A possible link between particulate matter air pollution and type 2 diabetes

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PREFACE

This report was written in the context of the master’s degree programme Energy and Environmental Sciences at the University of Groningen. The subject for this report was handed to me by prof. R. Vonk, who is a member of the medical biomics group at the University Medical Center Groningen (UMCG). I met him earlier during my biology study and decided to approach him for a master thesis subject.

Throughout the process of my master thesis the confidence in my presentation skills has really grown since I was challenged to present my results several times. Furthermore, in comparison to my previous researches I have positively developed my writing skills and time planning skills. Overall, it was a very good learning experience for me.

I would like to thank my first supervisor prof. R. Vonk and second supervisor prof. T. Schoot Uiterkamp (IVEM) for their useful comments, and for keeping me on track despite my rather complex subject. I enjoyed these meetings, as well as the coffee breaks at IVEM which were always inspiring due to my fellow students.
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Summary

Particulate matter (PM) air pollution is most commonly referred to as PM$_{10}$ and can be subdivided into coarse particles, fine particles and ultrafine particles. Sources of PM air pollution include combustion from car engines and industrial processes. Exposure to PM air pollution is associated with adverse health effects including lung—and cardiovascular disease and mortality. The inflammatory response induced by PM exposure is thought to play an important role in these complications.

Another disease associated with inflammation is diabetes mellitus type 2 (T2D), which is the most common metabolic disease in the world. Inflammatory mediators have been shown to be elevated in diabetic subjects and to predict the development of T2D. Since both T2D and PM exposure are associated with inflammation, PM exposure may contribute to the development of T2D. Several studies have already indicated a relation between PM air pollution and T2D and in most of these studies a role for inflammatory mechanisms was mentioned explicitly.

PM-induced inflammation can be seen in the lungs but also throughout the body, which is referred to as systemic inflammation. Furthermore, the smallest PM category; the ultrafine particles (UFPs), have the ability to enter the blood as a whole and induce additional damage in the circulation as well as other organs.

PM exposure may contribute to the development of T2D since inflammation has been shown to be closely linked to insulin signaling. Indeed studies have shown that mediators of inflammation can induce insulin resistance and decreased insulin secretion, which are the main features of T2D. Since many chronic inflammatory diseases have been associated with the development of T2D, it is suggested that the development of T2D can be triggered by many inflammatory stimuli and that it is an inflammatory disease rather than just a metabolic disease.

Overall, it is suggested that a general state of inflammation can result in the development of diabetic complications, regardless of the stressor. Thus, it is plausible that PM exposure contributes to the development of T2D since PM exposure is also associated with the induction of inflammation. The economic burden of T2D on society is already significant and is projected to increase strongly in the coming decades due to dietary and lifestyle factors. Thus, in the context of increasing urbanization, PM effects may raise this burden even more. However, whether an individual actually develops T2D as a consequence of (PM-induced) inflammation is extremely difficult to predict, since this may be dependent on many factors.

PM air pollution should be subject of future research since the effects of these particles on human health and the mechanisms behind it are still partly unknown. The potential relation between PM exposure and T2D indicates that PM effects may be even broader than previously thought.

The smallest PM category, the ultrafine particles (UFPs), deserve special attention in future research since UFP emissions are likely to increase in the coming years due to the application of new technologies in automobile engines. Even though it is known that UFPs can travel to organs, the health effects of these particles are as yet unknown and may be underestimated.
1 INTRODUCTION

1.1 Problem definition

The prevalence of diabetes mellitus type 2 (T2D) is becoming a global burden and it is projected that within 25 years, 366 million people will suffer from this life-threatening disease (WHO, 2004). Obesity, the state of severe overweight, is a main risk factor for the development of T2D (Klein et al., 2002). However, the relation between obesity and the development of T2D is not well understood.

Evidence is now accumulating that suggests that obesity is a state of chronic low-level inflammation and that inflammatory mechanisms may play a role in the development of T2D (Dandona et al., 2005; Wellen & Hotamisligil, 2005). Increased levels of plasma inflammatory markers such as interleukin-6 and C-reactive protein have been observed in obese persons and are predictive for the development of T2D (Cancello & Clement, 2006; Schmidt & Duncan, 2003). Interestingly, some evidence indicates that other chronic inflammatory conditions, such as rheumatoid arthritis and inflammatory lung diseases, can also increase the risk of T2D (Wellen & Hotamisligil, 2005). Another condition that might induce inflammatory processes is the exposure to particulate matter (PM).

Since motor vehicles are the primary source of PM emissions, these emissions are released very close to humans. Substantial epidemiological evidence suggests that fine PM air pollution has adverse human health effects; air-pollution in the form of PM increases the risk of cardiovascular and cardiopulmonary diseases (Pope III et al., 2002; Pope III et al., 2004). The underlying mechanisms that lead to these diseases as a consequence of PM exposure are not well understood. Some studies associate high concentrations of PM with inflammatory factors such as C-reactive protein (Zeka et al., 2006). This indicates that exposure to PM may induce inflammatory processes that are similar to those that have been observed in obese persons (Van der Hoek, 2006). If so, PM exposure could ultimately result in a higher risk of diseases such as T2D.

At the moment, there is not much known about the relation between PM exposure, inflammation and T2D and therefore more research is needed.

1.2 Research aim

This research aims to find more evidence for the hypothesis that the inflammatory pathways involved in the development of T2D as a consequence of obesity are similar to the pathways of inflammation caused by PM exposure. If the outcome of this research indicates that there is evidence for this hypothesis, then more specific research can be done in the future.

1.2.1 Research question

The main research question of this research is:
- Can PM exposure lead to a higher risk of developing T2D?

In order to tackle the main research question in a convenient way, this question is divided into the following sub questions:
- Are there any lines of evidence that indicate a possible connection between T2D and PM air pollution?
- Which inflammation pathways are induced by PM exposure?
- How can PM-induced inflammation contribute to the development of T2D?
- What can influence the potential effect of PM exposure on the development of T2D?
1.3 Method
In order to give adequate answers to the research and sub questions, information on PM exposure, inflammatory processes, and T2D had to be found. Therefore, a literature study was performed.

1.3.1 Boundaries
This research will be focused on T2D. Other diseases are not emphasized in this research. However, if relevant information is found on other diseases, then this will not be excluded from the research. Further, the focus will be on the development of T2D as a consequence of inflammatory processes found in obese persons. Moreover, if interesting information is found on the development of T2D as a consequence of other kinds of processes, then this will be taken into account.

1.4 Structure of this report
In chapter 2 some background information on PM air pollution and T2D is presented.
Chapter 3 describes several lines of evidence that indicate a potential relationship between PM air pollution and T2D.
In the 4th chapter, PM-induced inflammation is described rather detailed.
Chapter 5 describes inflammation in the context of T2D and discusses the potential contribution of PM exposure to the development of this disease.
Chapter 6 describes several factors that may influence an individual’s response to inflammation.
In the 7th chapter the conclusion is given together with some points of discussion.
Chapter 8 gives a recommendation for future research.
2 BACKGROUND

First of all, some background information on particulate matter air pollution and diabetes type 2 is given.

2.1 Particulate matter air pollution

Particulate matter (PM) is an air pollutant consisting of a mixture of particles that can be solid, liquid or both and that may vary in mass, size and chemical composition (WHO, 2005). PM levels relevant to human health are commonly referred to as PM\(_{10}\), which are particles with a diameter smaller than 10 µm. This is because only these particles can penetrate into the lungs (Van Bree & Cassee, 2000). Next, PM\(_{10}\) is further discussed.

2.1.1 PM\(_{10}\)

PM\(_{10}\) can be variable and complex in composition. Some of the more common components include nitrates, sulphates, elemental and organic carbon, organic compounds (such as polycyclic aromatic hydrocarbons; PAHs), biological compounds (for example endotoxins and cell fragments), and a variety of metals (such as iron, copper, nickel, zinc, and vanadium), but there are thousands of chemicals that have been detected in particulate matter in different locations (Brook et al., 2004).

Depending on its particle size, PM\(_{10}\) can be subdivided into coarse particles, fine particles and ultrafine particles.

- Coarse particles have a diameter between 2.5 and 10 µm (PM\(_{2.5}\) – PM\(_{10}\)) and are derived primarily from suspension or re-suspension of dust, soil, or other crustal materials from roads, farming, mining, windstorms, volcanoes, and so forth. Coarse particles also include sea salts, pollen, mold, spores, and other plant parts (Pope III & Dockery, 2006).

- Fine particles (PM\(_{2.5}\)) have a diameter of about 0.1-2.5 µm. These particles are products of atmospheric transformation of nitrogen oxides (NO) mainly emitted by traffic and some industrial processes (such as building, mining and smelting), and sulfur dioxide (SO\(_2\)) resulting from the combustion of sulfur-containing fuels (WHO, 2005). In comparison to coarse particles, fine particles are considered more risky in terms of health effects since they can penetrate into deeper regions of the lungs due to their aerodynamic characteristics (Bai et al., 2007).

- Ultrafine particles (UFPs) have a diameter smaller than 0.1 µm. Ambient air in urban and industrial environments is constantly receiving fresh emissions of UFPs from combustion-related sources, such as vehicle exhaust (Pope III & Dockery, 2006). Because UFPs have a larger surface area in comparison to coarse and fine particles, they have been proposed to possess a much greater potential for interaction with biological targets, which can result in a more significant impact on health. There has been more interest recently in UFPs, because on the contrary to larger particles, UFPs have the ability to travel from the lungs to the blood and other parts of the body (Bai et al., 2007).

The size of the particles is important in determining the time they spend in the atmosphere. Sedimentation and precipitation remove coarse particles from the atmosphere within few hours of emission (WHO, 2005). Fine particles and UFPs remain suspended in the air for longer periods where they tend to aggregate into larger particles with the potential for their components to be altered before settling down (Bai et al., 2007). Also, fine particles and UFPs can be transported over longer distances in comparison to coarse particles.

In Figure 2-1 the various sizes of particulate matter are shown in comparison with a strand of human hair and grains of fine beach sand (Bai et al., 2007).
2.1.2 Health effects

The health effects of PM air pollution have been subject of intense study. Studies have observed statistical associations between short- and long-term PM exposure and increased morbidity and mortality (Van Bree & Cassee, 2000). The adverse health effects associated with PM exposure can be divided into those that are seen in the lungs (local effects) and those that impact on the cardiovascular system (systemic effects). In Box 2-1 some of the well-documented health effects are listed (Pope III & Dockery, 1999).

Box 2-1: Health effects associated with PM exposure (Pope III & Dockery, 1999).

- Increased use of medication for asthma
- Attacks of asthma in patients with pre-existing asthma
- Attacks of chronic obstructive pulmonary disease (COPD), which is the umbrella term for chronic bronchitis, emphysema and a range of other lung disorders
- Admission to hospital for cardiovascular causes
- Deaths from heart attacks
- Deaths from strokes
- Deaths from respiratory causes

A number of mechanisms has been proposed to explain the adverse health effects of PM exposure. Effects of PM that have experimental support are inflammation, cytokine and chemokine release, production of white blood cells, oxidative stress-generation in the lungs, endotoxin-mediated cellular and tissue responses, stimulation of receptors, and alteration of enzyme function (Nel, 2005).
2.1.3 Role of inflammation
In humans, the inflammatory response induced by PM exposure is best described and is thought to play a vital role in the development of PM-associated cardiovascular disease. Since PM-induced inflammation is the subject of this research, it is discussed more detailed in chapter 4.

2.2 Diabetes type 2
Diabetes mellitus is the most common metabolic disease in the world and has reached virtually epidemic proportions. Projections are that the number of people with diabetes will more than double over the next 25 years, to reach a total of 366 million by 2030. This increase will largely be the result of population growth and aging, and dietary and other lifestyle factors. Diabetes has become one of the major causes of premature illness and death in most countries, mainly through the increased risk of cardiovascular disease (CVD) (WHO, 2004).

2.2.1 Obesity
Most persons with diabetes have type 2, which means they can not use insulin effectively (see next paragraph). One of the most important risk factors for type 2 diabetes (T2D) is obesity, which is characterized by abnormal or excessive accumulation of adipose tissue (fat tissue). A body mass index (BMI)\(^1\) of 30 or more indicates obesity (WHO, 2004).

Adult weight gain, the degree of obesity and the duration of obesity are all independent and strong predictors of the risk of T2D. It has been calculated that in white people around 65%-75% of incident cases of diabetes could be avoided if the whole population would not exceed a BMI of 25 kg/m\(^2\) (Seidell, 2000). Current trends in obesity suggest that in the coming years the prevalence of T2D may be even greater than projected.

2.2.2 Pathogenesis of T2D
A combination of insulin resistance and pancreatic β-cell dysfunction underlies most cases of T2D. These two features are explained next and illustrated by Figure 2-2 (Stumvoll et al., 2005).

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\(^1\) Body mass index (BMI) is defined by weight (in kilograms) divided by height (in metres) squared.
Insulin, the hormone secreted by the β-cells of the pancreas, controls the blood glucose level by attaching to cells and removing glucose from the bloodstream so that it can be used as an energy source. In normal state, insulin secretion from the pancreas reduces glucose output by the liver, enhances glucose uptake by skeletal muscle, and suppresses fatty acid release from adipose tissue. However, in the case of obesity or severe overweight, adipocytes (fat cells) become resistant to the ability of insulin to suppress the breakdown of fat. Insulin resistance of adipose tissue can ultimately result in increased release and increased circulating levels of free fatty acids in the blood, which aggravates insulin resistance in skeletal muscle and liver, leading to abnormal high levels of glucose in the blood (hyperglycemia). In turn, the raised concentrations of glucose and fatty acids in the bloodstream will feed back to worsen both insulin resistance and β-cell dysfunction.

Many factors have been proposed to play a role in the development of insulin resistance and β-cell dysfunction. These include hyperglycemia, free fatty acids, adipokines (cytokines produced by adipose tissue), genes, but also inflammation.

### 2.2.3 Role of inflammation

Over the past decade, obesity has been associated with inflammation (Dandona et al., 2005). This association was first proposed in the landmark article by Hotamisligil et al, in which tumor necrosis factor-alpha (TNF-a), an inflammatory cytokine, was shown to be over-expressed in the adipose tissues of rodent models of obesity (Hotamisligil et al., 1993). Since then, more data have accumulated to support the concept that obesity is a state of chronic low-grade inflammation. For example, increased levels of plasma inflammatory markers have also been observed in obese persons.

The fact that obesity is a state of inflammation has led to the hypothesis that inflammatory mechanisms may play a role in the development of T2D (Dandona et al., 2005; Wellen & Hotamisligil, 2005). The relation between inflammation and T2D is further described in chapter 5.
3 PARTICULATE MATTER AND DIABETES

Both PM air pollution and T2D have been associated with inflammation. This was already briefly discussed in the previous chapter. In addition, cardiovascular complications have also been linked to both PM air pollution and T2D (Grundy et al., 1999; Pope III & Dockery, 2006). These similarities indicate that PM exposure and the development of T2D may involve some of the same pathways, and suggest the possibility of a synergistic effect. In this chapter, several lines of evidence that link PM air pollution to T2D are discussed.

3.1 Diabetics are a susceptible population

In 2005, O’Neill et al. examined whether endothelium-dependent and -independent vascular reactivity was associated with particle exposure in individuals with and without diabetes. The results indicated that T2D enhances vulnerability to particles associated with coal-burning power plants and traffic (O’Neill et al., 2005).

Results from earlier studies suggested that the PM associated acute risk for cardiovascular events in patients with diabetes mellitus may be 2-fold higher than for non-diabetics (Zanobetti & Schwartz, 2001, 2002). These epidemiological studies suggest that people with diabetes are vulnerable to cardiovascular health effects associated with exposure to particle air pollution.

In 2007, O’Neill and colleagues provided additional evidence suggesting that the enhanced susceptibility of people with diabetes to air pollution may be partly due to inflammatory mechanisms (O’Neill et al., 2007).

3.2 Cigarette smoke and insulin resistance

Exposure to PM air pollution can occur both outdoors and indoors. Besides cooking and home heating sources, cigarette smoke is one of the main contributors to indoor PM pollution. Besides the fact that smoking is a major risk factor for atherosclerosis and cardiovascular disease (CVD), considerable evidence exists for the view that smoking is associated with insulin resistance (Reaven & Tsao, 2003).

In 1992, it was demonstrated that smokers, compared to a matched group of non-smokers, were insulin resistant and hyper-insulimic (abnormal high plasma insulin levels). This was soon confirmed by the evidence that smoking one cigarette per hour for six hours was associated with a decrease in insulin sensitivity. In addition to these results, other population based reports have indicated that smokers have higher insulin levels (which is an indicator of insulin resistance) than non-smokers. Furthermore, it was documented that smoking cessation was associated with improved insulin sensitivity; even though this was associated with weight gain as well. Smoking has also been shown to aggravate the degree of insulin resistance in patients with T2D (Reaven & Tsao, 2003).

Several studies have indicated that cigarette smoke induces inflammation (Ambrose & Barua, 2004). Cigarette smoke is for example associated with an increased level of various inflammatory markers including C-reactive protein, Interleukin-6 and TNF-a in both female and male smokers. Elevations of certain pro-inflammatory cytokines increase the level of peripheral blood leukocytes and indeed, several studies have indicated that cigarette smoke causes an increase in peripheral blood leukocyte count of about 20-25 percent (Ambrose & Barua, 2004).
3.3 COPD, asthma and risk of T2D in women
Epidemiological evidence suggests that asthma and COPD symptoms can be worsened by increases in PM air pollution (Pope III & Dockery, 1999).
In both COPD and asthma inflammation plays a key role. Since inflammation has also emerged as a risk factor for the development of T2D, this has led to the hypothesis that COPD and asthma may increase risk for T2D. Rana and colleagues have tested this hypothesis in a cohort study involving almost 100,000 women and results indicated that only subjects with COPD had a statistically significant increased risk of T2D (Rana et al., 2004).
The fact that COPD, but not asthma, was related to T2D could be explained by the differences in the type of inflammation in COPD versus asthma. In contrast to asthma, COPD is associated with the inflammatory markers that have also been linked to the development of T2D. This suggests that inflammation may be the common link.

3.4 Traffic related air pollution and T2D
Brook and colleagues explored the question of whether traffic-related air pollution (using NO₂ as a marker) associates with the prevalence of diabetes. A significant relationship was identified among women, which was not confounded by other variables related to diabetes in the cohort. Thus, results suggest that air pollution is associated with diabetes. However, more investigation is necessary to determine if this is a cause-and-effect relationship (Brook et al., 2008).

3.5 Conclusion
Several studies indicate a relation between PM air pollution and the development of T2D or features of this disease. Inflammation has repeatedly been mentioned as the underlying mechanism for this potential relationship. Therefore, in the next chapter, inflammation in the context of PM exposure is discussed more detailed.
4 PARTICULATE MATTER AND INFLAMMATION

As mentioned in chapter 2, there is strong evidence that indicates that exposure to particulate matter (PM) is an important independent risk factor for increased cardiovascular morbidity and mortality. Several mechanisms responsible for PM associated cardiovascular events have been explored. The inflammatory response induced by PM plays a large role in this. In this chapter, inflammation in the context of PM exposure is described.

4.1 The innate immune system

The innate or natural immune system is the body’s first line of defense against environmental threats such as microbial infection and physical or chemical injury. In innate immunity, various reactions repair damage, avoid and isolate threats and restore homeostasis (Fernandez-Real & Pickup, 2008). Inflammation is such a reaction and is a key component of innate immunity.

4.1.1 Inflammation

Inflammation is the local protective response to tissue injury (Pickup, 2004). Signs of inflammation are redness, swelling, heat and pain. The main mediators of inflammation are inflammatory cytokines, which are polypeptides produced by many cells.

Besides local effects in inflammation, there is a systemic effect known as the acute-phase response (APR) (Pickup, 2004). The acute-phase response is best characterized by significant changes in the concentration of certain circulating proteins and other substances, called acute-phase proteins. An example of an acute-phase protein is C-reactive protein (CRP). Acute phase proteins such as CRP are mostly synthesized in the liver, and production is stimulated by pro-inflammatory cytokines such as Interleukin-6 (IL-6), Interleukin-1B (IL-1B) and tumor necrosis factor alpha (TNF-a). In general, acute-phase proteins limit injury or aid healing (Pickup, 2004).

4.2 Particle-induced inflammation

PM air pollution has been shown to have the ability to cause inflammation in humans exposed to concentrated airborne ambient particles and instilled PM. Inflammation was also observed in animal models following instillation (Donaldson et al., 2003). PM exposure gives rise to inflammation on both the local and systemic scale. The local and systemic inflammatory responses induced by PM exposure are illustrated by Figure 4-1.

4.2.1 Local inflammation

In the lungs, the deposition of PM leads to activation of two pathways of inflammation. First, PM exposure induces the generation of pro-inflammatory cytokines (such as IL-6, IL-1B and TNF-a) by alveolar macrophages. And second, PM exposure induces the production of chemokines (such as monocyte chemoattractant protein-1, MCP-1) by the epithelium. Inflammation that is observed in the lungs is considered local inflammation. However, the inflammatory mediators released by alveolar macrophages and the epithelium are not only important in inducing local inflammation. It has been indicated that the inflammatory response induced by PM exposure is also seen systemically. For example, elevated blood levels of inflammatory mediators (including IL-6 and CRP) have been observed in association with particle exposure (Brook et al., 2004; Van Eeden et al., 2001; Zeka et al., 2006). Next, the systemic inflammatory response induced by PM exposure is further described. For additional references, see Bai et al., (2007).
4.2.2 Systemic inflammation

The hypothesis for how PM exposure induces a systemic inflammatory response is that inflammatory mediators derived from the lungs spill over in the circulation and trigger a cascade of inflammatory reactions in the circulation and other organs (Bai et al., 2007). Indeed, studies have shown that exposure to PM induces an acute phase response (Bai et al., 2007). For example, data has indicated that CRP levels are positively associated with particle exposure (Zeka et al., 2006).

Besides the stimulation of acute phase protein synthesis in the liver, PM exposure is associated with stimulation of the bone marrow (Bai et al., 2007). Studies have indicated that PM-induced cytokine production in the lungs stimulates the bone marrow which results in an increase in circulation leukocytes. This also suggests that there is a systemic inflammatory response induced by PM exposure.

In addition to an increase in levels of pro-inflammatory cytokines and chemokines, PM exposure also induces the release of adhesion molecules and growth factors, all of which are components that contribute to the occurrence of cardiovascular events, such as thrombosis and heart attack (Bai et al., 2007). A detailed description of these mechanisms is not included in this report, because of time limitations and the need not to make the subject of this research more complex or broader than it already is.

For a detailed description of the mechanisms involved in PM air pollution-induced cardiovascular dysfunction, and additional references, see (Bai et al., 2007).

![Figure 4-1: Schematic illustration of the local and systemic inflammatory response induced by PM air pollution. Illustration from (Bai et al., 2007).](image-url)

4.2.3 Translocation of UFPs

Besides the ‘spillover’ hypotheses, in which inflammatory markers from the lungs spillover into the blood circulation, there is also the hypothesis that the smallest PM category, the ultrafine particles (UFPs), can enter the blood and can induce inflammation in the circulation as well as other organs (see also Figure 4-1). The first support for this was gained from the observation that labeled UFPs were detected in hamster blood after 1 minute (Nemmar et al., 2001). In a later study, this was also observed in humans (Nemmar et al., 2002).
Besides the lung-blood barrier, studies have also reported on other passages by which UFPs travel from the lung to the circulation and other organs. One example of this is the blood-brain barrier (Kreuter, 2001). The translocation of UFPs provides a possible explanation for the observation that PM exposure is capable of causing adverse effects in organs, independent of the systemic inflammatory response (Khandoga et al., 2004). Altogether, local and systemic inflammation induced by PM exposure and the effect of UFP translocation may contribute to cardiovascular morbidity and mortality, either independently and/or synergistically (Bai et al., 2007).

4.3 Origin of inflammation: oxidative stress

It has been demonstrated that several markers of oxidative stress are enhanced in humans exposed to PM (Brook et al., 2004). Thus, oxidative stress has been extensively implicated to be the central mechanism in the inflammatory effects of PM air pollution (Donaldson et al., 2003).

In essence, oxidative stress refers to the situation of a persistent imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, leading to potential tissue damage (Halliwell, 1995).

4.3.1 Role of oxidative stress in inflammation

Oxidative stress is considered to be a fundamental factor in the generation of inflammation. Failure to overcome oxidative stress leads to the activation of inflammatory signaling pathways, such as the nuclear factor-kappa B (NF-kB) pathway. NF-kB is a protein transcription factor that is required for the transcription of many pro-inflammatory mediators, including the pro-inflammatory cytokines IL-1B, TNF-a and IL-6 (Donaldson et al., 2003). These products are produced locally as well as systemically and can lead to widespread inflammatory effects remote from the site of damage (see paragraph 4.2.2).

4.3.2 Cellular mechanisms

Studies have shown that PM exposure induced strong oxidative activity and the depletion of lung lining fluid antioxidants (Romieu et al., 2008). The oxidative stress mediated by PM may arise from several sources. Data suggest that important sources include ultrafine particle surfaces, transition metals and organic components (Donaldson & MacNee, 2001). Between these components, there is the potential for additive or synergistic interactions. Evidence was provided that suggested synergistic interactions between transition metals and UFPs in causing oxidative stress and lung inflammation (Bai et al., 2007).

Particulate matter may induce oxidative stress by altering the function of mitochondria and by activating inflammatory cells capable of generating ROS, as well as oxidative DNA damage (Risom et al., 2005).

Also, PM may induce the expression of pro-inflammatory mediators via the stimulation of intracellular calcium signaling events (Donaldson et al., 2003). The calcium signals are in part initiated, and may be enhanced, in response to particle induced oxidative stress (Donaldson & MacNee, 2001). Increased calcium stimulates signaling pathways such as NF-kB and the expression of pro-inflammatory mediators in macrophages and epithelial cells.

In addition, PM appears to inhibit protective enzymes involved in oxidative stress, such as superoxide dismutase and catalase, resulting in excessive oxidants in the cardiopulmonary system (Bai et al., 2007).

In Figure 4-2, the effects of PM components on a lung cell are shown, which may lead to inflammation through the generation of oxidative stress (MacNee & Donaldson, 2003).
4.4 Conclusion

Components of PM air pollution have the ability to cause oxidative stress. Failure to overcome oxidative stress leads to the activation of intracellular signaling pathways that regulate the expression of inflammatory mediators. These products are produced locally in the lungs as well as systemically, and lead to widespread pro-inflammatory effects remote from the site of damage. In addition to local and systemic inflammation, UFPs can enter the blood and may cause additional damage to the circulation and other organs.
5 FROM PM-INDUCED INFLAMMATION TO DIABETES

In chapter 4, the PM-induced inflammatory response was described. Next, inflammation in the context of T2D, and the potential contribution of PM exposure, is described.

5.1 Evidence for a role of inflammation in T2D
Diabetes as a consequence of obesity is basically explained by insulin resistance and pancreatic B-cell dysfunction (see chapter 2). However, new theories have evolved to explain these features. One of these is the concept the inflammation may play a role in the development of T2D since obese persons are characterized by a state of chronic inflammation (Cancello & Clement, 2006).

Indeed, evidence suggests a role for inflammation in the development of T2D (Fernandez-Real & Pickup, 2008; Schmidt & Duncan, 2003). For example, many markers of inflammation are known to be increased in T2D and show a graded increase with increasing insulin resistance. Also, studies have demonstrated that elevated levels of certain inflammatory markers, including the cytokine IL-6 and the acute-phase protein CRP, are predictive for the development of T2D. In addition, anti-inflammatory drugs have shown to reduce blood glucose levels and circulating inflammatory markers and possible even reduce the risk of developing T2D.

Altogether, T2D is associated with the activation of the innate immune system, in which there is a cytokine-mediated state of chronic, low-grade inflammation (Fernandez-Real & Pickup, 2008). Pro-inflammatory cytokines can affect many tissues and influence metabolism. This is discussed next.

5.2 Inflammation and metabolism
T2D is associated with the activation of the innate immune response (inflammation) which is primarily coordinated by pro-inflammatory cytokines such as IL-6. Many tissues have shown to be affected by pro-inflammatory cytokines, including blood, endothelium, liver and brain (Fernandez-Real & Pickup, 2008). Examples of the effects of pro-inflammatory cytokines on tissues include stimulation of the APR in liver, increased clotting tendency in blood and the elevation of blood lipids (hyperlipidemia).

Altogether, cytokine actions can result in cardiovascular complications such as atherosclerosis, which in turn can lead to strokes and myocardial infarctions. However, it is most interesting to note that cytokine actions can directly interfere with insulin signaling (Greenberg & McDaniel, 2002).

5.2.1 Interference with insulin signaling
Experimental models have shown that adipose tissue–derived pro-inflammatory cytokines can actually cause insulin resistance in adipose tissue, muscle and liver (Greenberg & McDaniel, 2002). Multiple mechanisms may be involved in the induction of insulin resistance by cytokines, including the modulation of lipolysis and alteration of glucose uptake by adipose cells. Further evidence suggests that cytokines may induce insulin resistance indirectly through increases in free fatty acid levels as well as directly through blockade of insulin signaling pathways. Besides their effect on insulin sensitivity in liver, muscle and adipose tissue, cytokines have also shown to modify insulin secretion by pancreatic β-cells (Greenberg & McDaniel, 2002).

Overall, findings suggest an important role for cytokine-mediated inflammation in the development of both the key defects in T2D; insulin resistance and impaired β-cell function.
5.3  **Explanations for the link between inflammation and insulin resistance**

Two hypotheses have been put forward for the creation of an insulin resistant state as a consequence of inflammation.

5.3.1  **Fuelling immune tissue**

One hypothesis for the link between inflammation and insulin signaling is that glucose is a major fuel for the cells of immune tissue (Grimble, 2002). The creation of an insulin resistant state will reduce the uptake of glucose in tissues in which the process is insulin dependent, such as for example in muscle and adipose tissue. Consequently, this increases the availability of glucose for the tissue that needs it most in times of inflammation and in which the process is not insulin dependent: the immune tissue.

5.3.2  **Insulin as an anti-inflammatory hormone**

Recently, Dandona and colleagues have conceptualized a new hypothesis in which macronutrients and food are potentially pro-inflammatory and whereby insulin is secreted in response to these agents because of its anti-inflammatory properties (Dandona et al., 2002). In other words, overeating (obesity) maintains inflammation at such a level that it can not be controlled by insulin in spite of marked increases in plasma insulin levels. Consistent with this are the results from large clinical trials in which insulin infusion therapy was tested. This had beneficial effects on acute myocardial infarction as well as on severely ill patients (Schmidt & Duncan, 2003). However, this hypothesis is rather new and unexplored.

5.4  **T2D: a disease of the innate immune system**

Besides obesity, there are more chronic inflammatory conditions associated with the development of T2D, and associated features such as CVD. Examples are smoking, physiological stress, inactivity, rheumatoid arthritis, inflammatory lung disease and chronic hepatitis C (Fernandez-Real & Pickup, 2008; Wellen & Hotamisligil, 2005). Because of this, it has been proposed that T2D is not just a metabolic disease, but rather a disease of the innate immune system that can not cope appropriately with a chronic threat.

Innate immunity has survival advantages on the short term because it enables an organism to recover from injury. However, when the response is not proportional to this threat, or when the threat is continuous (such as overeating or smoking) disease develops rather than repair (Fernandez-Real & Pickup, 2008).

5.4.1  **Role of PM exposure**

In the context of the above, one may imagine that the exposure to PM can contribute to the development of T2D, since PM exposure also induces a cytokine-mediated inflammatory response (see chapter 4).

So in theory, chronic exposure to PM air pollution may induce chronic release of pro-inflammatory cytokines and thus lead to chronic state of inflammation. Ultimately this may result in a chronic insulin resistant-state and the development of T2D.

In figure 5-1 a model is shown in which the linkages are illustrated between the inflammatory response and diseases including T2D (Grimble, 2002). PM exposure would fall under the inflammatory stimuli ‘environmental factors’ whereas for example the hepatitis C virus would fall under ‘pathogens’.
5.5 Cellular mechanisms

As described previously, inflammation is linked to insulin resistance because in the case of an external aggressor glucose needs to be made available for immune tissue. Next, the cellular mechanisms behind inflammation and insulin resistance are described and compared to those associated with PM exposure.

5.5.1 JNK and NF-κB

Recently, two transcription factor-signaling pathways have been linked to inflammation-induced insulin resistance. One that appears to play a major role is the NF-κB pathway, which is activated by I kappa B kinase-beta (IKKB). The other one is the c-Jun NH2-terminal kinase (JNK) pathway (Shoelson et al., 2007; Shoelson et al., 2006).

Both JNK and NF-κB are activated by many of the same pro-inflammatory stimuli which include fatty acids, reactive oxygen species (ROS), endoplasmic reticulum (ER) stress and ceramides. In Figure 5-2, the cellular mechanisms involved in inflammation-induced insulin resistance are illustrated.

JNK activation has been shown to promote insulin resistance through the fosforylation of serine residues in insulin receptor substrate 1 (IRS-1) whereas NF-κB stimulation leads to increased expression of inflammatory markers and mediators, such as pro-inflammatory cytokines (Shoelson et al., 2006). Because of its complexity, a more detailed description of these pathways will not be given here. For details see (Shoelson et al., 2006).
Comparison with PM-activated signaling pathways

In chapter 4, the cellular mechanisms were described through which PM exposure induces inflammation. Comparing those mechanisms with the mechanisms described above shows that both include the activation of the NF-κB pathway by oxidative stress (in the form of ROS). This leads to the release of inflammatory mediators, such as pro-inflammatory cytokines, that can interfere with insulin signaling, as described in paragraph 5.2.1. Overall, it is suggested that PM exposure can contribute to the development of T2D through the activation of the oxidative stress-sensitive NF-κB pathway because this is the pathway responsible for the release of inflammatory mediators, including pro-inflammatory cytokines, which have the ability to induce insulin resistance.

Conclusion

It is now suggested that T2D is a disease of the innate immune system and that the development of this disease can be triggered by many inflammatory stimuli. It is plausible that PM exposure contributes to the development of T2D since PM exposure is associated with the same type of inflammatory mechanisms compared to those associated with the development of T2D.
6 MODIFIERS FOR AN INDIVIDUAL’S RESPONSE TO INFLAMMATION

Many factors can modify an individual’s response to inflammation. Nutritional status and chronic disease are candidates to determine susceptibility to the adverse inflammatory effects of PM exposure (Romieu et al., 2008). The risk of developing T2D is also dependent on several factors including genetics and lifestyle.

6.1 Nutrition

As described in chapter 4, oxidative stress has been identified as the main feature underlying the inflammatory effects of PM exposure. Antioxidants protect against oxidative stress and inflammation and can be derived from nutrition in the form of for example vitamin E or C. The effects of nutrient supplementation on air pollutant toxicity have been studied mainly in animals (Romieu et al., 2008).

In one experimental animal study it has been shown that temporary vitamin E deficiency may induce irreversible changes in the expression of pro-inflammatory markers. Further animal studies using antioxidants support the role of oxidative stress as mediator of PM effects. It has also been observed that the activation of NF-kB by pro-inflammatory cytokines is prevented after treatment with antioxidants. In addition, the powerful antioxidant N-acetylcysteine had a protective effect on inflammatory response and oxidative stress damage in rats exposed to coal dust. This effect was also shown on cardiac dysfunction in rats exposed to PM.

There is very little known about the impact of antioxidant supplementation on the effects of air pollution exposure in humans (Romieu et al., 2008). Most studies in humans focused on the changes in acute lung function. In comparison to the animal studies, the outcomes of human experiments are less consistent. However, one study performed in nursing home residents showed that supplementation with fish oil, which contains the antioxidants omega-3 fatty acids, significantly decreased the adverse effect of PM exposure on heart rate variability. This was one of the first studies that provided evidence that oxidative stress is a mechanism behind PM-induced cardiovascular disease.

In the context of T2D, there are data that show that vitamin E administration to patients with insulin resistance reduces the production of inflammatory cytokines (Dandona et al., 2005).

6.2 Chronic disease

Besides T2D, most chronic diseases are associated with inflammation. It has been suggested that the common initiator of inflammation in inflammatory conditions such as obesity and T2D is oxidative stress (Ceriello & Motz, 2004). Indeed, oxidative stress has been implicated to play an important role in the pathogenesis of T2D (Rosen et al., 2001). This might increase susceptibility to the additional oxidative stress caused by PM exposure. In chapter 3 was already described that diabetics are a vulnerable population regarding PM exposure.

Furthermore, asthma, COPD and CVD are all diseases associated with increased levels of oxidative stress and subjects with these conditions have been shown to be more susceptible to the effects of air pollution (Romieu et al., 2008).

Overall, PM-induced oxidative stress may aggravate already increased levels of oxidative stress in subjects with chronic disease, resulting in excessive inflammation. This may then result in the aggravation of existing health complications or in additional adverse health effects. Thus, subjects with pre-existing respiratory or cardiovascular disease may be at increased risk for developing T2D when exposed to PM air pollution.
6.3 Genetics
Blood concentrations of inflammatory markers predict T2D but are not related to the duration of this disease, suggesting that individuals may have an inherited level of innate immune response at birth (hence the term ‘innate’) (Fernandez-Real & Pickup, 2008). Several studies have indeed indicated that genetics influence components of the innate immune system and are associated with several risk factors for the development of T2D (Fernandez-Real & Pickup, 2008). For example, it has been shown that subjects with the highest transcription rates of genes encoding the pro-inflammatory cytokines IL-6 and TNF-a, are at increased risk for developing obesity, insulin resistance and T2D. Also, ethnicity is an important risk factor for T2D. For example, higher rates of T2D have been reported in people of Asian and African origin, and in native peoples of the America and Australia (WHO, 2004). Thus, genetics may determine the risk of developing T2D during a subject’s lifetime in the context of adverse environmental stimuli such as exposure to PM air pollution.

6.4 Lifestyle
Besides a healthy diet rich in vitamins, other lifestyle factors can influence susceptibility to inflammation and the risk of developing T2D. For example smoking has been shown to lower antioxidant defenses and increase oxidative stress, resulting in adverse health consequences including insulin resistance (Reaven & Tsao, 2003; Romieu et al., 2008). Another lifestyle factor that influences inflammation is exercise. Exercise results in a fall in the indices of inflammation such as plasma CRP levels (Dandona et al., 2005). The mechanism behind this effect is unknown. However, it is important to note that lifestyle changes can influence inflammation and the risk of developing T2D.

6.5 Conclusion
Many factors may influence an individual’s response to inflammation. This makes it very difficult to predict whether a person will actually develop T2D as a result of (PM-induced) inflammation.
7 CONCLUSION AND DISCUSSION

7.1 Conclusion
The exposure to PM air pollution may induce local inflammation in the lungs, as well as systemic inflammation throughout the body. Since it is becoming more and more apparent that T2D is an inflammatory disease, rather than just a metabolic disease, it is plausible that PM exposure may contribute to the development of T2D. Indeed, several inflammatory conditions and diseases are associated with the development of T2D, indicating that a general state of inflammation plays an important role in the pathogenesis of T2D.

7.1.1 An integrated picture
Figure 7B1 represents an integrated picture (Fernandez-Real & Pickup, 2008). Cells such as macrophages and adipocytes detect environmental threats such as particulate matter and overeating. Through signals including oxidative stress, the inflammatory pathway NF-kB is activated which results in the release of pro-inflammatory cytokines. Pro-inflammatory cytokines act on many cells in the body to produce the features of T2D. The inflammatory pathway is probably modulated by both innate predisposition (genetics) and metabolic lifetime changes such as in insulin.

In the case of chronic overstimulation, innate immunity could be the basic pathogenic mechanism for the development and maintenance of T2D (Schmidt & Duncan, 2003).

![Diagram](image_url)

Figure 7-1: Particulate matter, inflammation and type 2 diabetes. Illustration modified after (Fernandez-Real & Pickup, 2008).
7.1.2 Implications for society

Because of its chronic nature and the severity of its complications, T2D is a burdensome disease for both affected individuals and their families, but also for a country’s health system. It is expected that the number of people worldwide with T2D will increase significantly due to population growth, ageing, unhealthy diets, and obesity, leading to an increased economical burden on health system (WHO, 2004). The suggested effect of PM exposure (see figure 7B1) on the development of T2D could also be a contributor to this. If so, than future projections of the prevalence of T2D may be even higher than expected since people are living more and more closer to highways and PM emissions, due to increasing urbanization. Results suggest a necessity for health care professions treating diabetic patients to be aware of the environmental conditions, such as PM levels, that surround the homes and workplaces of their patients. Moreover, environmental professionals should be aware of the potential diabetic complications associated with PM air pollution.

7.2 Discussion points

7.2.1 Threshold levels

Even though it is known that inflammation plays a role in the development of T2D, it is unclear what the level of inflammation should be in order to trigger this development. In addition, it is unclear how high the induced levels of inflammation are in the context of different PM exposure levels. Even if the level of PM exposure is similar for several subjects, a large number of factors influence the inflammatory status of an individual. Examples of such factors are nutritional status, physical activity and genetics. Currently, it is not possible to say anything more about the relationship between PM exposure and T2D besides that it is likely that there is one.

7.2.2 Types of inflammation and the development of T2D

There may be different types of inflammation and not every type of inflammation may lead to T2D. An example of this was given in a research done by Rana and colleagues (Rana et al., 2004). In this research the relationship between COPD, asthma and T2D was studied and results indicated a relation between COPD and T2D, but not between asthma and T2D. The explanation for this was that COPD was associated with the release of a set of pro-inflammatory cytokines (including TNF-a and IL-6), which are also believed to play a major role in the development of T2D. Asthma, though, was not associated with these specific cytokines.

The above indicates that not every inflammatory condition is linked to diabetic features. This complicates the understanding of the relationship between inflammation and T2D and raises new questions.
8  RECOMMENDATIONS FOR FUTURE RESEARCH

PM air pollution should be subject of intense research since the effects of these particles on human health and the mechanisms behind it are still partly unknown. Especially the potential relationship between PM exposure and type 2 diabetes is unexplored and deserves attention. However, in my opinion there is one specific subject that has been neglected and needs mentioning. This subject is the smallest PM category; the ultrafine particles (UFPs).

8.1  UFPs

More than a decade ago one thought that UFPs did not form a threat to human health. Arguments for this were that UFPs are very short-lived and disappear through aggregation within seconds or minutes and are therefore toxicologically irrelevant (Oberdorster & Utell, 2002). However, since then the attitude towards UFPs has changed. It is now known that, on the contrary to larger particles, UFPs have the ability to travel across the epithelium after being inhaled in the lungs. Depending on the duration of exposure, UFPs can travel to organs such as the liver, heart, spleen, bladder, kidney and bone marrow (Buzea et al., 2007). This was also described in chapter 4.

8.1.1  Effects on organs unknown

Up to now there is little knowledge on the effect of UFPs on organs. However, it has been shown that UFPs localize in mitochondria, where they induce major structural damage. How exactly UFPs gain access to mitochondria and induce damage there is unknown. One possibility is that ROS generated outside of the mitochondrion may damage this organelle, allowing access to the particles (Nel, 2005).

Of special interest for this research is the translocation of UFPs to adipose tissue and the pancreas, since these organs play a key role in the development of insulin resistance and decreased insulin secretion (the characteristics of T2D). Pancreatic β-cells are particularly sensitive to oxidative stress because they are low in antioxidant enzymes such as catalase and superoxide dismutase (Evans et al., 2003). Thus, translocation of UFPs to the pancreas could damage β-cells and their organelles severely, leading perhaps to the development of dysfunctional insulin secretion and ultimately T2D.

However, there is no data available regarding the effect of UFPs on organs such as the pancreas.

8.1.2  ‘Clean’ engines and the emission of UFPs

Anthropogenic sources of UFPs are mostly internal combustion processes. Diesel fuel and gasoline engines all emit high numbers of UFPs. Even compressed natural gas powered engines, which are considered to be ‘clean’, emit high numbers of UFPs.

Since vehicle emissions are regulated by mass output, modern technologies for internal combustion engines favor the generation and formation of UFPs because they contribute minimally to the mass output of PM (Oberdorster & Utell, 2002). Due to this, ‘clean’ engines are built to conform to present standards of mass output, despite emitting high numbers of UFPs.

In a study done on Minnesota highways, it was shown that UFP-concentrations were as high as 10 million particles per cm$^3$ (Kittelson et al., 2004). These high UFP concentrations were lower at a short distance from the highway. However, individuals in cars on the highways are directly exposed to the high concentrations and furthermore, these UFPs are freshly generated. Also, due to increasing urbanization, houses are situated closer to busy roads and highways. Thus, in the context of the application of newer and ‘cleaner’ technologies in the automobile industry, and increasing urbanization, it is of importance not to underestimate the effects of UFPs on human health. Therefore, more research should be done on this specific area of PM air pollution.
## APPENDICES

### 9.1 Appendix 1: List of abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>APR</td>
<td>acute phase response</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>CRP</td>
<td>c-reactive protein</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>IKKB</td>
<td>I kappa B kinase-beta</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
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<tr>
<td>IRS-1</td>
<td>insulin receptor substrate-1</td>
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<tr>
<td>JNK</td>
<td>c-Jun NH2-terminal kinase</td>
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<tr>
<td>MCP-1</td>
<td>monocyte chemoattractant protein-1</td>
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<tr>
<td>NF-kB</td>
<td>nuclear factor-kappa B</td>
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<tr>
<td>NO$_2$</td>
<td>nitrogen dioxide</td>
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<tr>
<td>PAHs</td>
<td>polycyclic aromatic hydrocarbons</td>
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<td>PM</td>
<td>particulate matter</td>
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<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
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<td>SO$_2$</td>
<td>sulfur dioxide</td>
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<tr>
<td>T2D</td>
<td>type 2 diabetes</td>
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<tr>
<td>TNF-a</td>
<td>tumor necrosis factor-alpha</td>
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<tr>
<td>UFPs</td>
<td>ultrafine particles</td>
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<td>WHO</td>
<td>World Health Organization</td>
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10 REFERENCES


