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Chapter 5

Fine Particulate Matter ($PM_{2.5}$) Air Pollution and Type 2 Diabetes Mellitus (T2DM): When Experimental Data Explains Epidemiological Facts

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Additional information is available at the end of the chapter

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Abstract

Epidemiologic and experimental studies suggest that environmental exposures to air pollutants can increase prevalence of metabolic and cardiorespiratory diseases. Among the risk factors, many studies have shown that air pollution, especially by fine particulate matter ($PM_{2.5}$), can lead to the development of type 2 diabetes mellitus (T2DM) or make diabetics more susceptible to other health complications. This chapter aimed to discuss the pathophysiologic mechanisms evolved in susceptibility to cardiorespiratory $PM_{2.5}$ effects in T2DM subjects, as well as the enhancing effect of $PM_{2.5}$ exposure on development of T2DM. We discussed the pathophysiologic mechanisms of $PM_{2.5}$ exposure and T2DM based on pro−/anti-inflammatory balance, metabolic regulation, redox status, and heat shock response, reinforcing the complex nature of T2DM etiology and highlighting the $PM_{2.5}$ air pollution as a critical health problem.

Keywords: fine particulate matter, type 2 diabetes mellitus, inflammation, oxidative stress, HSP70

1. Introduction: Epidemiology of sum of environmental and metabolic risk

In the last century, many epidemiological data demonstrated that the urbanization phenomenon corroborates to increasing prevalence of metabolic diseases and cardiorespiratory diseases. It is well known that high energy food offer and sedentarism are risk factors for metabolic

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diseases such as diabetes, while high levels of air pollutant emission represent a risk for cardio-respiratory diseases. Thus, almost all people living in great cities are exposed simultaneously to these two risk factors: food consumption in quantities above the necessary for health maintenance and exposure to environmental air pollution above the limits proposed by WHO.

Some numbers from WHO are really impressive. Data from Global report on diabetes (2016) show that at least 422 million people are diabetic in worldwide and that diabetes prevalence has been rising more rapidly in middle- and low-income countries [1]. In the same risk direction, Global Urban Ambient Air Pollution Database update 2016 [2] showed that 98% of these cities, with more than 100,000 inhabitants, do not meet WHO air quality guidelines. This data represents that 92% of the world population lives in places where air quality levels exceed WHO limits. Thus, we can hypothesize that probably a great amount of people are simultaneously exposed to urbanization risk factors to health.

Based on a biologically plausible hypothesis from 2004 [3], Brook et al. published data from respiratory clinics (n = 5228 patients) and conclude that traffic-related air pollutants were associated with type 2 diabetes mellitus (T2DM) prevalence among women [4]. Thus, in few years, at least eight studies corroborate with the first study and provide data from association between exposure to fine particulate matter (<2.5 μm, $PM_{2.5}$) and T2DM prevalence (for review, please see Rajagolapan and Brook, 2012).

Actually, the WHO air quality guidelines (WHO-AQG) [6] recommend that $PM_{2.5}$ levels not exceed annual mean concentration of 10 $\mu g/m^3$ and confirm that 92% of the world's population lives in places where air-quality levels exceed WHO limits. Interestingly, the information is presented via interactive maps, highlighting areas within countries that exceed WHO limits. Data obtained from "Most searched cities" and others in http://breathelife2030.org/ [7] and WHO ambient (outdoor) air pollution database 2016 are shown in **Figure 1**.

Just for hypothesize the population under $PM_{2.5}$ pollution risk, we listed in **Table 1** an estimate of habitants in each city listed in **Figure 1**. We may conclude that at least 140 millions of people are breathing an inadequate level of $PM_{2.5.}$ Additionally, according to WHO diabetes database, 1 person in each 11 is diabetic; thus, we can hypnotize that, only in these cities, more than 12 million of people are simultaneously under exposure of these 2 risk factors to health: diabetes and $PM_{2.5.}$

As can be observed in the data listed above, air pollution in middle- and low-income countries, in majority in Asia, Latin America, and Africa, is a significant public health burden. Here, we highlighted places that often present high concentrations of $PM_{2.5}$ and simultaneously a high population density suggesting an industrialized and modernized life style that corroborates to T2DM development. Accordingly, as was demonstrated more than 10 years ago, the sum of these conditions is critical for health. Diabetic patients are more susceptible to air pollution-induced cardiovascular morbidity and mortality [8, 9], and this susceptibility to $PM_{2.5}$ cardiovascular effects was associated with vasoconstrictive effects observed in episodes of high levels of pollution in T2DM [10].

In terms of "hard cardiovascular events," the recent review of Brook, et al. resume several meta-analyses assessing the impact of short-term exposures to $PM_{2.5}$. Accordingly, data extracted from 34 studies, each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration (during few hours to

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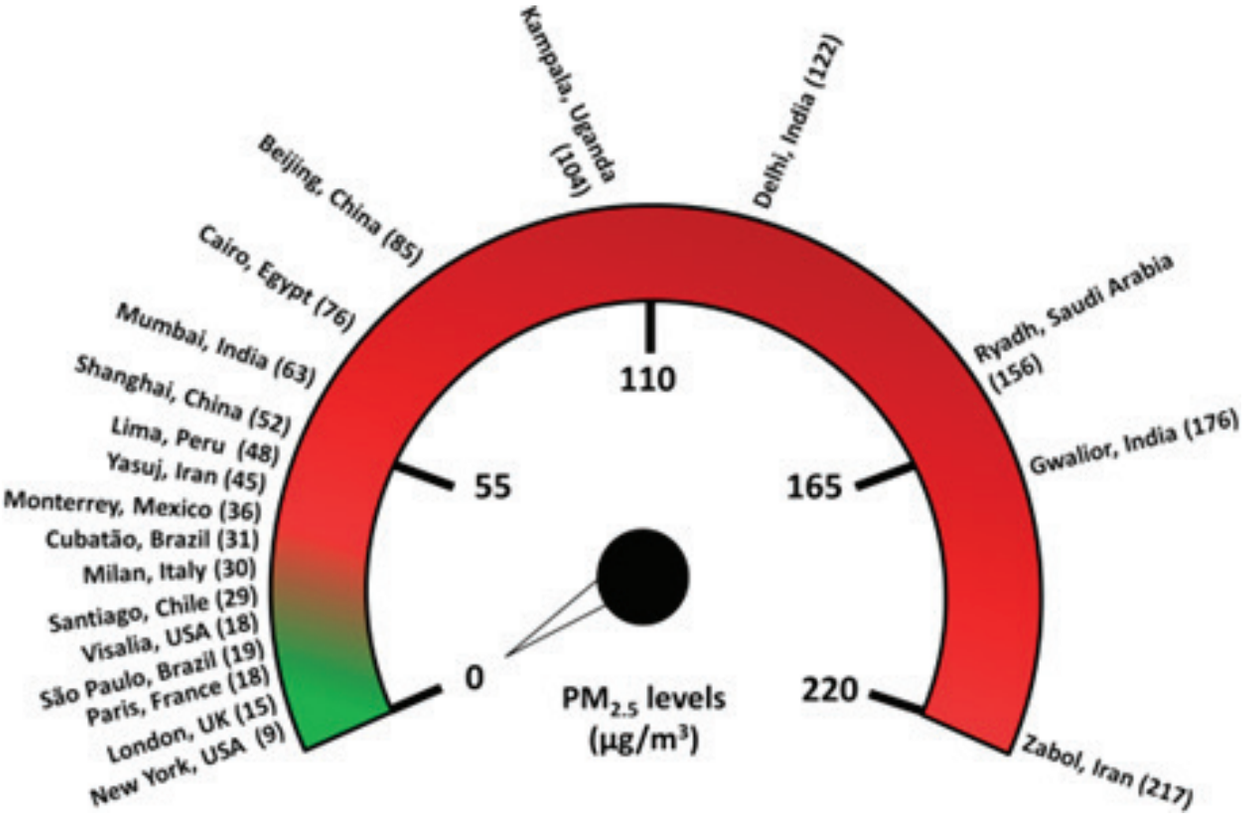


Figure 1. Fine particulate matter annual mean concentration in cities worldwide. Data obtained from WHO 2016 database [2] and published by breathlife2030.Org [7]. Data presented in terms of concentration of particles per air volume in $\mu g/m^3$.

City, Country	Population	City, Country	Population
Zurich, Switzerland	401,144	Shanghai, China	24,152,700
London, UK	8,787,892	Mumbai, India	12,442,373
Paris, France	2,229,621	Cairo, Egypt	9,500,000
Visalia, US	131,074	Beijing, China	21,700,000
São Paulo, Brazil	12,038,175	Kampala, Uganda	1,507,080
Santiago, Chile	7,314,176	Delhi, India	16,349,832
Milan, Italy	1,368,590	Bamenda, Cameroon	2,000,000
Cubatão, Brazil	127,006	Riyadh, Saudi Arabia	6,506,700
Monterrey, Mexico	1,130,960	Gwalior, India	1,953,505
Yasuj, Iran	108,505	Zabol, Iran	130,642
Lima, Peru	10,852,210	**Total**	**140,732,185**

Data extracted from wikipedia.com

Table 1. Estimate of population of cities listed in **Figure 1**.

days), increased the risk for acute myocardial infarction (by 2.5%), hospitalization or death from heart failure (2.1%), stroke (1.1%), and arrhythmia (1.5%). The risk increases for long-term exposure when people live in unhealthy urban area that exceeds $PM_{2.5}$ levels, reaching more than 10% increase in cardiovascular mortality. Also, if people live in polluted area, a peak of $PM_{2.5}$ levels increases 10–50 fold the risk for cardiovascular events [11]. Furthermore, elderly people and women are high susceptible profile to $PM_{2.5}$ effects and for T2DM development, mainly in menopause [11].

The pathophysiologic mechanisms evolved in susceptibility to cardiorespiratory $PM_{2.5}$ effects in T2DM subjects, as well as the enhancing effect of $PM_{2.5}$ exposure on development of T2DM, are discussed below. The number and the complexity of these mechanisms are positive correlated to the importance for life maintenance. In this chapter, we presented pathophysiologic mechanisms based on oxidative stress, inflammation, and heat shock response, with major contribution from experimental studies. These issues were selected considering as representative of the ability of an organism to respond physiologically (by adequate and quick ways) to the environmental challenges or internal changes in the metabolism as an essential characteristic that permits the life. As background of this discussion, there is the comprehension of the concept that homeostasis regulation of one variable is dependent on many cooperative or synergic mechanisms, that may be activated simultaneity or by steps, in terms of redox response, cell by cell signaling, and/or by molecular stress response. Since T2DM and $PM_{2.5}$ may be considered as stress situations that can promote damage to organism, and also are conditions that require adaptation/protection responses in the stressed cells, the comprehension of multi-integrative physiologic response can provide mechanistic explanation of epidemiological data listed above. Whereas high-intensity challenges to organism can overload the defensive response mechanisms, chronic and moderate intensity challenges can induce internal "recalibration" of many systems to survive [12]. Then, in the light of this "integrative" and "evolutionary" perspective is important to consider the expressive and complex effects of $PM_{2.5}$ exposure and T2DM on these variables discussed below: (a) the pro/anti-inflammatory balance; (b) the metabolic regulation (flux and consumption of energy sources); (c) the redox status (pro/antioxidant balance); and (d) heat shock response.

2. Pathophysiology of T2DM development: Role of inflammation, oxidative stress, and heat shock proteins

The plasma glucose level at any given time is determined by the balance between the amount of glucose entering the bloodstream and the amount leaving it. The principal determinants are therefore the dietary intake; the rate of entry into the cells of muscle, adipose tissue, and other organs; and the glucostatic activity of the liver. Thus, there are biochemical abnormalities as fundamental defects to T2DM development as reduced entry of glucose into various peripheral tissues and increased release of glucose into the circulation from the liver. The extracellular glucose excess (hyperglycemia) represents for many cells challenge to maintenance of intracellular glucose level [13, 14].

In animals, hyperglycemia state can be produced by pancreatectomy, by toxins administration that in appropriate doses cause selective destruction of the β cells of the pancreatic islets (as streptozocin or alloxan), by administration of drugs that inhibit insulin secretion, or by administration of anti-insulin antibodies. Also, strains of mice, rats, hamsters, guinea pigs, miniature swine, and monkeys that have a high incidence of spontaneous diabetes mellitus have also been described. However, due to high prevalence of T2DM related to lifestyle, several experimental data obtained from high fat diet (HFD) animal models have been used with success to induce the disruption of insulin signaling in liver, skeletal muscle, or adipose tissue causing hyperinsulinemia and thus, the development of T2DM [15, 16].

The HFD models help us to comprehension of the mechanisms described up to now for T2DM. As reviewed recently, it was proposed that the activation of transcription factor forkhead box protein O1 (FOXO1) in the liver and disruption of glucose-transporter translocation (GLUT4) to the surface membrane in skeletal muscle as the first steps of insulin resistance [17]. The resultant hyperglycemia and chronic hyperinsulinemia are hypothesized to disrupt insulin suppression of adipocyte lipolysis [17]. Additionaly, the active metabolism of adipose tissue may contribute to hyperinsulinemia since in HFD feeding, it occurs in the deregulation of hepatocyte gluconeogenesis (such as FOXO1), which causes increased hepatic glucose output, and deregulate the glucose transporter GLUT4 response to insulin in muscle, which results in decreased glucose uptake by muscle. In this case, the hypertrophy of adipose tissue can be interpreted as the first step of insulin resistance development that results in hyperglycemia and T2DM.

Persistent hyperglycemia causes tissue damage by different mechanism that involves oxidative stress. Increased uptake of glucose results in increased intracellular glucose concentration, that in turns, increased polyol pathway flux. This metabolic pathway uses dihydronicotinamide adenine dinucleotide phosphate (NADPH) that is required for maintaining the levels of the major intracellular nonenzymatic antioxidant defense, the glutathione. Nonenzymatic reaction of glucose and other glycation compounds formed advanced glycation products (AGEs) that modify intracellular proteins functions. Also, AGEs binding to specific receptors (RAGES) can induces reactive oxygen species (ROS) production. Finally, increased levels of AGEs and glucose (intracellularly and extracellularly) increased protein kinase C activation and hexosamine pathway flux. All these mechanisms listed above are involved in decrease nitric oxide (NO) production (vascular impaired function) and activation of factor nuclear kappa B (NF-kB), major pro-inflammatory transcript factor (for details, please see Giacco and Borwnlee, 2010).

Chronic hyperglycemia is strongly associated with enhanced oxidative stress with overproduction of ROS and nitrosative species (RNS), a reduction of the activity of antioxidant enzymes is known to cause endothelial dysfunction and insulin resistance [19]. Thus, oxidative stress constitutes as an important factor implicated not only in the T2DM development itself but also in the development of diabetic complications [18, 20]. T2DM is well known a cause of microangiopathies, observed at least by the three major diabetic complications, namely, diabetic retinopathy, nephropathy, and neuropathy. Also, T2DM constitutes a major risk factor for macroangiopathy, such as coronary artery disease and cerebrovascular disease.

Thus, oxidative stress in T2DM is associated with a wide array of complications associated with decreased quality of life of affected patients, thus contributing to the staggering increase in health-care expenditure.

Overweight and obesity is a risk factor for development of T2DM and is strongly related to chronic low grade inflammatory state. Adipose tissue metabolism is responsible for systemic oxidative stress and increase pro-inflammatory signaling, observed by increased plasma/serum cytokine levels. The development and the severity of the disease are related to immuno-inflammatory responses and thus, biomarkers. Inflammatory cells (monocytes/macrophage and Th1 lymphocytes) are stimulated to express high amounts of the inducible form of nitric oxide synthase (iNOS, that is, encode by NOS-2 gene) by activation of transcriptors factor of inflammation, as NF-kB [21]. Studies in human obesity and insulin resistance (as well as in animal models) have revealed a clear association between the chronic activation of pro-inflammatory signaling pathways and decreased insulin sensitivity.

Elevated levels of TNF-α, IL-6, and IL-8 have all been reported in various diabetic and insulin-resistant states. As part of the chronic inflammatory process, locally secreted chemokines attract pro-inflammatory macrophages to the adipose tissue, where they form crown-like structures around large dead or dying adipocytes. These "infiltrated" macrophages release cytokines that further activate the inflammatory response in neighboring adipocytes, exacerbating inflammation and insulin resistance. In addition, overnutrition and obesity are often accompanied by elevations in tissue and circulating free fat acids (FFA) concentrations, and saturated FFAs can directly activate pro-inflammatory responses in vascular endothelial cells, adipocytes, and myeloid-derived cells. Excess of free fatty acids accumulate (FFA), resulting in lipotoxicity and an increase in potentially harmful intracellular lipid products activating the NF-κB pathway and inflammation. Adipose tissue macrophages (ATMs) infiltrate adipose tissue to clear these excess lipids and produce pro-inflammatory cytokines, such as IL-1β, TNF-α and IL-6, which further propagate inflammation [22].

According Fontana et al., obesity is strongly associated with plasma IL-6 levels so that has been calculated that one third of total circulating concentrations of IL-6 originate from adipose tissue. A feed-forward paracrine inflammatory cycle involves co-cultured adipocyte release of FFA and macrophage FFA-induced TNF-α production, which blocks insulin-stimulated glucose uptake in adipocytes, and leads to increased release of FFA. TNF-α induces insulin resistance through several mechanisms including inhibition of insulin receptor signaling and increases in FFA. In addition, macrophages secrete a chemotactic pro-inflammatory lectin Galectin-3 that directly decreases insulin signaling and promotes adipose tissue inflammation. Thus, the overexpressed pro-inflammatory cytokines in obesity are considered the link between obesity and inflammation [23–25] and also, obesity and the concomitant development of inflammation are major components of insulin resistance [26].

Additionally with pro-inflammatory signaling and oxidative stress, hyperglycemia in T2DM is also associated with modifications in the cell stress response ability, with markedly undesirable effects in the metabolism. Cell stress response may be studied observing heat shock proteins (HSP) amount, synthesis, and release from cells and tissues. Since HSP are classified by their molecular weight, in this chapter, we use the term "HSP70" to describe all proteins

from 70 kDa HSP family, including inducible 72 kDa and constitutive 73 kDa forms. Also we use the prefix "e" or "i" to identify protein location, as extracellular (eHSP70) or intracellular (iHSP70) located.

Pro-inflammatory signaling, oxidative stress, and hyperglycemia in T2DM is related to decreased iHSP70 levels. In obesity, it observed a reduction in iHSP70 levels and an increase in JNK activation in skeletal muscle. This effect may be a result of heat shock factor (HSF-1) inhibition. The levels of iHSP70 are correlated with the level of insulin resistance and negatively correlated with fast glucose levels [27]. Heat therapy, that increases iHSP70 levels and decreases JNK activation in muscle, protects against hyperglycemia, hyperinsulinemia, glucose intolerance, and insulin resistance [28].

Studies about cell stress response and oxidative stress using biopsies from T2DM patients showed that mRNA expression of HSP70 and heme-oxygenase-1 is reduced in this subjects. Furthermore, mRNA HSP70 levels were correlated with β-hidroxiacil-CoA dehydrogenase and citrate synthase enzymes activities, suggesting that insulin resistance is associated with poor heat shock and antioxidant defense of muscle [29]. In this way, mitochondrial dysfunction plays an essential role in T2DM development [30]. This organelle dysfunction may be a result of hyperglycemic state and/or oxidative state. The activation of key pathways that increases lipid oxidation and decreases lipid esterification reduces insulin resistance levels.

In a study with wild type and HSP70-knockout mice (HSP70-KO), it was demonstrated that HSP70 level is critical to maintenance of mitochondrial morphology and is a biomarker/sensor of mitochondrial stress levels and insulin signaling function in skeletal muscle. HSP70-KO mice showed impaired glucose homeostasis, insulin resistance, and increased adiposity levels. Also, muscles of HSP70 mice accumulated lipids probably as a result of reduction in fat acids oxidation, which in turns, promotes muscle inflammation. Moreover, muscle cells without HSP70 showed low levels of basal oxygen consumption and high levels of ROS mitochondrial production [31], whereas HSP72 overexpression mice are protected against insulin resistance by positive regulation of oxidative metabolism. Induction of HSP70 expression in skeletal muscle of these mice promoted an increase in mitochondrial number and oxidative capacity decreasing insulin resistance [32].

Intracellular HSP70 expression is associated with antiapoptotic and anti-inflammatory actions. Inhibition of NF-KB activation and translocation is a marked anti-inflammatory function of iHSP70 with great implications in immune system, inflammatory process and cell survival regulation [33]. Thus, HSP70 is well known by its molecular chaperon cytoprotective roles. However, this protein is also found in blood of health subjects [34] and a crescent number of studies have been demonstrated higher levels of HSP70 in blood in T2DM, T1DM, and gestational diabetes [35, 36]. The role of HSP70 in the extracellular space (eHSP70) involves immune regulatory actions, pro-inflammatory signaling, and alert/danger signal of cell damage [37].

In T2DM patients, it observed an increase in eHSP70 levels, and this increase is associated with diabetes duration, a biomarker of chronicity of the disease [36]. Also, chronic exposure of pancreatic β-cell *in vitro* to high levels of eHSP70 induces cell death and modifies cellular

bioenergetics profile. Since T2DM and T1DM patients exhibit higher eHSP70 levels, the perpetuation of this pro-inflammatory signal may induce loss of cell integrity and consequently β-cell dysfunction [38].

In obese T2DM subjects, the eHSP70 level is higher than nonobese T2DM suggesting that adiposity, mainly visceral adiposity and its complications, may contribute to increasing eHSP70 levels. Actually, iHSP70 may be considered a cytoprotective proteins by anti-inflammatory functions associated with normal insulin sensitivity. On the other hand, increased levels of eHSP70 chronically may be a result of chronic low-grade inflammatory state of visceral obesity [39]. Therefore, the unbalance between eHSP70 and iHSP70 levels (eHSP70/iHSP70 ratio), known as H-index, can reveal the full context of inflammatory process and insulin resistance state [16, 40].

3. T2DM and $PM_{2.5}$: The mechanism of enhanced risk

Epidemiologic evidences have shown many effects of exposure to air pollution in the increase of hospital admissions in more susceptible individuals, as well as the increase of incidence of some diseases, from respiratory to cardiovascular diseases (Cote et al., 2008). In the last decade, the association between diabetes and air pollution was highlighted by some studies [10, 41–43].

Meo et al. reviewed studies that discuss insulin resistance, diabetes mellitus, and air pollution and conclude that in 10 studies, among 11 analyzed, the $PM_{2.5}$ exposure to is associated with abnormalities in glucose homeostasis and this effect is related with inflammation, insulin resistance mitochondrial alteration, cardio-metabolic disorders, and thus, related to T2DM development. The same work confirms a clear and strong association between T2DM and exposure to particulate material especially, the exposure to small particulate matter of 10 microns (PM_{10}) or less in diameter, such as $PM_{2.5}$ [15, 45].

The polluted air, mainly by $PM_{2,5}$, is related to inflammation, vascular dysfunction, and atherosclerosis by the toxicology mechanisms invocated by the $PM_{2,5}$ invasion into the bloodstream [42]. Beyond this, $PM_{2,5}$ is related to induction of insulin resistance and adiposity in high fat diet mice models [16, 43]. Chronic $PM_{2,5}$ exposure can induce glucose intolerance, oxidative stress, and mitochondrial alteration in Langerhans islet and adipose tissue. Thus, $PM_{2,5}$ inhalation represents a novel additional risk factor to T2DM [16, 43, 46].

Experimental studies attempt to explain the pathophysiological mechanisms that lead to metabolic outcomes described above. Xu et al. showed that $PM_{2.5}$ exposure for 12 weeks promoted significant liver damage, evidenced by elevated levels of hepatic stress biomarkers, such as transaminases (ALT and AST) and reduced glycogen levels, alterations involved in impaired glucose tolerance and insulin resistance in mice. Also, this work demonstrated that $PM_{2.5}$ exposure triggered Nrf2-mediated oxidative responses and activated the JNK-mediated inhibitory signaling pathway, resulting in hepatic dysfunction. Wherefore, hepatic insulin resistance can also be a potential mechanism of diabetes pathogenesis due to pollutants [45].

Oxidative stress is a common factor in both conditions, T2DM and $PM_{2,5}$. Furthermore, the oxidative stress induced by $PM_{2,5}$ also represents a pathogenic stimulus for pancreatic β-cell dysfunction [47], since it is responsible for debility on the antioxidant defenses [48].

The redox unbalance promoted by exposure to air pollution can stimulates an inflammatory processes, contributing to installation of a metabolic disorder. The role of inflammation in the toxicity mediated by $PM_{2,5}$ is associated to the increase in alveolar immunological response (increased phagocytic cell count) and to pro-inflammatory cytokines production by these cells in the alveolar surface [49], accompanied by increased lung oxidative damage [50–52], which generally evolute to systemic oxidative stress, a risk for diabetes complications.

Postulated mechanisms of action include oxidative stress and low-grade inflammation, endothelial dysfunction, visceral adipose tissue inflammation, endoplasmic reticulum stress, and mitochondrial dysfunction [5, 53]. Thus, both acute and chronic $PM_{2,5}$ exposures are associated to inflammatory and oxidative markers, as well as in T1DM and T2DM, but it is not clear the real effects of diabetes plus air pollution combination. However, the pathophysiology involved in this case increases the global risk of death by increasing the susceptibility to air pollution damage [10].

Cell stress response, observed by alteration in HSPs levels in different organs, is a defensive and cytoprotective response in both conditions, exposure to pollutants and metabolic diseases. However, there are few pieces of evidence about $PM_{2,5}$ exposure concomitant to T2DM development that explores heat shock response [16].

The HSPs naturally are very sensitive elements to any chemical attack to the cells and are extensive used as biomarker of environmental exposures. In this sense, the iHSP70 expression during cellular challenges indicates that these proteins can be candidate to monitoring air pollution aggression to the health organism [54]. One study showed increase in the iHSP70 in the lung and heart one day after course particle exposure [55], and the authors discussed the plausibility of oxidative stress and/or cytokines in HSPs-induced expression as cellular defense at molecular levels, inhibiting pro-inflammatory pathways. In this way, low doses (12.5 μg/ml) of $PM_{2,5}$ can increase eHSP70 in human bronquial epithelial culture [56]. Thus, the strong correlation among oxidative stress and inflammation induced by $PM_{2,5}$ inhalation promotes both increase in the iHSP70 and eHSP70 content, reinforcing the purpose of use these proteins as an important biomarker of homeostatic equilibrium in environmental challenges [16, 57, 58].

Simulating urbanized conditions (consumption of high fat diet and exposure to $PM_{2.5}$) [16] showed that subchronic exposure to $PM_{2.5}$, even at low doses (5 μg-day, intranasal administration), potentiates metabolic dysfunction in HFD-fed mice, which are T2DM-susceptible. The effects of $PM_{2.5}$ in T2DM mice presented a positive correlation between adiposity, increased body weight and glucose intolerance, and increased glucose and triacylglycerol plasma levels. Also, in this study, pancreas exhibited lower iHSP70 expression, accompanied by 3.7-fold increase in the plasma to pancreas [eHSP72]/[iHSP70] ratio (H-index). This study represents an experimental evidence that the combination of two relevant challenges to the organism, from different origins (environmental and dietary factors), promotes alterations in

cell stress response (measurable by plasma/tissue H-index), reinforcing the chaperone balance [([eHSP72]/[iHSP70]) status] as a biomarker of T2DM risk.

If a short-term $PM_{2.5}$ exposure promotes innumerous damages, long-term exposure may evidence chronic effects on human health. Xu et al. showed in experimental mice model that long-term $PM_{2.5}$ exposure induces alterations on adipose tissue and leads to mitochondrial dysfunction. If $PM_{2.5}$ exposure is associated with other risk factors for T2DM, such as inadequate eating behavior, it observed an increase in adiposity, body weight, and glucose intolerance [16], as well as increase in glucose and triacylglycerol plasma levels. Exposure to $PM_{2.5}$ can markedly potentiate metabolic dysfunction in an already compromised organism, promoting relevant alteration in cell stress response.

The implications to health of a link between $PM_{2.5}$ pollutants exposure and T2DM are critical problems to public health since air pollution is a pervasive risk factor that affects many people worldwide. In this way, it is important to highlight that modest reduction of pollution exposure may provide substantial public health benefits [45]. The underlying mechanisms responsible for this adverse effect in response to ambient $PM_{2.5}$ air pollution need to be further investigated [43]. Both experimental and epidemiologic studies suggest that environmental exposures to air pollutants can increase the risk of insulin resistance, which lead to a link between air pollution and T2DM.

4. Conclusion

This chapter aimed to describe pathophysiological mechanisms of the association between exposure to atmospheric pollution by $PM_{2.5}$ and T2DM development, which are being highlighted in experimental studies connected to epidemiological data. The highlighted mechanisms involve inflammation, oxidative stress, and a clear participation of impaired cell stress response observed by alterations on HSP70 levels. Finally, epidemiological together with experimental studies reinforce the complex nature of T2DM etiology and highlights the $PM_{2.5}$ air pollution as a critical health problem.

It is known that type 2 diabetes results from the interaction between genetic susceptibility, environmental factors, and lifestyle choices, commonly accepted causes for the development of T2DM. However, it is argued that these factors alone cannot fully explain the rapid rise in the prevalence of diabetes [45]. If the high prevalence of T2DM is a result of an association between several risk factors, and air pollution is one, environmental protection represented by prioritization of steps to minimize the air pollution levels may be considered as health strategy to avoid T2DM [44]. Given the enormous number of people exposed to air pollution as shown in **Figure 1**, even conservative reduction of $PM_{2.5}$ emission would translate into a substantial decrease in the population attributable fraction of T2DM related to environmental factors [45]. In perspective, it is expected that future studies will describe molecular mechanisms involved, highlight the responsible pollutants and the role of combined exposures to mixtures, and susceptibility factors. These discoveries of metabolic effects of air pollution may help relevant public health guidelines discussion and government decision in this current context of global urbanization [59].

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Appendices and nomenclatures (Optional)

AGEs:	advanced glycation products.
ALT:	alanine aminotransferase.
AST:	aspartate aminotransferase.
ATMs:	Adipose tissue macrophages.
eHSP70:	70 kDa extracellular heat shock proteins.
FFA:	free fat acid.
FOXO1:	forkhead box protein O1.
GLUT4:	glucose-transporter type 4.
HFD:	high fat diet.
HSF-1:	heat shock factor.
HSP:	heat shock proteins.
HSP70:	70 kDa heat shock proteins.
HSP70-KO:	70 kDa heat shock proteins knockout mice.
iHSP70:	70 kDa intracellular heat shock proteins.
IL-1β:	interleukin-1beta.
IL-6:	interleukin-6.
IL-8:	interleukin-8.
iNOS:	inducible nitric oxide synthase.
kDa:	kilodalton.
mRNA:	messenger RNA.
NADPH:	dihydronicotinamide adenine dinucleotide phosphate;
NF-kB:	factor nuclear kappa B.
NO:	nitric oxide.
NOS-2:	nitric oxide synthase-2.
$PM_{2,5}$:	Fine Particulate Matter.
RAGES:	advanced glycation products binding to specific receptors.
RNS:	nitrosative species.
ROS:	reactive oxygen species.
T2DM:	type 2 diabetes mellitus.
TNF-α:	tumor necrosis factor alpha.
WHO:	world health organization.

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References

[1] World Health Organization. Global Report on Diabetes. Isbn [Internet]. 2016;**978**:88. Available from: http://www.who.int/about/licensing/%5Cnhttp://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf

[2] World Health Organization. Global Urban Ambient Air Pollution Database (update 2016) Available from http://www.who.int/phe/health_topics/outdoorair/databases/cities/en/

[3] Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, et al. Air Pollution and Cardiovascular Disease: A Statement for Healthcare Professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation [Internet]. June 2004;**109**(21):2655-2671. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15173049 [Accessed: 31 July 2017]

[4] Brook RD, Jerrett M, Brook JR, Bard RL, Finkelstein MM. The relationship between diabetes mellitus and traffic-related air pollution. Journal of Occupational and Environmental Medicine [Internet]. January 2008;**50**(1):32-38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18188079 [Accessed: 31 July 2017]

[5] Rajagopalan S, Brook RD. Air pollution and type 2 diabetes: Mechanistic insights. Diabetes. 2012;**61**(December):3037-3045

[6] World Health Organization. WHO Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide: Global Update 2005: Summary of Risk Assessment. Geneva: World Health Organization [Internet]; 2006. p. 1-22 Available from: http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf?ua=1

[7] BreatheLife [Internet]. Available from: http://breathelife2030.org/ [Accessed: 31 July 2017]

[8] Zanobetti A, Schwartz J. Cardiovascular damage by airborne particles: Are diabetics more susceptible? Epidemiology [Internet]. September 2002;**13**(5):588-592. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12192230 [Accessed: 31 July 2017]

[9] Goldberg MS, Burnett RT, Yale J-F, Valois M-F, Brook JR. Associations between ambient air pollution and daily mortality among persons with diabetes and cardiovascular disease. Environmental Research. 2006;**100**:255-267

[10] O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, et al. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circulation [Internet]. 7 June 2005;**111**(22):2913-2920. Available from: http://circ.ahajournals.org/cgi/doi/10.1161/CIRCULATIONAHA.104.517110 [Accessed: 31 July 2017]

[11] Brook RD, Newby DE, Rajagopalan S. Air pollution and cardiometabolic disease: An update and call for clinical trials. American Journal of Hypertension [Internet]. June 2017; Available from: http://www.ncbi.nlm.nih.gov/pubmed/28655143; [Accessed: 31 July 2017]

[12] Hochachka PW, Somero GN. Biochemical Adaptation: Mechanism and Process in Physiological Evolution. Oxford: Oxford University Press; 2002. p. 480

[13] Barrett KE, Ganong WF. Ganong's review of medical physiology. McGraw-Hill Medical. 2012;752

[14] Heck TG, Ludwig MS, dos Santos AB, Goettems-Fiorin PB. Lifestyle and aging effects in the development of insulin resistance — Activating the muscle as strategy against insulin resistance by modulating cytokines and HSP70. In: Muscle Cell and Tissue [Internet]. InTech; 2015. Available from: http://www.intechopen.com/books/muscle-cell-and-tissue/lifestyle-and-aging-effects-in-the-development-of-insulin-resistance-activating-the-muscle-as-strate [Accessed: 17 August 2017]

[15] Xu J, Zhang W, Lu Z, Zhang F, Ding W. Airborne PM 2.5 -Induced Hepatic Insulin Resistance by Nrf2/JNK-Mediated Signaling Pathway. 2017

[16] Goettems-Fiorin PB, Grochanke BS, Baldissera FG, dos Santos AB, Homem de Bittencourt PI, Ludwig MS, et al. Fine particulate matter potentiates type 2 diabetes development in high-fat diet-treated mice: Stress response and extracellular to intracellular HSP70 ratio analysis. Journal of Physiology and Biochemistry. 2016;**72**(4):643-656

[17] Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nature Medicine [Internet]. July 2017;**23**(7):804-814. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28697184 [Accessed: 31 July 2017]

[18] Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circulation Research. 2010;**107**(9):1058-1070

[19] Roman-Pintos LM, Villegas-Rivera G, Rodriguez-Carrizalez AD, Miranda-Diaz AG, Cardona-Munoz EG. Diabetic polyneuropathy in type 2 diabetes mellitus: Inflammation, oxidative stress, and mitochondrial function. Journal of Diabetes Research. 2016; **2016**:3425617

[20] Kayama Y, Raaz U, Jagger A, Adam M, Schellinger I, Sakamoto M, et al. Diabetic cardiovascular disease induced by oxidative stress. International Journal of Molecular Sciences

[Internet]. October 2015;**16**(10):25234-25263. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26512646 [Accessed: 31 July 2017]

[21] Newsholme P, de Bittencourt PIH. The fat cell senescence hypothesis: A mechanism responsible for abrogating the resolution of inflammation in chronic disease. Current Opinion in Clinical Nutrition and Metabolic Care [Internet]. July 2014;**17**(4):295-305. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24878874 [Accessed: 10 June 2015]

[22] Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes [Internet]. April 2007;**56**(4):1010-1013. Available from: http://diabetes.diabetesjournals.org/cgi/doi/10.2337/db06-1656 [Accessed: 31 July 2017]

[23] Kirwan AM, Lenighan YM, O'Reilly ME, McGillicuddy FC, Roche HM. Nutritional modulation of metabolic inflammation. Biochemical Society Transactions [Internet]. July 2017;**45**(4):979-985. Available from: http://biochemsoctrans.org/lookup/doi/10.1042/BST20160465 [Accessed: 31 July 2017]

[24] Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: The linking mechanism and the complications. Archives of Medical Science [Internet]. 2017;**4**:851-863. Available from: https://www.termedia.pl/doi/10.5114/aoms.2016.58928 [Accessed: 31 July 2017]

[25] de Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS Letters [Internet]. January 2008;**582**(1):97-105. Available from: http://doi.wiley.com/10.1016/j.febslet.2007.11.057 [Accessed: 31 July 2017]

[26] Thomas D, Apovian C. Macrophage functions in lean and obese adipose tissue. Metabolism [Internet]. July, 2017;**72**:120-143. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0026049517301130 [Accessed: 31 July 2017]

[27] Hooper PL, Hooper JJ. Loss of defense against stress: Diabetes and heat shock proteins. Diabetes Technology & Therapeutics [Internet]. February 2005;**7**(1):204-208. Available from: http://online.liebertpub.com/doi/abs/10.1089/dia.2005.7.204 [Accessed: 31 July 2017]

[28] Chung J, Nguyen A-K, Henstridge DC, Holmes AG, Chan MHS, Mesa JL, et al. HSP72 protects against obesity-induced insulin resistance. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**(5):1739-1744

[29] Bruce CR, Carey AL, Hawley JA, Febbraio MA. Intramuscular heat shock protein 72 and heme oxygenase-1 mRNA are reduced in patients with type 2 diabetes: Evidence that insulin resistance is associated with a disturbed antioxidant defense mechanism. Diabetes [Internet]. September 2003;**52**(9):2338-2345. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12941774 [Accessed: 31 July 2017]

[30] Morino K, Petersen KF, Shulman GI. Molecular mechanisms of insulin resistance in humans and their potential links with mitochondrial dysfunction. Diabetes [Internet].

December 2006;**55**(Suppl 2):S9-S15. Available from: http://diabetes.diabetesjournals.org/cgi/doi/10.2337/db06-S002 [Accessed: 31 July 2017]

[31] Drew BG, Ribas V, Le JA, Henstridge DC, Phun J, Zhou Z, et al. HSP72 is a mitochondrial stress sensor critical for parkin action, oxidative metabolism, and insulin sensitivity in skeletal muscle. Diabetes [Internet]. May 2014;**63**(5):1488-1505. Available from: http://diabetes.diabetesjournals.org/lookup/doi/10.2337/db13-0665 [Accessed: 31 July 2017]

[32] Henstridge DC, Bruce CR, Drew BG, Tory K, Kolonics A, Estevez E, et al. Activating HSP72 in rodent skeletal muscle increases mitochondrial number and oxidative capacity and decreases insulin resistance. Diabetes [Internet]. June 2014;**63**(6):1881-1894. Available from: http://diabetes.diabetesjournals.org/cgi/doi/10.2337/db13-0967 [Accessed: 31 July 2017]

[33] Ran R, Lu A, Zhang L, Tang Y, Zhu H, Xu H, et al. Hsp70 promotes TNF-mediated apoptosis by binding IKK gamma and impairing NF-kappa B survival signaling. Genes & Development [Internet]. June 2004;**18**(12):1466-1481. Available from: http://www.genesdev.org/cgi/doi/10.1101/gad.1188204 [Accessed: 31 July 2017]

[34] Pockley AG, Shepherd J, Corton JM. Detection of heat shock protein 70 (Hsp70) and anti-Hsp70 antibodies in the serum of normal individuals. Immunological Investigations [Internet]. December 1998;**27**(6):367-377. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9845422 [Accessed: 31 July 2017]

[35] Garamvölgyi Z, Prohászka Z, Rigó J, Kecskeméti A, Molvarec A. Increased circulating heat shock protein 70 (HSPA1A) levels in gestational diabetes mellitus: A pilot study. Cell Stress Chaperones [Internet]. July 2015;**20**(4):575-581. Available from: http://link.springer.com/10.1007/s12192-015-0579-y [Accessed: 31 July 2017]

[36] Nakhjavani M, Morteza A, Khajeali L, Esteghamati A, Khalilzadeh O, Asgarani F, et al. Increased serum HSP70 levels are associated with the duration of diabetes. Cell Stress & Chaperones [Internet]. November 2010;**15**(6):959-964. Available from: http://link.springer.com/10.1007/s12192-010-0204-z [Accessed: 31 July 2017]

[37] Williams JHH, Hunter-Lavin C. Roles of extracellular heat shock proteins: A new sense of danger. In: . Heat Shock Proteins: Potent Mediators of Inflammation and Immunity. Netherlands. Springer. p. 39-57. Available from: http://linkspringer.com/10.1007/978-1-4020-5585-0_4 [Accessed: 31 July 2017]

[38] Krause M, Keane K, Rodrigues-Krause J, Crognale D, Egan B, De Vito G, et al. Elevated levels of extracellular heat-shock protein 72 (eHSP72) are positively correlated with insulin resistance in vivo and cause pancreatic β-cell dysfunction and death in vitro. Clin**ical** Sci**ence** (Lond) [Internet]. May, 2014;**126**(10):739-752. Available from: http://clinsci.org/lookup/doi/10.1042/CS20130678 [Accessed: 31 July 2017]

[39] Krause M, Heck TG, Bittencourt A, Scomazzon SP, Newsholme P, Curi R, et al. The chaperone balance hypothesis: The importance of the extracellular to intracellular HSP70 ratio to inflammation-driven type 2 diabetes, the effect of exercise, and the implications for

clinical management. Mediators of Inflammation [Internet]. January 2015;**2015**:249205: [Accessed: 1 April 2015]Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4357135&tool=pmcentrez&rendertype=abstract

[40] Heck TG, Scomazzon SP, Nunes PR, Schöler CM, da Silva GS, Bittencourt A, et al. Acute exercise boosts cell proliferation and the heat shock response in lymphocytes: Correlation with cytokine production and extracellular-to-intracellular HSP70 ratio. Cell Stress & Chaperones. 2017;**22**(2):271-291

[41] Jacobs L, Emmerechts J, Mathieu C, Hoylaerts MF, Fierens F, Hoet PH, et al. Air pollution related prothrombotic changes in persons with diabetes. Environmental Health Perspectives [Internet]. February 2010;**118**(2):191-196. Available from: http://ehp.niehs.nih.gov/0900942 [Accessed: 31 July 2017]

[42] Pearson J, Bachireddy C, Shyamprasad S, Goldfine A, Brownstein J. Association between fine particulate matter and diabetes prevalence in the U.S. Diabetes Care. 2010; **33**(10):2196-2201

[43] Xu X, Liu C, Xu Z, Tzan K, Zhong M, Wang A, et al. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. Toxicological Sciences. 2011;**124**(1):88-98

[44] Meo SA, Memon AN, Sheikh SA, Rouq FA, Usmani AM, Hassan A, et al. Effect of environmental air pollution on type 2 diabetes mellitus. European Review for Medical and Pharmacological Sciences [Internet]. January 2015;**19**(1):123-128. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25635985 [Accessed: 31 July 2017]

[45] Esposito K, Petrizzo M, Maiorino MI, Bellastella G, Giugliano D. Particulate matter pollutants and risk of type 2 diabetes: A time for concern? Endocrine. 2016;**51**(1):32-37

[46] Liu C, Yang C, Zhao Y, Ma Z, Bi J, Liu Y, et al. Associations between long-term exposure to ambient particulate air pollution and type 2 diabetes prevalence, blood glucose and glycosylated hemoglobin levels in China. Environment International. 2016;**92**:416-421

[47] Zhang F, Li L, Krafft T, Lv J, Wang W, Pei D. Study on the association between ambient air pollution and daily cardiovascular and respiratory mortality in an urban district of Beijing. International Journal of Environmental Research and Public Health. 2011;**8**(6):2109-2123

[48] Domínguez C, Ruiz E, Gussinye M, Carrascosa A. Oxidative stress at onset and in early stages of type 1 diabetes in children and adolescents. Diabetes Care [Internet]. 1998;**21**(10):1736-1742. Available from http://www.ncbi.nlm.nih.gov/pubmed/9773740

[49] Dubowsky SD, Suh H, Schwartz J, Coull BA, Gold DR. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. Environmental Health Perspectives. 2006;**114**(7):992-998

[50] Rhoden CR, Lawrence J, Godleski JJ, González-Flecha B. N-acetylcysteine prevents lung inflammation after short-term inhalation exposure to concentrated ambient particles. Toxicological Sciences. 2004;**79**:296-303

[51] Rhoden CR, Wellenius GA, Ghelfi E, Lawrence J, González-Flecha B. PM-induced cardiac oxidative stress and dysfunction are mediated by autonomic stimulation. Biochimica et Biophysica Acta (BBA)-General Subjects. 2005;**1725**:305-313

[52] Rhoden CR, Ghelfi E, González-Flecha B. Pulmonary inflammation by ambient air particles is mediated by superoxide anion. Inhalation Toxicology. 2008;**20**:11-15

[53] Liu C, Xu X, Bai Y, Wang TY, Rao X, Wang A, et al. Air pollution-mediated susceptibility to inflammation and insulin resistance: Influence of CCR2 pathways in mice. Environmental Health Perspectives. 2014;**122**:17-26

[54] Mukhopadhyay I, Nazir A, Saxena DK, Kar CD. Heat shock response: Hsp70 in environmental monitoring. Journal of Biochemical and Molecular Toxicology. 2003;**17**(5):249-254

[55] Farina F, Sancini G, Battaglia C, Tinaglia V, Mantecca P, Camatini M, et al. Milano summer particulate matter (PM10) triggers lung inflammation and extra pulmonary adverse events in mice. PloS One. 2013;**8**(2):e56636

[56] Watterson TL, Hamilton B, Martin R, Coulombe RA. Urban particulate matter causes ER stress and the unfolded protein response in human lung cells. Toxicological Sciences. 2009;**112**(1):111-122

[57] El Golli-Bennour E, Bacha H. Hsp70 expression as biomarkers of oxidative stress: Mycotoxins' exploration. Toxicology [Internet]. 2011;**287**(1-3):1-7 Available from: http://dx.doi.org/10.1016/j.tox.2011.06.002

[58] Kido T, Bai N, Yatera K, Suzuki H, Meredith A, Mukae H, et al. Diesel exhaust inhalation induces heat shock protein 70 expression in vivo. Inhalation Toxicology. 2011; **23**(May):593-601

[59] Liu C, Ying Z, Harkema J, Sun Q, Rajagopalan S. Epidemiological and experimental links between air pollution and type 2 diabetes. Toxicologic Pathology. 2012; (October 2012)

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