecules in neurons and the cerebral circulation; they are also required for signal processes in connection with synaptic plasticity, memory formation, neurotransmitter release, long-term potentiation, depression and synaptogenesis (Oswald et al., 2018; Kishida and Klann, 2007; Smythies, 1999; Massaad and Klann, 2011; Bókkon, 2012). These reactive species are produced mostly by the mitochondrial respiratory chain, NADPH (nicotinamide adenine dinucleotide phosphate) oxidases, lipoxygenases, cyclooxygenases, cytochrome P450 oxidases, xanthine oxidase, nitric oxide synthase (NOS), among others (Dröge et al., 2002; Pham-Huy et al., 2008). The harmful effects of reactive species are due to the imbalance between reactive species production and antioxidant defenses called oxidative stress.

#### \*\*Footnote

Epigenetic regulations are heritable yet reversible changes in gene expression within genotypically identical cells without altering the DNA sequence. Most important epigenetic regulations include DNA methylation, histone post-translational modifications (such as methylation, acetylation, ubiquitination and phosphorylation), and regulatory non-coding RNAs (ncRNAs), such as micro-RNA (miRNA), PIWI-interacting RNA (piRNA) and long noncoding RNA (lncRNA), and chromatin organization (Clark et al., 2016; Imani et al., 2015; Peschansky et al., 2014). DNA methylation is almost always down-regulating, but the outcome of histone epigenetic modifications can be positive or negative, depending on which amino acid is affected by methylation, phosphorylation, ubiquitination (Kimura, 2013). ncRNAs can regulate the expression of proteins at the transcriptional and translational levels (Pagiatakis et al., 2019). The chromatin 3D structure is also under epigenetic regulation (Kim and Kaang, 2017). Telomere length is also an important regulator of gene expression and cellular signaling, and its length is heritable and can increase or decrease reversibly, similar to other epigenetic mechanisms. Epigenetic modifications are not separated mechanisms, but these processes could interact and regulate each other at multiple levels (Marczylo et al., 2016; Vaissière et al., 2008; Weissmann and Lyko, 2003). Perturbed epigenetic changes (epimutations) (Epimutation refers to a heritable change in gene activity that is not associated with a DNA mutation, but rather with a gain or loss of DNA methylation or other heritable modifications of chromatin.) by environmental and lifestyle risk factors may be inherited via inter- and transgenerational programming. For example, endocrine disruptors, maternal separation and maternal stress, heavy metals, air pollution, etc. can produce heritable epimutations (Manikkam et al., 2013; Ho et al., 2012; Klein et al., 2002; Carvan et al., 2017; Legoff et al., 2019; Shukla et al., 2019).



## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content.

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