# The impact of environmental pollution on metabolic health and the risk of non-communicable chronic metabolic diseases in humans

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Invited Review

# The impact of environmental pollution on metabolic health and the risk of non-communicable chronic metabolic diseases in humans

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ABSTRACT

*Aims:* This review aims to provide a comprehensive overview to understand the role of pollution in the development of noncommunicable diseases (NCDs), with a focus on metabolic diseases.

*Data synthesis:* In the context of NCDs, the incidence of metabolic diseases such as obesity and diabetes are increasing at an alarming rate. In addition to the well-known role of the so-called "obesogenic" environment, characterized by unhealthy diet and physical inactivity, great attention has been paid in recent years to the effects of pollution. Indeed, progressive urbanization has been associated with increased exposure to pollutants. The harmful effects of some pollutants on the endocrine system have been known for decades, but data on the metabolic impact of pollution are rather recent. Pollution in its various forms promotes a systemic inflammatory state, insulin resistance, and oxidative stress, which appear to be closely associated with increased risk of NCD, particularly obesity and diabetes.

*Conclusions:* In conclusion, urbanization has so far had a predominantly negative impact on collective health, but a better understanding of the mechanisms linking pollution to metabolic health is crucial to implement preventive strategies, including careful urban planning to improve community health, understood not only as the absence of disease but also as psychological and social well-being, overcoming the risks associated with urbanization.

## 1. The impact of environmental pollution on metabolic health and the risk of non-communicable chronic metabolic diseases in humans

The progressive industrialization and consequent urbanization witnessed in recent decades has been accompanied by a dramatic rise in the incidence of some chronic noncommunicable diseases (NCDs), namely cardiovascular diseases, cancers, chronic respiratory diseases and metabolic diseases, especially diabetes mellitus [1], which cannot be explained by genetic predisposition alone [2]. NCDs have a significant impact on global mortality: according to WHO, about 80 % of all premature deaths globally are attributable to NCDs [1]. Despite the average increase in life expectancy, NCDs lowers the disability-free life expectancy in both sexes and account for the majority of the costs of health systems.

Urbanization is associated with unhealthy lifestyles, characterized by sedentary lifestyles, altered sleep-wake patterns, air and noise pollution, and increased stress levels, which have negative consequences for human health in the short term (e.g., increased risk of obesity and diabetes mellitus), but also with climate change and increased frequency of 'extreme' weather phenomena, which pose a serious risk to long-term global health (e.g., related to reduced biodiversity, impacting food production and resource availability). Alarmingly, more than half of the world's population lives in urban settings, exposed to multiple risk factors for NCDs.

It has long been recognized that the risk of NCDs is determined by a complex interaction between genetic susceptibility and the environmental factors an individual encounters throughout life, known as *exposome*, a term coined in 2005 by Christopher Wild to describe the set of factors to which an individual is exposed in his entire life. In more recent years, epigenetic studies elucidated the molecular mechanisms by which the environment influences the phenotype. Epigenetic processes modulate gene expression through modifications that do not alter DNA sequence but change the accessibility of chromatin itself to transcription factors, regulating gene transcription [2–4].

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**Nomenclature**

| | |
|---|---|
| AGE | advanced glycation endproducts |
| ALAN | artificial light at night |
| BMI | body mass index |
| BPA | bisphenol A |
| EDCs | endocrine disruptors compounds |
| ERS | endoplasmic reticulum stress |
| GDM | gestational diabetes mellitus |
| HPA | hypothalamic-pituitary-adrenal axis |
| IDF | International Diabetes Federation |
| IR | insulin resistance |
| NCDs | non-communicable chronic diseases |
| PCBs | polychlorinated biphenyls |
| PM | particulate matter |
| POPs | persistent organic pollutants |
| RAGE | receptor for advanced glycation endproducts |
| ROS | reactive oxygen species |
| SCRD | sleep and circadian rhythms disruption |
| SNS | sympathetic nervous system |
| T2DM | type 2 diabetes mellitus |
| T1DM | type 1 diabetes mellitus |
| WC | waist circumference |
| WHO | World Health Organization |

## 2. Environmental pollution and NCDs

The industrialization process has speeded up from the second half of the XX century, leading to a progressive increase in pollutant emissions. The Global Burden of Disease [5] has recently published the estimates of the number of deaths attributed to widely recognized risk factors, showing that environmental pollution, with particular reference to air pollution, represents one the principal risk factors for both death and disease burden. Environmental risks are responsible for approximately a quarter of all deaths, thus creating a healthier environment could be the most effective disease control strategy. Suffice it to say that 20–30 % of NCDs could be prevented by reducing air pollution [6].

Major forms of pollution include air, soil, and water pollution originating from a variety of emission sources, although the most significant source of pollution from industrialization is anthropogenic pollution, whether intentional or unintentional (e.g., through spills or leaks into water and soil). Air pollution has the most harmful effects on human health. Air pollution is a complex mixture of gases (ozone, nitrogen dioxide, carbon monoxide, sulfur dioxide) and particulate matter (classified according to its micrometer size into PM10 and PM 2.5), and can be distinguished into "outdoor," typically produced by industrial processes and fossil fuel combustion, and "indoor" produced by household appliances [6,7].

Other forms of pollution include noise pollution, which encompasses roadway noise, aircraft noise and industrial noise, the accumulation of plastic products and microplastics in the environment, Electromagnetic and radioactive contamination, and light pollution [6]. It should also be noted that chemicals are now widely distributed in the environment and their production is growing at an alarming rate. Not all chemicals produced have been adequately studied to determine their potential toxicity (e.g., at the reproductive or immune level and on neuronal development), so the impact of chemical pollution is certainly underestimated. Most chemicals act as endocrine disrupting compounds (EDCs), i.e., substances that can alter endocrine functions, from synthesis to transport to hormonal action. Although an exhaustive description of the classification is beyond the scope of this review, it should be noted that several criteria for classifying EDCs have been proposed [8–10]. EDCs are ubiquitous in the environment and derive mainly from water and soil contamination and agriculture, but they are also present in many everyday products, from personal care products, children's products, textiles and furniture materials.

The increasing pollution parallels the growing incidence of obesity and diabetes mellitus, the two most common metabolic diseases. Both conditions are multifactorial diseases, arising in subject genetically predisposed after exposure to favoring risk factors, mainly represented by unhealthy lifestyle (i.e. increased caloric intake and sedentary lifestyle) and environmental factors. Indeed, although the main cause of the current pandemic of *diabesity* is believed to be an energy-dense diet coupled with sedentary lifestyle, the progressive increase of metabolic diseases even in countries where food availability has not undergone significant variations suggests that there are other contributing risk factors and in particular, attention is being focused on environmental pollution [11]. Recent data from the NCD Risk Factor Collaboration [12] recognized that the prevalence of obesity has more than tripled in the last five decades, with 880 million adults and 159 million children aged 5–19 years suffering from this condition. Similarly, the prevalence of diabetes mellitus is steadily increasing. According to International Diabetes Federation (IDF), by 2045 1 in 8 adults will be suffering from diabetes mellitus [13] in particular type 2 diabetes mellitus (T2DM), which accounts for 90 % of all forms of diabetes. The predominant impact of the so-called "obesogenic environment" in the onset of T2DM has been extensively studied, although plenty of evidence suggests a strong genetic component in T2DM, as evidenced by the high concordance in homozygous twins and the high incidence in first-degree relatives of affected patients compared with the general population [11,14–16]. In contrast, the impact of environmental factors on the incidence of type 1 diabetes mellitus (T1DM) has been less investigated to date, although supported by several epidemiological data: the progressive increase in disease prevalence in populations with 'low risk' genotypes and in populations migrating from low to high incidence areas, the seasonal pattern of new case onset, the increase in new cases with late onset, after age 50 [17–23].

## 3. Air pollution and metabolic diseases

There is growing interest towards air pollution and the consequences on metabolic health, but the relationship with obesity and T2DM remains unclear, and the underlying mechanisms are not fully understood. While a number of cohort and cross-sectional studies identified an association between certain air pollutants, widely distributed in urban areas, and several measures of obesity and IR, as well as incident T2DM, mechanistic data clearly explaining the molecular pathways through which air pollutants cause alterations in glucose metabolism are still lacking [24–32]. Several authors linked the harmful effects of air pollution to systemic inflammation, which is known to impair glucose metabolism, and favor visceral adipose tissue dysfunction and insulin resistance (IR) [7,32–34]. In vitro and in vivo studies suggest that inhaled PM penetrate the small airways triggering the release of pro-inflammatory cytokines from macrophages and epithelial cells and the production of reactive oxygen species (ROS) [7,34–38]. The inflammatory response is also able to disrupt both the innate and adaptive immune response, promoting susceptibility to autoimmunity [35,39]. After inhalation, pollutants disrupt lung immune regulation by affecting the activity of specialized immune cells and promoting loss of self-tolerance through antigen oxidation [39]. The innate immune system provides the first line of defense against inhaled pollutants, such as through mucus production, secretion of cytokines, chemokines, and co-stimulatory molecules, and mucosal infiltration by polymorphonuclear neutrophils, mononuclear phagocytes, and natural killer (NK) cells. Dendritic cells (DC) act as a link between the innate and

adaptive immune response through antigen presentation to T- and B-lymphocytes in the regional lymph nodes, resulting in their activation [35]. Pollutants up-regulate antigen presentation in DC and promote the secretion of cytokines such as IL-6, which, in turn, up-regulate the T-cell response while inhibiting regulatory T cells. Air pollutants have also been shown to affect antiviral activity, enhancing viral adhesion to respiratory mucosa and disrupting phagocytic activity of macrophages. Environmental pollutants can also alter immunity by altering the gut microbiota, favoring dysbiosis, and increasing intestinal permeability [39]. Finally, some evidence points to a role of pollutant-induced epigenetic modifications, showing, for example, that inhalation of PM2.5 and PM10 is associated with DNA methylation of genes involved in immune cell activity [32,39].

Oxidative stress results in β-cell dysfunction, since pancreatic β cells are highly sensitive to ROS-induced damage due to their poor antioxidant capacity. ROS could directly damage β-cells (i.e. destruction of the mitochondrial structure), and indirectly interfere with the insulin signaling pathway, through NF-κB-mediated inflammatory response [34,40]. Exposure to air pollution promotes β cells apoptosis through increased endoplasmic reticulum stress (ERS), leading to impaired insulin synthesis and secretion [34]. Indeed, unfolded protein response (UPR) is triggered by ERS to remove unfolded or misfolded proteins from endoplasmic reticulum lumen, but when this adaptive response is insufficient UPR activates an apoptotic signaling pathway [34]. PM 2.5 can also induce endothelial dysfunction, causing inflammation and vascular injury [36,41,42]. Even episodic exposure to PM 2.5 is able to promote an inflammatory, anti-angiogenic blood profile, associated with increased cardiovascular risk [36,40]. There is also evidence in animals indicating that inhaled pollutants promote the expansion of visceral adipose tissue, also associated with IR [32]. PM 2.5 exposure in mice elicits oxidative stress and mitochondrial alterations in brown adipose tissue, causing an imbalance between white and brown adipose tissue activity, with subsequent metabolic dysfunction [38]. Furthermore, exposure to atmospheric pollutants has been reported to increase global methylation and alter the epigenetic milieu [7].

There is growing evidence that air pollution contributes to the energy imbalance underlying obesity: on the one hand, media alerts, perceptions of smog and hazy weather, concerns about inhalation risk during exercise, and personal sensitivity to air pollution are associated with increased inactivity [43–50]; on the other hand, pollution affects appetite through dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) [51,52]. Exposure to PM 2.5 activates the Ikk/NF-kB pathway in the arcuate nucleus of the hypothalamus in rodents, a brain area involved in hunger-satiety regulation [53], while in humans it increases hunger and self-reported calorie intake [54]. Some recent data suggest an association between air pollution and anorexigenic hormones, such as leptin and PYY. It has been observed that patients with obesity are leptin resistant and display decreased levels of ghrelin and PYY and higher levels of leptin [55,56]. Exposure to PM 2.5 was positively associated with leptin levels, while exposure to carbon monoxide (CO) was negatively associated with PYY levels, suggesting a link between air pollution and dysfunctional eating behaviors [57].

Air pollution (particularly nitrogen oxide and ozone) is also suspected of increasing the risk of developing T1DM, as well as other autoimmune diseases. In support of this association, there is evidence of increased systemic oxidative stress - resulting from pollution - in children and adolescents with T1DM [32,58]. In a recent study involving 19 European countries, authors found a positive association between T1DM diagnosis between 0 and 15 years of age and exposure to pollution [59]. Other authors found greater pre-diagnosis ozone exposure in children with early-onset T1DM than in nondiabetic subjects [58,60].

Oxidative stress, endothelial dysfunction, systemic and peripheral inflammation have also been proposed to explain the link between maternal exposure to air pollution and the risk of developing gestational diabetes (GDM) [7,32,61–65].

It is worth noting that some authors suggest a different impact of air pollution-and subsequent T2DM-between developed and developing countries, suggesting that people living in lower and middle-income countries may be more vulnerable. One possible explanation for this lies in the population expansion and faster industrialization in these countries, compared to developed countries. However, data in this regard are too sparse and conflicting to draw firm conclusions [34].

## 4. EDCs and metabolic impairment

As anticipated, EDCs widely found in the outdoor environment and in everyday use products, like food and drinks processing and packaging [66]. As an example, bisphenol A (BPA) and phthalates are used for the packaging of consumer and food products, including canned foods, and can be found in meat products and seafood [67,68].

The close correlation between obesity and diabetes mellitus makes it difficult to distinguish ECDs with purely obesogenic or diabetogenic effect. Obesogens can compromise adipogenesis, by inducing hyperplasia and hypertrophy of white adipose tissue cells and dysregulation of brown adipose tissue [66]. Diabetogens preferentially induce insulin IR and hyperinsulinemia, by directly affecting pancreatic β- and α-cells, adipocytes, and liver cells [68]. In addition, EDCs can promote inflammation and oxidative stress, interfere with gut and brain hormone signaling involved in satiety, alter epigenetic regulation, through miRNAs and DNA methylation [66]. The most studied EDCs involved in metabolic derangement are persistent organic pollutants (POPs), especially BPA, phthalates and pesticides. There is substantial evidence of an association between POPs - particularly organochloride pesticides and polychlorinated biphenyls (PCBs) – and T2DM [69–71]. Indeed, POPs accumulate in adipocytes and are able to induce IR, decrease glucose uptake and trigger a pro-inflammatory response [69,71]. POPs accumulation in adipose tissue aims to limit their systemic toxicity, however, in the long term, this adaptive mechanism becomes maladaptive and the adipose tissue releases POPs into the circulation, becoming a source of POPs [71]. Studies in adipocyte cell lines show that lipophilic POPs alter the expression of genes involved in insulin response and lipid homeostasis and, in addition, reduce glucose uptake and induce a proinflammatory response [69,71]. POPs, such as DDT, as well as heavy metals, such as inorganic mercury, arsenic and cadmium, exert a direct toxic effect on β-cells, causing death and suppressing insulin secretion [32,72–74]. Urinary levels of BPA are also correlated with the incidence of T2DM [75,76] and obesity [76–81]. Indeed, BPA significantly affects insulin sensitivity and causes the release of pro-inflammatory molecules [82]. Studies in mice have shown that acute BPA exposure causes a rapid increase in insulin levels, while long-term exposure induces IR, glucose intolerance, and impaired glucagon secretion [9,70,83]. Interestingly, significant consumption of ultra-processed foods was associated with higher urinary levels of BPA and phthalates than consumption of healthy foods [84,85] linking unhealthy diet, exposure to ECDs and excess weight. In addition, studies in rats show that offspring of mothers exposed to phthalates exhibit downregulation of Pdx1, a gene involved in β-cells development and mitochondrial function, while perinatal exposure appears to alter glucose homeostasis, especially in adult females [32,86]. Given that phthalate and BPA are known to affect fetal development and can be found in food, it is evident that maternal diet is a major determinant of pregnancy and fetal outcomes. Indeed, several studies suggest that certain components of diet as well as specific dietary patterns are important sources of these compounds in pregnancy [67].

Regarding the role of EDCs in the pathogenesis of T1DM, emerging data indicate that EDCs may have different effects that taken together contribute to disease onset in predisposed individuals. Indeed, EDCs seems able to induce β-cell apoptosis and epigenetic modifications of several metabolic pathway, disrupt the microbiota and impair intestinal permeability, altering immune system development and function [87,88]. For example, the results of animal and human studies summarized in a recent review show, that dioxin blocks insulin secretion likely through dysregulation of genes involved in the physiological

**Table 1**
EDCs sources and effects.

| EDC | Source | Proposed mechanisms of action [8,9,32] |
|---|---|---|
| DDT | Pesticides | β-cell apoptosis; promote promotes adipogenesis (↑ fatty acids and lipid accumulation); induces IR in adipocytes |
| Dioxin | Industrial solvents | Blocks insulin secretion; ↑ pro-inflammatory cytokines; altered gene expression in β-cell |
| Phthalates | Food contact materials, personal care products, children's products | Pdx1 down-regulation; induces glucose intolerance, interferes with insulin receptor; ↑ ROS; PPARγ agonism |
| BPA | Food contact materials | ↑insulin and leptin; ↓ adiponectin (↓ adipocytes sensitivity to insulin); ↑ pro-inflammatory cytokines; ↑ insulin release (acute response); hyperinsulinemia, impaired glucagon secretion (long-term response); promotes adipogenesis through 11b-HSD1 |
| Other POPs | Ubiquitous | Induce glucose intolerance induction; ↓ glucose uptake in adipocytes; ↑ pro-inflammatory cytokines and ROS; ↑ lipid peroxidation; ↓ adiponectin; alter mitochondrial function |
| Cadmium | Children's product; contaminated food and water | β-cell apoptosis; β-cell lipid accumulation; ↓ insulin secretion; ↑ pro-inflammatory cytokines; hyperplasia and hypertrophy of adipose tissues; alters appetite/satiety |
| Mercury | Contaminated food (fish) | ↓ GSIS; β-cell apoptosis |
| Arsenic | glass manufacturing; herbicides and pesticides; electronics; foods, particularly shellfish | Blocks GSIS; β-cell apoptosis; ↓ glucose uptake; affects insulin signal transduction and adipocyte differentiation; ↑ hepatic lipid accumulation and oxidative damage; ↑ gluconeogenesis |
| AGEs | Heat-treated foods | ↑ fasting glucose, hyperinsulinemia; ↓ GSIS; β-cell apoptosis; loss of Langerhans islet architecture |

(*) GSIS: glucose-stimulated insulin secretion.

functioning of the β-cell, while cadmium promotes lipid accumulation in the beta-cell and the release of proinflammatory cytokine [32]. In contrast, few and inconclusive data are available regarding the effect of pesticides and PCBs, although some studies suggest an immunomodulatory effect [88].

Beyond the contamination of food and beverages by chemicals and toxins, some EDCs are the result of food production and storage processes, as in the case of advanced glycation endproducts (AGEs), the main source of which is the intake of heat-treated food. The binding of AGEs to the receptor (RAGE) results in decreased glucose-stimulated insulin secretion and elevated cell apoptosis, due to increased oxidative stress. Exposure to exogenous AGEs also appears to be associated with loss of pancreatic islet architecture [9,72]. A summary of EDCs effects is provided in Table 1.

## 5. Noise pollution and metabolic diseases

Noise pollution is drawing attention for its potentially dangerous effects on health. Among noise sources, traffic noise includes noise from roads, railways and aircrafts and affects over 100 million of people in Europe. Another possible source of noise pollution is occupational noise, which is less extensively investigated, also due to the obligation to wear individual protection equipment. In 2018, a WHO expert panel recognized chronic exposure to road traffic noise as a risk factor for ischemic heart disease, while the link to other diseases was less clear [89]. Since then, several cohort studies and meta-analysis consistently demonstrated an association between noise exposure and diabetes [89–94], especially with road traffic noise, while evidence of an association with occupational noise is still lacking, despite the results should be interpreted with caution due to discrepancies across the studies.

Further supporting noise as a risk factor for type 2 diabetes, a number of studies find that noise increases the risk of overweight, an important risk factor for diabetes. A recent meta-analysis showed that road traffic noise was associated with a significant increase in waist-to-hip ratio, waist circumference (WC), and risk of overweight and obesity, while railroad noise was associated only with WC and body mass index (BMI) [95]. A recent Iranian study found an association between occupational noise and the risk of overweight and obesity in a group of textile workers, a risk that was mitigated using hearing protections [96]. Although plausible, the evidence for an effect of noise exposure in pregnancy on maternal-fetal outcomes is uncertain [97]. Only a few studies have examined the impact of noise pollution on children and adolescents, with conflicting results: some authors found no association with early obesity, while others reported an increased risk of obesity in younger children [98–100]. Some authors speculated that the effect may be age-dependent, with limited impact in early childhood [101].

From an etiopathological point of view, noise acts as a stressor and activates the HPA axis and sympathetic nervous system (SNS). The resulting release of stress hormones (cortisol and catecholamines) leads to altered metabolism, inflammation and oxidative stress [89–91]. In addition, noise (especially nocturnal noise) alters circadian rhythms, and the resulting sleep deprivation can alter glucose metabolism and insulin sensitivity, leptin, ghrelin, and cortisol levels, and appetite/satiety modulation [89,91], resulting in an overall increased risk of central obesity and diabetes.

## 6. Light pollution and metabolic diseases

Electrification and artificial light have brought significant benefits to human activities, but the reduced need to adhere to the light-dark cycles found in nature has prolonged the photoperiod (i.e., the period during which the body receives light) with significant disruptions in sleep and circadian rhythm (SCRD) [102–104]. Given that circadian rhythms are crucial in the regulation of biological processes such as sleep, reproduction, nutrient metabolism and feeding behaviors, and hormone signaling, a prolonged photoperiod may adversely affect human health [102–104].

Artificial light at night (ALAN) is nowadays considered as a risk factor for the development of obesity and diabetes. ALAN can have outdoor and indoor sources; the former comprises both direct light emissions, such as street lightning, commercial and residential lighting, and lights from industrial facilities, and indirect light emissions due to the skyglow [105].

Although a detailed description of sleep-wake cycle regulation and its alteration is beyond the scope of this review, the effect of SCRD can be summarized as follows. Sleep deprivation has been associated with sympathovagal imbalance (i.e. relative sympathetic dominance and a lower vagal tone) and evening cortisol release, with metabolic consequences such as increased lipolysis and fatty acids release, leading to ectopic fat accumulation, reduction in insulin sensitivity and glucose uptake, stimulated gluconeogenesis [102]. SCRD is also responsible of circadian misalignment. The circadian rhythm is regulated by the master clock in the hypothalamic suprachiasmatic nucleus (SCN), mainly driven by light signals thus, changes in light cycle results in transcriptome changes in SCN and its downstream targets [102,104]. The main mechanism by which ALAN disrupts circadian rhythm is suppression of melatonin production, which affects hormone signaling (e.g., HPA axis, leptin, insulin), energy expenditure and appetite regulation, and mitochondrial activity [104]. In addition, there is a bidirectional relationship between the circadian clock and eating habits: while loss of

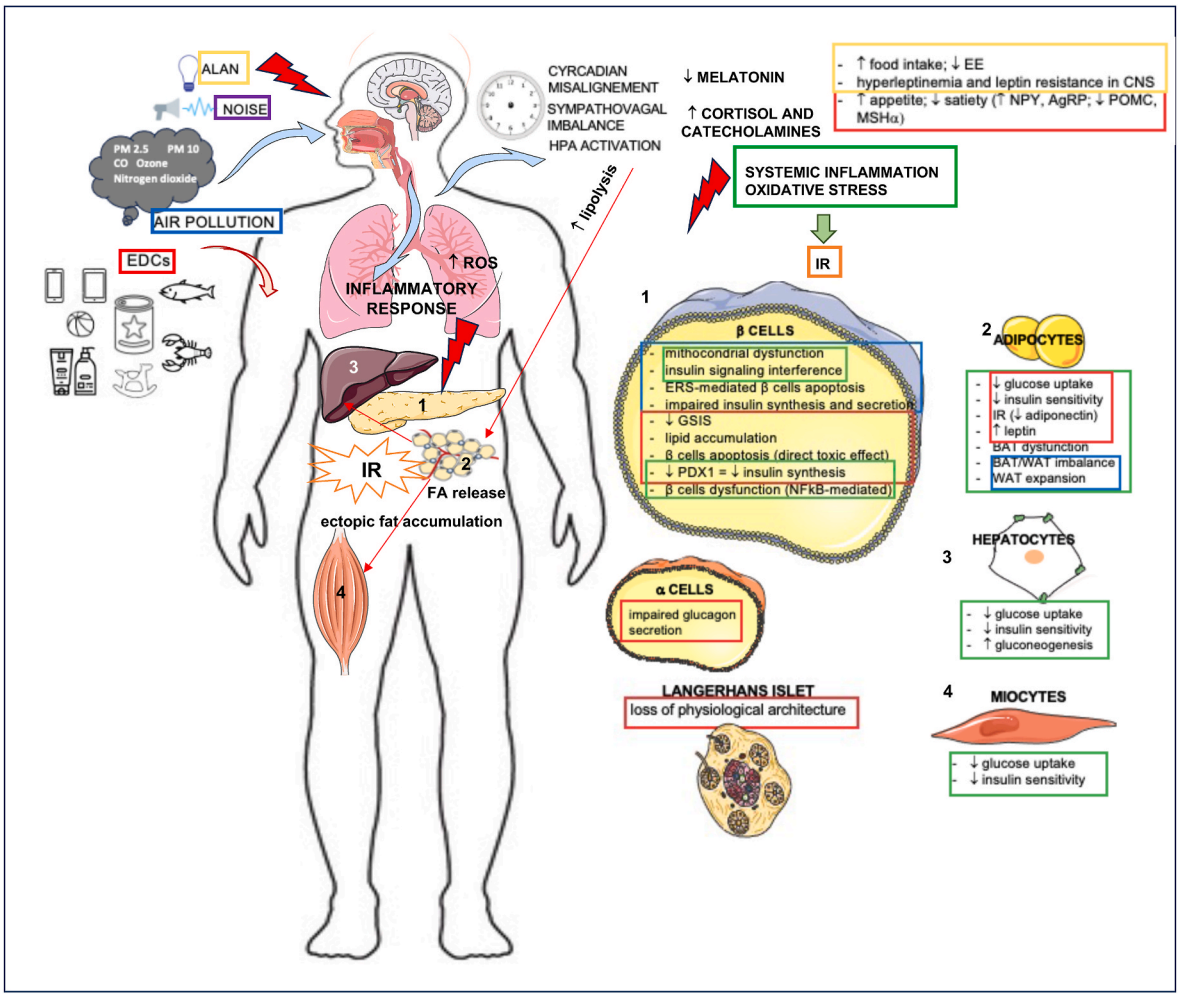


**Fig. 1.** Pollution and Metabolism. Impact of pollutants on glucose and adipose tissue metabolism is mainly driven by systemic inflammation and oxidative stress, both elicited by pulmonary response to inhaled pollutants and central stress response. Several molecular mechanisms in specific insulin-sensitive tissues (adipose tissue, muscle, liver) and Langerhans islets have been suggested for different pollutants (indicated by the colored boxes). ALAN: artificial light at night; EDCs: endocrine disruptor compounds; ROS: reactive oxygen species; IR: insulin resistance; FA: fatty acids; HPA: hypothalamus-adrenal axis; EE: energy expenditure; NPY: neuropeptide Y; AgRP: agouti-related protein; POMC: pro-opiomelanocortin; MSHα: α-melanocyte stimulating hormone; GSIS: glucose-stimulated insulin secretion; BAT: brown adipose tissue; WAT: white adipose tissue. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

circadian rhythm promotes food intake and hunger, with a preference for high-fat foods, the time of food intake can affect circadian rhythms in peripheral organs and, in turn, the master clock in SCN [102].

SCRD has been implicated in the risk of T2DM, as confirmed in night shift workers and patients with sleep apnea syndrome. Both cross-sectional studies and meta-analyses have shown that an optimal sleep duration is 7–8 h, with an increased risk of weight gain and glucose impairment for both longer and shorter sleep durations [102]. Determinants of the harmful effects of light on T2DM risks are light intensity, duration and timing of exposure, with the worst effect on metabolism for extended exposure to light during the dark phase, especially high intensity light [103]. Indeed, exposure to light during the dark phase can increases food intake, decreases energy expenditure, and increases body weight, along with reducing insulin sensitivity [104]. Evidence from preclinical and clinical studies identifies prolonged photoperiod as a risk factor for adiposity and associated metabolic disorders, by inducing hyperleptinemia and leptin resistance in CNS and also attenuating brown adipose tissue activity [104].

Several studies have reported that exposure to outdoor ALAN was an independent risk factor for obesity [106,107]. The relationship between outdoor ALAN exposure and obesity has been also observed in pediatric population [108,109]. A recent Chinese study of nearly 100.000 participants confirmed the association between outdoor ALAN and BMI in all sex and age categories, except for adults aged 18–39 years; in particular, the per quintile increase in outdoor ALAN levels was associated with a 10–30 % increase in obesity prevalence [110]. Inadequate light exposure is also associated with abnormal eating behavior. Several observational studies conducted on shift and night workers suggest a correlation between eating at night and increased risk of obesity, and eating dinner later has been shown to increase postprandial glucose in healthy subjects [103]. Outdoor ALAN has been associated with higher HbA1c, glucose levels and IR in a Chinese nationwide survey, with a significantly higher prevalence of T2DM in the highest quintile of exposure [111] and with increased risk of disease among middle-aged UK population [112], while other authors only found an association between increased night-time light intensity and BMI but not with fasting glucose [113].

Few studies addressed the impact of indoor ALAN on weight gain. However, authors agree that, similarly to outdoor ALAN, also indoor ALAN exposure is associated with higher risk of overweight and obesity [114–116]. Regarding T2DM, indoor ALAN might be more significant than outdoor ALAN in personal exposure to light pollution, consistently pointing at a positive association with impaired glucose metabolism and T2DM risk [105], both in the elderly [117,118], and young adults [119].

Interestingly, the detrimental effect on glucose metabolism is seen shortly after exposure and a single day exposure to bright light is sufficient to increase insulin levels next morning, indicating a compensatory response to maintain normoglycemia in a situation of increased insulin resistance. Interestingly, the highest insulin levels were found within 30′ of the oral glucose load (i.e., in the initial phase of insulin secretion), an interesting finding given that a higher acute insulin response is considered a predictor of T2DM onset [119]. Recently, the widespread use of electronic at night raised concerns because of their short wavelength of blue-light-emitting displays, which may cause SCRD and indeed some studies investigated the effects of electronic devices on suppressed melatonin and increased arousal [103].

## 7. Conclusion

Industrialization has been a turning point in human history, but it led to unbridled urbanization and a decisive increase in pollution. Life in urban settings is characterized by unhealthy lifestyles, exemplified by excessive consumption of high-calorie and nutritionally inadequate foods, physical inactivity, sleep disturbances, and higher levels of stress, but it is also associated with increased exposure to environmental pollutants, which mostly have negative effects on human health. It is no coincidence that in the post-industrial era we have witnessed a marked increase in the incidence of chronic noncommunicable diseases (NCDs), whose risk factors include pollutants in their own right. In the context of NCDs, metabolic diseases such as obesity and diabetes mellitus are closely associated with lifestyle factors, from well-known ones such as diet to emerging ones such as pollution in its various forms. Recent data show a significant contribution to disease onset from air pollutants, endocrine disruptors, excessive noise and light in city settings - and beyond (Fig. 1). All these factors contribute by multiple mechanisms to cause insulin resistance, systemic inflammation and oxidative stress, which ultimately results in the onset of obesity and diabetes mellitus. Given the pandemic dimensions that these two diseases are reaching and the associated costs to health care systems, a better and more complete understanding of the mechanisms linking urban pollution with the metabolic alterations underlying the onset of these diseases is necessary to put in place preventive strategies, to be complemented by the therapies already available. Strategies of diabetes prevention should aim at promoting a 'diabetes-protective lifestyle' whilst simultaneously enhancing the resistance of the human organism to pro-diabetic environmental and lifestyle factors.

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## Declaration of competing interest

The authors have declared the absence of any potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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