Air Pollution in Reykjavík and Dispensation of Drugs for Angina Pectoris

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60 credit thesis submitted for a
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I declare that this thesis is supported by my research work, written by myself and has not, partly or as whole, been published before to a higher educational degree.

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Ragnhildur Guðrún Finnbjörnsdóttir

Abstract

Introduction: Ambient air pollution is associated with increase in morbidity from heart diseases. Air pollutant concentrations in the Reykjavík area are known to surpass official health limits many times every year.

Objectives: To evaluate the association between ambient air concentration of NO_2, O_3, PM_{10}, and H_2S in the Reykjavík area and the dispensing of drugs for the heart disease, angina pectoris.

Methods: Data on the daily dispensing of drugs for angina pectoris were obtained from The Icelandic Pharmaceuticals Data Bank. Data on concentrations of NO_2, O_3, PM_{10}, and H_2S were obtained from The City of Reykjavík, and The Environment Agency of Iceland. A time-stratified case-crossover design was used and the study period was January 1st 2005 to December 31st 2009.

Results: The exposure to air pollution was associated with the dispensing of drugs for cardiovascular disease (C01DA). For every 10 µg/m^3 increase of NO_2 concentration levels the dispensing of *glyceril trinitrates* (sub-group C01DA02) increased by 11.6% (at lag 0) and 7.1% (at lag 1). Similarly, each 10 µg/m^3 increase of O_3 concentration was associated with 9.0% (at lag 0) and 7.2% (at lag 1) increase in *glyceril trinitrate* dispensations.

Conclusion: Caution is needed in the conclusion as this is the first study to examine the association between ambient air pollution and dispensing of drugs for angina pectoris. However, the findings suggest that increased air pollution levels are associated with increased dispensing of *glyceril trinitrate* and this may be used as a sensitive indicator on health effects of air pollution.

Útdráttur

Inngangur: Sýnt hefur verið fram á að breytingar í styrkleika loftmengunarefna hafa áhrif á heilsufar hjartasjúklinga. Loftgæði á Íslandi eru almennt talin góð en við ákveðnar aðstæður getur styrkleiki loftmengunar farið yfir heilsuverndarmörk í Reykjavík.

Markmið: Markmið þessarar rannsóknar var að rannsaka hvort samband er milli loftmengunarefnanna NO_2, O_3, PM_{10} og H_2S og afgreiðslu á hjartalyfjum sem gefin eru við hjartaöng í Reykjavík.

Aðferðir: Gögn um daglegan fjölda afgreiddra lyfja í lyfjaflokki C01DA var fenginn úr lyfjagagnagrunni Landlæknisembættisins. Gögn um magn níturdíoxíðs (NO_2), ósóns (O_3), svifryks (PM_{10}) og brennisteinsvetnis (H_2S) voru fengin frá Umhverfissviði Reykjavíkurborgar og Umhverfisstofnun. Tilfella-víxlunar rannsóknarsnið (e. case-crossover design) var notað og rannsóknartímabilið var frá 1. janúar 2005 til 31. desember 2009.

Niðurstöður: Jákvætt samband reyndist vera milli loftmengunar og fjölda afgreiðslna á lyfjum í ATC flokki C01DA. Fyrir hverja 10 $\mu g/m^3$ hækkun á styrkleika NO_2 í lofti jókst afgreiðsla lyfja í undirflokknum C01DA02 (glýserýlnitrat; nitróglýserín) um 11,6% sama daginn. Samsvarandi varð 9% aukning á afgreiddum lyfjum fyrir hverja 10 $\mu g/m^3$ hækkun á styrkleika O_3. Það var 7,1% og 7,2% aukning í afgreiðslum lyfja fyrir hverja 10 $\mu g/m^3$ hækkun í styrkleika NO_2 og O_3 miðað við mengun daginn fyrir afgreiðslu.

Ályktun: Þar sem þetta er fyrsta rannsóknin, hér á landi og erlendis, sem metur samband milli loftmengunar og fjölda afgreiðslna á hjartalyfjum verður að ályktа með varúð. Engu að síður benda niðurstöðurnar til að aukning í loftmengun auki fjölda afgreiðslna á lyfjum við hjartaöng og að þetta gæti verið unnt að nota sem ábendingu um heilsufarsáhrif af loftmengun.

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Abbreviations

$\mu g/m^3$	Micrograms per cubic meter
24-hr mean	Daily 24-hour mean value
3-day mean	3-day mean value
ATC	Anatomical Therapeutical Chemical classification system
C01	Cardiac therapy drug classification according to ATC
C01DA	Organic nitrates drug classification according to ATC
C01DA01	Glyceryl trinitrates drug classification according to ATC
CH_4	Methane
CI	Confidence Interval
CO	Carbon Monoxide
DDD	Defined Daily Dose
EU	European Union
H_2S	Hydrogen Sulfide
Max	Maximum value
Mean 1-hr peak	Maximum daily 1- hour mean value
MI	Myocardial Infraction
Min	Minimum value
MOT	Margin of Tolerance
NMHC	Non-Methane Hydrocarbons
NO	Nitrogen Monoxide
NO_2	Nitrogen Dioxide
NO_x	Nitrogen Oxides
O_3	Ozone
OR	Odds Ratio
PM	Particulate Matter
$PM_{0.1}$	Ultra-fine particulates (less than 0.1 µm in diameter)
$PM_{2.5}$	Fine particulates (less than 2.5 µm in diameter)
PM_{10}	Coarse particulates (less than 10 µm in diameter)
RH	Relative Humidity
RR	Relative Risk
SD	Standard Deviation
SO_2	Sulfur Dioxide
Temp	Temperature
THC	Total Hydrocarbons
TSP	Total Suspended Particles
VOC	Volatile Organic Compounds
WHO	World Health Organization
WHOCCC	WHO Collaborating Centre for drug statistics methodology

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1 Introduction

The science of environmental epidemiology has grown over the years. It is the branch within public health that is used to identify environmental factors that might affect human health. Studies in environmental epidemiology are useful for general policy making; to conduct risk assessments, set health-based guideline limits, provide medical evaluation and surveillance of adverse health effects of environmental factors.

Air quality has recently been of great interest and various epidemiological studies have linked air pollution exposure to increased human mortality and morbidity (Samet, et al., 2000). Within these studies there are some that have shown an association between ambient air pollution levels and hospital admissions due to various causes (Guo, et al., 2009). Most of these studies focus on the adverse effects of air pollution on respiratory and cardiovascular disease and many found a positive association between these factors. The air pollutants of main interest are often NO_2, O_3, $PM_{2.5}$, PM_{10}, and $SO_{2.}$ More recently attention has also been drawn to the potential health effects of H2S. Most of the studies on the adverse health effects of air pollution come from North American and European cities (Pope, et al., 2009; Sunyer, et al., 2006) and have found an elevated risk of deaths or cardiovascular morbidity with short-term air pollution exposure. This needs to be studied further due to the fact that some studies have found different results. Levy et al. (2001) for example, did not find an association between daily $PM_{2.5}$ concentration levels and out of hospital cardiac arrest (Levy, et al., 2001).

A new possible health indicator has been introduced to this subject which is pharmaceutical dispensing, or drug sales. This was first introduced by Zeghnoun et al. in 1999 by studying the association between air pollution and respiratory drug sales in the city of Le Havre, France. Zeghnoun et al. pointed out that hospitalization and mortality only reflected a limited proportion of patients with respiratory disease. Given that drug sales comprise of a larger group of patients it would furthermore give more power for statistical analyses. This health indicator may thus be more sensitive to the relationship between air pollution exposure and adverse health effects.

Here, the health effects of ambient air pollution in the Reykjavík area on cardiovascular disease were studied by using cardiovascular drug (ATC C01DA) dispensing as an outcome. A case-crossover analysis was considered most suitable for this analysis and thus applied to the study. The thesis is divided into a background where previous epidemiologic studies on the subject are reviewed, an outline of the research questions and hypotheses posed in this study, an overview of the study data and methods used, a chapter of results and finally a discussion of the study results and how they concur with previous research findings in environmental epidemiology on air pollution and cardiovascular disease.

2 Background

In this chapter some background research will be elaborated. First, the outdoor environment in Reykjavík city will be described by detailing the air quality and various pollutants. Then, the climate factors that affect air quality will be defined and previous studies on the health effect of air pollution outlined. Finally, Icelandic laws and regulations on air quality will be overviewed.

2.1 Outdoor Environment

2.1.1 Air Quality in Reykjavík

Fluctuations in the levels of pollutants in the air are known to be correlated with changes in the morbidity of cardiovascular patients (Dockery & Pope, 1997; Kunzli & Tager, 2005; Le Tertre, et al., 2002; Pope & Dockery, 2006; Pope, et al., 2009; Samet, et al., 2000; Symons, et al., 2006; Zanobetti & Schwartz, 2005).

A European multinational cooperation study (Sunyer, et al., 2006) included data from Iceland over the years 2000 to 2001. According to measurements for 460 randomly chosen individuals in Reykjavík, Suneyer et al. concluded that air pollution levels in Iceland were quite low compared to other countries (Sunyer, et al., 2006).

Even though air quality in Iceland is generally good, heavy traffic in the capital area and specific weather conditions can cause concentrations of several pollutants to surpass official health limits many times every year (Böðvarsdóttir, 2007; Jóhannsson, 2007). Under certain weather conditions, such as calm cold weather in winter, when sand, salt and soot have accumulated on the streets for longer periods, particle matter concentrations may reach very high levels and other traffic related pollutants can accumulate. Studded tires are one of the main contributors of particulate matter (PM) in Iceland as well as transportation vehicles. Hourly air pollution levels, particularly PM concentrations, in Reykjavík may therefore at times go well beyond the pollution levels of many European capitals (Böðvarsdóttir, 2007; Jóhannsson, 2007). This is, however not reflected in the mean 24 hour health limit, which determines when public warnings are given.

Reykjavík is the capital of Iceland and is located on the south-west part of Iceland. In the capital area there are seven municipalities including Reykjavík and are called Álftanes, Garðabær, Hafnarfjörður, Kópavogur, Mosfellsbær, Reykjavík and Seltjarnarnes and it is difficult to locate the boundaries of each municipality since they lie tight together. In the Reykjavík capital area there were at average 142.789 inhabitants (18 years and older) at during the study period 2005 to 2009 (Hagstofan, 2009). The automobile ownership among the residence of the Reykjavík capital area is quite high or at average 635 per 1000 inhabitants over the study period (Hagstofan, 2009). Due to this high car ownership number the traffic related air pollution is likely to be higher than it would be if the population owned fewer cars.

The weather in Iceland is often harsh over the winter months and contributes to poor driving conditions and therefore it is rather common that car owners drive around on studded tires even

though it is widely considered to adversely affect the roads by tearing up the asphalt. This increases the particulate matter concentration and therefore there have been campaigns made by the municipalities to increase the awareness of the negative effects of studded tires and to decrease the usage of these kinds of tires. This is one of many efforts of the city to decrease traffic related air pollution.

2.1.2 Particulate Matter (PM)

PM is composed of particles of various shapes, that because of their size they are ambient in the atmosphere, i.e. airborne particles. Motor vehicles and wind blow up the particles and therefore increase the concentration. PM is a mixture of liquid droplets and solid particles that vary in size, origin and composition. PM includes dust, fumes and smoke comprising particles from biomass combustion, industrial processes, long-range transported air pollution road abrasion, waste incineration and more (Dockery & Pope, 1997; Schwarze, et al., 2006; Simkhovich, et al., 2008).

The composition of high level PM_{10} in Reykjavík over winter months has been studied and according to Skúladóttir et al. (Figure 1). The greater part of PM_{10} in Reykjavík is asphalt mostly due to road depletion (55%), and soil (25%). Soot, salt, and break lining are approximately 20%. The composition is likely to change by season and this is, however, the only available study on the composition of PM_{10} in Reykjavík (Skúladóttir, et al., 2003).

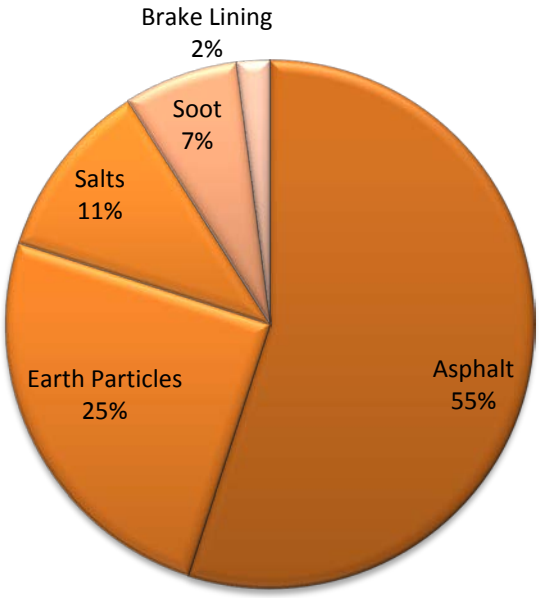

Figure 1. Composition of PM_{10} in Reykjavík over winter months of 1999 to 2002 (Skúladóttir, et al., 2003).

PM is often measured as airborne particles less than 10 µm in diameter (PM_{10}). As a comparison the human hair is about 60 µm in diameter. Visible smoke consists of particulates larger than 10 µm but particulates smaller than 2.5 µm ($PM_{2.5}$) are not visible to the human eye. PM is therefore classified by three size distributions and measured by their aerodynamic properties (Dockery & Pope, 1997).

PM_{10}, or Coarse Particulates, are particles less than 10 µm in diameter. These particles usually contain wind-blown dust particles from agricultural processes, gravel roads, soil, and industries as well as from road depletion combustion and more. Coarse Particles (PM_{10}) can be inhaled into the upper throat and in the bronchi (Figure 2) (Brook, et al., 2004; Dockery & Pope, 1997; Franchini & Mannucci, 2007; Schwarze, et al., 2006; Simkhovich, et al., 2008).

$PM_{2.5}$, often called Fine Particulates, contains particles less than 2.5 µm in diameter. These particles mainly originate from combustion particles and contain aerosols in which gases have dissolved and reacted. $PM_{2.5}$ can be respired and reach the gas exchange region of the lung (alveoli) when inhaled (Figure 2) (Brook, et al., 2004; Dockery & Pope, 1997; Franchini & Mannucci, 2007; Schwarze, et al., 2006; Simkhovich, et al., 2008).

$PM_{0.1}$, usually called Ultra-Fine Particulates, contains particles less than 0.1 µm in diameter and is mainly derived from primary combustion sources. These particles are believed to be able to migrate from the lungs into the blood stream via bronchi and the alveoli (Figure 2) (Brook, et al., 2004; Dockery & Pope, 1997; Franchini & Mannucci, 2007; Schwarze, et al., 2006; Simkhovich, et al., 2008).

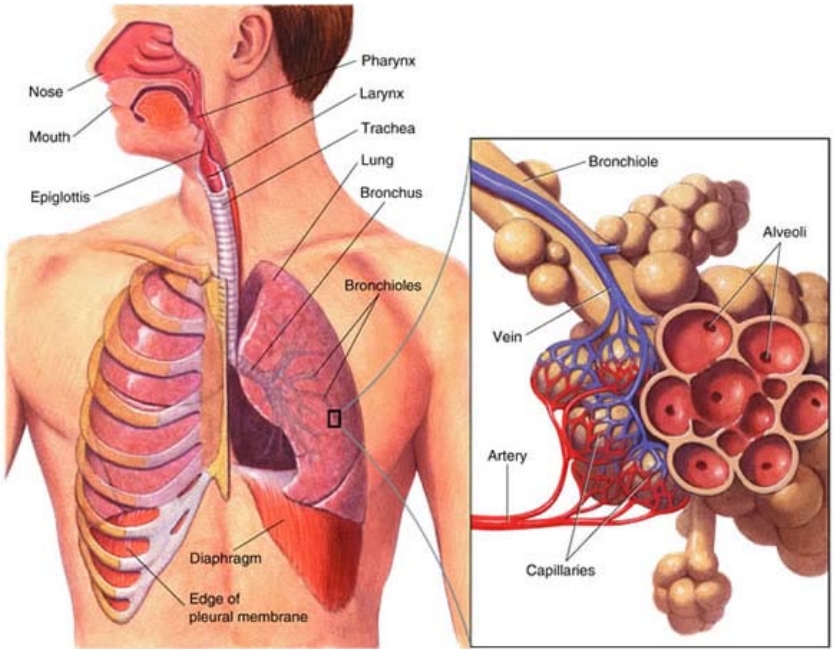

Figure 2. Infrastructure of a lung. The smallest particles can reach all the way down to the alveoli. (Source: http://www.goldiesroom.org/).

The concentration of PM is usually measured in µg/m^3 and the health impacts of PM vary depending on ambient concentrations and particulate size. The guideline limit for PM_{10} in Iceland is shown in Table 2 (chapter 2.4). Particles within the respiratory range, i.e. particles that can reach the alveoli (<5 µm), are considered to be able to cause the most serious health effect. The smaller the particulates, the deeper they can reach in the respiratory system. Particles with aerodynamic diameter less than 5 µm and those less than 2.5 µm can reach the gas-exchange region of the lungs and introduce a potential health hazard. The smallest particles can penetrate into the alveoli

and can be absorbed into the blood stream and therefore have a greater health hazard potential than PM_{10} (Dockery & Pope, 1997; Franchini & Mannucci, 2007; Schwarze, et al., 2006).

2.1.3 Nitrogen Dioxide (NO_2)

Nitrogen dioxide is often used as an indicator for a complex mixture of mainly traffic related pollutants and is a yellow-brown gas with a pungent-sweetish odor. It is formed by combustion at high temperatures of, for example, engines and therefore the main anthropogenic source of NO_2 in ambient air is fossil fuel combustion. A review from WHO Europe (2004) concludes from toxicological studies that there are indications of adverse health effects from long-term NO_2 exposure in terms of, disrupted pulmonary function (mainly asthmatics), increase in airway allergic inflammatory reactions as well as an increase in hospital admissions and mortality. NO_2 also stunts plant growth and damages leaves (Brook, et al., 2004; Nadakavukaren, 1995; WHO, 2004).

The WHO air quality guideline value for nitrogen dioxide is 40 µg/m^3 as an annual mean but in Iceland it is 20 µg/m^3 (Table 1) and WHO (2004) have found evidence that NO_2 is associated with adverse health effects even though the concentrations are below the guideline limit (WHO, 2004).

2.1.4 Ozone (O_3)

Atmospheric ozone (O_3) is considered to be a vehicle associated pollutant even though it is not emitted directly from automobiles and is considered a photochemical oxidant. When nitrogen oxides (NO_x) and volatile organic compounds (VOCs, especially certain hydrocarbons from auto exhaust and various stationary sources) react with oxygen, UV radiation and sunlight, ozone originates and forms a photochemical smog or “summer smog”. Ozone usually peaks a few hours after the NO_x concentration levels are at their highest. This kind of photochemical smog often forms in various cities due to warm temperatures, sunlight, heavy traffic and frequent atmospheric inversions (see chapter 2.1.7) and Los Angeles is a good example (Brook, et al., 2004; Nadakavukaren, 1995). In Iceland the main source of ozone is the natural background concentration as well as long-range transport from Europe. The ozone concentration levels in the Reykjavík area usually decrease when nitrogen dioxide peaks, due to the fact that NO_2 can be synthesized through a chemical reaction of NO and O_3. Therefore, O_3 concentration levels are often higher when there is little traffic.

Ozone is a colorless and highly reactive gas which has adverse effects on human health. O_3 for example, irritates the mucous membranes of the respiratory system causing symptoms such as coughing, chocking and reduced lung capacity. Patients with heart disease and those suffering from lung diseases are at a higher risk of getting worse during periods with high O_3 ambient concentrations. Ozone can also cause eye irritation and watery eyes and damage plants either directly or indirectly by decreasing their ability to fight off insects (Brook, et al., 2004; Nadakavukaren, 1995; WHO, 2004). The guideline limit for O_3 in Iceland is 120 µg/m^3 (8-hour mean) as can be seen in Table 1.

Table 1. Guideline limits (µg/m^3) and margin of tolerance (MOT) for four air pollutants in Reykjavík. Source: (Böðvarsdóttir, 2006a, 2006b, 2006c, 2006d, 2007, 2009; EU, 1999).

	NO_2 (MOT)[a]	O_3 (MOT)[a]	PM_{10} (MOT)[a]	H_2S (MOT)[a]
1-hour mean	200/110[b] (175)	-	-	-
8-hour mean	-	120 (25)	-	-
24-hour mean	75 (7)	-	50 (7)	50 (5)
Annual mean	40/20[b]	-	20	5

[a] *Margin of tolerance: Number of days per year that are permissible to exceed the 24-hour limit value. Aimed to avoid, prevent or reduce harmful effects on human health.*

[b] *Limit value ordered by EU/limit value ordered by the Icelandic government.*

2.1.5 Hydrogen Sulfide (H_2S)

Hydrogen sulfide (H_2S) is a gas mainly emitted from geothermal processes and certain industrial processes such as paper mills. In September 2006 a geothermal power plant close to Reykjavík was put to stream and named Hellisheiðarvirkjun. Hellisheiðarvirkjun is located to the south-east of Reykjavík, some 25 kilometers away. This power plant was an addition to another power plant outside of Reykjavík located on Nesjavellir east of Reykjavík. Half a year before Hellisheiðarvirkjun began operation, monitoring of H_2S in Reykjavík was set out and by the opening of the plant in September 2006 a great increase in H_2S concentrations is evident (Figure 3). The hydrogen sulfide levels can become relatively high in Reykjavík when hydrogen sulfide is windborne from the east and over Reykjavík. Hydrogen sulfide concentrations can be very different across Reykjavík due to differences in landscape morphology and wind turbulence, respectively (Ólafsdóttir, 2007; WHO, 2000).

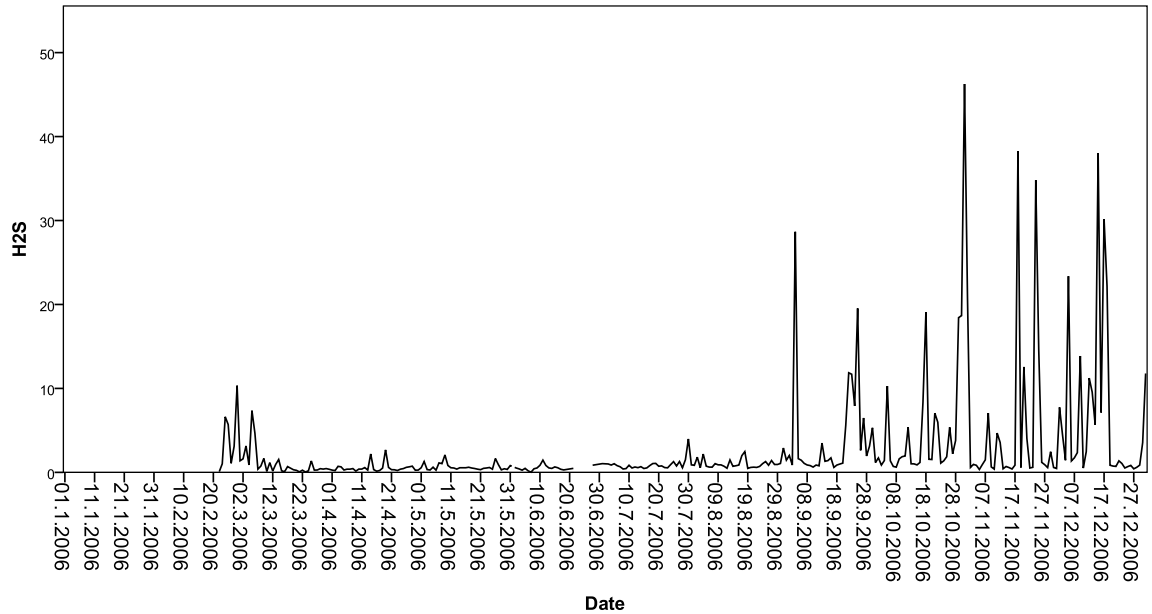

Figure 3. H_2S concentration levels (µg/m^3) in Reykjavík (Grensásvegur) the year 2006. Measurements started the 22nd of February 2006 and the geothermal station Hellisheiðarvirkjun started operating in September the same year.

The health effects of high hydrogen sulfide concentrations are quite well known but the effect of low-concentration exposure is quite limited. The first noticeable effect of ambient H_2S pollution is the reek in the atmosphere which some say similar to a rotten egg odor. A following symptom is eye irritation but other than that there are very few detectable negative health effects in a toxicological sense from long-term low-level H_2S exposure. On the other hand, some studies from Hawaii, New Zealand and Azores indicate a relation between H_2S long-term exposure and adverse health effects (Amaral & Rodrigues, 2007; Durand & Wilson, 2006). To support these findings, further epidemiological studies on adverse health effects of H_2S is needed (WHO, 2000).

WHO (2000) recommend H_2S limits not to exceed 7 $\mu g/m^3$ (30-minute mean) to avoid the odor nuisance or 150 $\mu g/m^3$ (24-hour mean) which is the health guideline limit (WHO, 2000). Iceland has just introduced a new regulation regarding the H_2S concentration levels in Iceland. The running 24-hour mean is not to exceed 50 $\mu g/m^3$ more than five times each year and there is also an occupational safety limit for H_2S of 15 $\mu g/m^3$ per 8-hour mean (Regulation, 2009, 2010).

2.1.6 Climate Factors

Various weather conditions effect the ambient air pollution. Wind, for example, has a great effect by dispersing the pollution and rain (wetness) binds it (Johansson, et al., 2007). Different weather conditions have different effect on pollution concentrations. For example dry, sunny and still days can lead to an increase in ambient air pollution due to accumulated gaseous pollutants. These weather conditions are considered to be associated with some events of high pollution levels in Reykjavík (Jóhannsson, 2007; Skúladóttir, et al., 2003).

The annual mean temperature in Reykjavík over the study period was 5.86°C. The winter mean was 2.23°C and the summer mean 9.45°C. The mean annual relative humidity was 77.82% and slightly higher in winter (Icelandig Meteorological Office: Reykjavík Yearly Mean weather, 2009).

2.1.7 Atmospheric Inversions

The atmospheric anomaly known as inversion is a condition that can greatly increase the ambient air pollution. It is a natural occurrence and in itself it presents no danger to human health. Atmospheric inversions (also known as temperature inversions) often become a problem when they occur in industrialized or highly populated areas.

When pollution has been emitted close to the ground it can migrate in any direction as well as vertically (upwards) and be diluted. As the air close to the ground is warmed it moves upwards (and in every direction) toward cooler air, carrying particles and gasses and new, cleaner air, takes it place (Figure 4). Under normal conditions the air is in a constant flux like this, with convection currents, warmer air moves to cooler air (Nadakavukaren, 1995).

In some occasions, this situation can be reversed, e.g. the air closest to the earth's surface is cooler than the layer above (Figure 4). Since the cool air is heavier than warm air the air is unable to rise and mix with the layer above (warmer air) which prevents the mixture of layers vertically and therefore decreases dilution of air pollutants. The lower layer stays down and remains atypically

stable and this is known as atmospheric inversion. The cool surface air is trapped by the warm overlaying air and the pollutants that are emitted in the lower layer may accumulate to high levels of concentration which could adversely affect human health (Nadakavukaren, 1995).

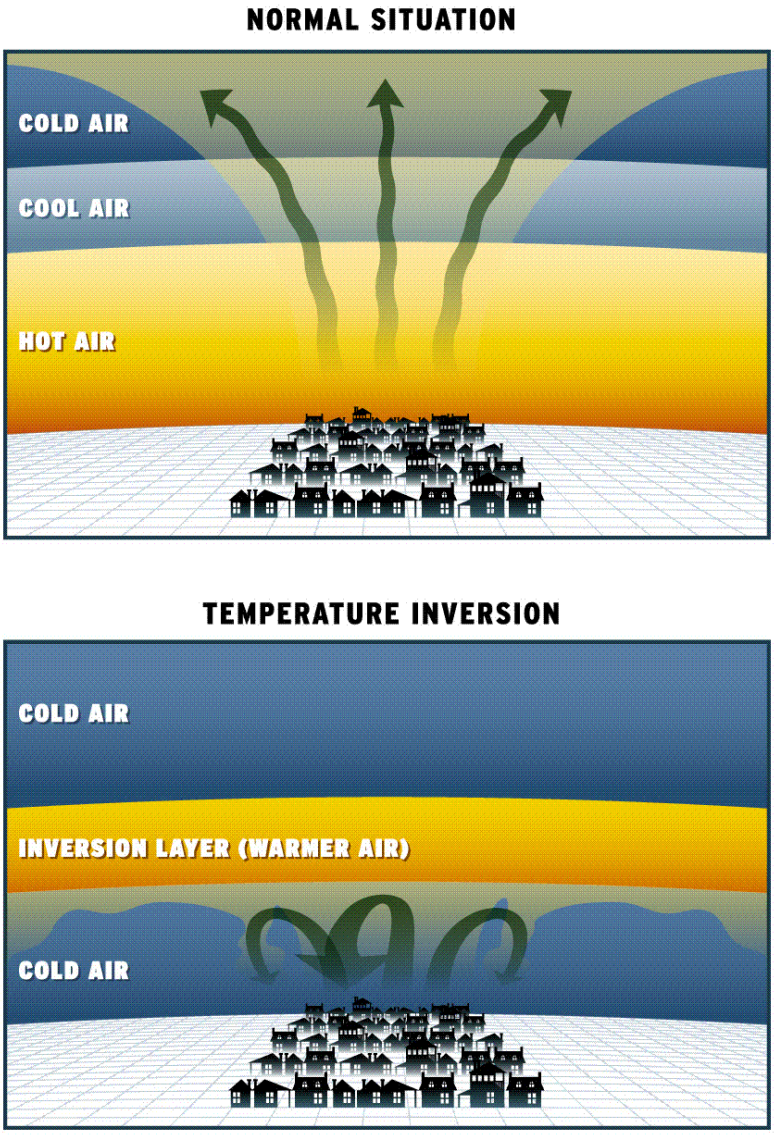

Figure 4. Schematic description of an atmospheric inversion (source: http://www.ec.gc.ca).

There are two types of atmospheric inversions, radiation inversions and subsidence inversions. Radiation inversions often occur on clear nights when the earth's heat is radiated quickly out to the atmosphere and the ground air becomes cooler than the upper layer. This sort of inversion usually converts back to a normal state as soon as the morning sun heats up the ground. The subsidence inversion, on the other hand, can last much longer and occurs when high pressure air mass settles down over a region. The above layer becomes compressed and therefore heated by the high pressure area above while the lower layer stays cooler. This state can last for days which could

lead to high levels of air pollution in the lower layers (Nadakavukaren, 1995). These sort of atmospheric inversions have though not been studied in Reykjavík.

2.1.8 Summary

As can be seen in these previous chapters there are many concerns to human health related to air pollution. In urban areas there are various factors that can adversely affect the human population and there are only a few accounted for. Very few studies have been conducted on the association of air pollution and these health effects in the Reykjavík area, or in Iceland in general. Studies need to be done on how the surrounding environment affects humans so it is possible to establish guidelines and limits to minimize these adverse effects. But, the subject is of great complex since there is a complicated association between many factors and it is often difficult to foresee those interactions.

2.2 Health Effects – Previous Studies

There are a number published epidemiological studies linking air pollution with adverse health effects. Some pollutants may cause disease individually but others have adverse health effects in combination, e.g. O_3, NO_2, H_2S etc. Here some studies will be reviewed considering the adverse effects of air pollutants on cardiovascular patients.

2.2.1 Particulate Matter (PM_{10} and $PM_{2.5}$)

The adverse effects of air pollution are many and well known (Freitas, et al., 2009; Kunzli & Tager, 2005; Lefranc, et al., 2009; Liang, et al., 2009; Pope & Dockery, 2006; Schwarze, et al., 2006). Some individuals are at greater risk than others of experiencing adverse health effects due air pollution such as people with cardiovascular or lung disease, the elderly and children (Pope & Dockery, 2006). Previous studies have shown that air pollution can adversely affect population health by, for example, increasing cardiovascular and respiratory mortality and morbidity (Dockery, et al., 1993; Ostro, et al., 2006; Samoli, et al., 2004).

Previous epidemiological studies from the United States and Europe have demonstrated that air pollution, such as PM, is linked to increased rates of morbidity and mortality due to cardiovascular events (Pope, et al., 2009). Furthermore, research shows that a fluctuation in the levels of pollutants in the air is correlated with changes in the morbidity of cardiovascular patients (Mills, et al., 2009; Simkhovich, et al., 2008). The London episode in 1952 is a clear example which resulted in a great increase in mortality parallel to a massive pollution period (Logan, 1956).

Pope et al. conducted a study to evaluate the changes in life expectancy of a population associated with changes in fine particulate air pollution. They used various characteristics for 211 country units in 51 U.S. metropolitan areas with matching data on air pollution for the late 1970s and early 1980s and late 1990s and early 2000s. Their results showed an increase of mean life expectancy of 0.6±0.2 years to every decrease of 10 $\mu g/m^3$ of $PM_{2.5}$ (Pope, et al., 2009).

Studies have also shown that the exposure to PM_{10} increase the cardiac morbidity and mortality and acute coronary events especially among those who suffer from underlying coronary artery disease (Miller, et al., 2007; Pope, et al., 2006; Samet, et al., 2000). Samet et al. found consistent evidence for this in their study of fine particulate air pollution in 20 U.S. cities and estimated an increase of death rate for cardiovascular and respiratory causes by 0.7±0.5 percent for each increase in the PM_{10} level of 10 $\mu g/m^3$ (Samet, et al., 2000).

A study by Miller et al. showed similar results as they studied the association of long-term exposure to $PM_{2.5}$ with cardiovascular events. Their data were based on 65,893 postmenopausal women without previous cardiovascular diseases. This was an extensive study which covered 36 metropolitan U.S. areas over four years (1994-1998) and a median follow-up time of six years. The results were shocking and revealed local levels of air pollution, especially $PM_{2.5}$, to be a risk factor for experiencing a cardiovascular event or dying from a cardiovascular disease. There was a 24 percent increase in the risk of cardiovascular event for each 10 $\mu g/m^3$ increase of $PM_{2.5}$. Furthermore, Miller et al. found a 76 percent increase in the risk of death from cardiovascular disease for the same increase in $PM_{2.5}$. These results are quite extreme and clearly show that long-term exposure to $PM_{2.5}$ increases the risk of cardiovascular events and mortality (Miller, et al., 2007).

Furthermore, Zanobetti and Schwartz studied the risk of emergency hospitalization associated with PM_{10} for over 300,000 elderly myocardial infarction (MI) patients over the years 1985 to 1999. They found that for each increase of 10 $\mu g/m^3$ of ambient concentrations of PM_{10} the risk for hospitalization of MI patients increased by 0.65 percent and that the effect size for particulate air pollution, PM_{10}, doubled for patients with previous admission for chronic obstructive pulmonary disease or a secondary diagnosis of pneumonia. They also found that the exposure-response relationship between MI hospitalization and PM_{10} ambient concentrations was positive and almost linear (Zanobetti & Schwartz, 2005).

Le Tertre et al. also studied hospital admissions for cardiac causes due to exposure to airborne particles in eight European cities. They found that for each increase of 10 $\mu g/m^3$ of PM_{10}, an increase of 0.5 percent in hospital admissions occurred among all ages. The increase for patients over 65 years of age was larger, or 0.7 and 0.8 percent respectively for admissions due to a simple cardiac event and ischemic heart disease (Le Tertre, et al., 2002).

Finally, another similar study was conducted by Symons et al. over the year 2002 in Baltimore, Maryland. They studied the association between exposure to $PM_{2.5}$ and congestive heart failure symptom exacerbation leading to hospital admission. Their data were based on 135 events of 125 patients with congestive heart failure and even though their results did not show statistical significant association between case events and exposure to $PM_{2.5}$, they found that more precise definition of congestive heart failure and exposure timing to PM would allow a potential analysis of a more specific relationship between these two factors (Symons, et al., 2006).

2.2.2 Nitrogen Dioxide (NO_2)

Many studies have demonstrated the adverse health effects of NO_2 on human health. It is known that NO_2 in the atmosphere can negatively affect humans in many ways and especially those with inflammatory disorders such as asthma or bronchitis, children and the elderly. NO_2 also adversely affects humans through the cardiovascular system (Alves, et al., 2010; Bernstein, et al., 2004; Brook, et al., 2004; Chang, et al., 2005; Freitas, et al., 2009; Liang, et al., 2009). Alves et al. (2010) evaluated the relationship between air pollution in Lisbon, Portugal and the emergency admissions for cardio-respiratory disease over the years 1999 to 2004. Alves et al. considered pollutants such as PM_{10}, SO_2, CO, NO, NO_2, and O_3 and found that there was a significant association between NO_2 and morbidity due to cardio-circulatory diseases in Lisbon among all age groups, with a lag of three days. The risk for circulatory disease increased by 0.5-2.2% for every 10 $\mu g/m^3$ NO_2 daily maximum level increase among all ages considered (Alves, et al., 2010).

Another study conducted in Lisbon, Portugal addressed the effects of the same pollutants as well as temperature and humidity on circulatory diseases. There a time series of daily hospital admissions was used along with daily means of environmental factors over the years 1999 to 2004. They found that there was a statistically significant ($p < 0.001$) association between NO_2 and hospital admissions due to circulatory conditions (except ischemic heart disease) (Freitas, et al., 2009).

Liang et al. (2008) used a time-series regression model to analyze the relative risk (RR) of cardiovascular diseases in Taiwan due to ambient air pollution and stratified the data down to summer and winter seasons. They used data on daily mortality due to cardiovascular disease (and other) as well as air pollution data of NO_2, PM_{10}, SO_2, O_3, and CO and found that there was a significant positive association between NO_2 and mortality from cardiovascular diseases during winter months among all age groups considered (Liang, et al., 2009). A study by Qian Z.M. showed similar results where the strongest effect occurred in winter for cardiovascular and stroke mortality (Qian, et al., 2010).

Another time-series study was conducted in France where the relationship between air pollution exposure indicators (NO_2 and PM_{10}) and mortality and hospitalizations due to cardiovascular diseases was analyzed. They found that there was a significant association between the levels of NO_2 and hospitalization due to cardiovascular, cardiac and ischemic heart diseases (Lefranc, et al., 2009).

A case-crossover study was conducted to evaluate the relative risk (RR) of hospital admissions and air pollution exposure in Taipei, Taiwan. The time period was 1997 to 2001 and in a single pollutant model a statistically significant positive association was found between levels of NO_2 and hospital admissions due to cardio vascular disease (Chang, et al., 2005).

2.2.3 Ozone (O_3)

Substantial epidemiological studies of the association between ambient air pollution and cardiovascular disease have demonstrated the effects of O_3 on human health. Studies also show that some people are more sensitive to high concentrations of O_3 than others and that high concentrations of the pollutant increase hospitalization and mortality due to cardiovascular diseases (Azevedo, et al., 2010; Brook, et al., 2004; Brook, et al., 2009; Freitas, et al., 2009; Gryparis, et al., 2004). In the previous mentioned study by Alves, (2010) (chapter 2.2.2) they found that there was some negative association between O_3 levels and cardiac and circulatory outcomes with a one day lag among all ages (Alves, et al., 2010). A study by Freitas (2010) was conducted from the same location over the same time period and showed similar results (Freitas, et al., 2009).

Ren et al. (2010) also studied the effects of O_3 on mortality due to cardiovascular diseases, using a case-crossover method and found similar results. The study period was from 1995 to 2002 and the pollution and health data were from Massachusetts, U.s. and it showed an increase of deaths by 0.44% for cardiovascular diseases and 6.5% for stroke for each 10 $\mu g/m^3$ increase in the four-day average of O_3 (Ren, et al., 2010). Ren et al. (2009) also demonstrated that temperature modifies the effect of O_3 where colder climate increases the adverse health effects of ozone (Ren, et al., 2009).

Chang et al. (2005) considered the effect of O_3 on hospital admissions due to high concentrations of ozone and found a statistically significant positive association between levels of O_3 and hospital admissions due to cardiovascular disease on warmer days (>20°C). On cooler days (<20°C) the association was not statistically significant (Chang, et al., 2005).

Azevedo et al. (2010) studied the long-range O_3 transfer and its impact on cardiovascular health in the north of Portugal. In this study the hospital admissions were considered as well as peak concentration levels of O_3 and they found results consistent with other studies that there is a clear positive association between O_3 concentration levels and hospital admissions (Azevedo, et al., 2010).

Liang et al. (2008) conducted a study that considered the health effects of different air pollutants on daily mortality due to cardiovascular disease, stratified by seasons, and found a significant positive correlation with O_3 and mortality rates of people who are 65 years and older during summer months. This consists with the study from Chang (2005) where the association was stronger during warmer days (Liang, et al., 2009). Another study that showed the different association between cold and warm seasons was conducted by Gryparis et al. (2004) which showed that daily number of cardiovascular deaths increased by 0.45% with every 10 $\mu g/m^3$ increase in 1-hour concentrations of O_3 during the warm season and the corresponding figures for the 8-hour ozone were similar (Gryparis, et al., 2004).

2.2.4 Hydrogen Sulfide (H_2S)

Chronic health effects of hydrogen sulfide (H_2S) exposure have been suggested and mostly regard respiratory diseases. It has been shown that H_2S can affect human health in various ways such as causing headaches, skin complications, respiratory and mucous membrane irritation and other respiratory problems, and much more. Not to forget the nuisance due to the odor of rotten eggs (Durand & Wilson, 2006). The possible effects of H_2S on cardiovascular diseases have though not been studied thoroughly despite suggestions that the pollutant adversely affect humans in that way. A study conducted by Bates et al. (2002) in New Zealand showed exposure-response trend between four cardiovascular diseases (Bates, et al., 2002) and it is believed that high exposure to H_2S can cause initial loss of coronary reflex.

2.2.5 Cardiovascular Symptoms and Mechanisms

Why air pollution such as PM_{10} contributes to cardiovascular disease in a physiological way is not well known. The biological pathways on how PM affects cardiovascular systems are still largely unknown and remain incompletely understood. A research by Kunzli et al. (2005) on the effects of PM on human health (Garrison, 2001; Künzli, et al., 2005) indicates that the pollution increases the rate of atherosclerosis and it seems that PM can be harmful even when it does not contain any harmful substances (Dockery, & Pope, 1997; Kunzli & Tager, 2005; Pope, et al., 2006; Simkhovich, et al., 2008).

Recent studies tend to relate air particle exposure to heart rate variability and congestive heart failure. PM exposure also seems to affect blood pressure, blood coagulation ability, the progression of atherosclerosis as well as the triggering of myocardial infarction, increased plasma viscosity, increase in plasma fibrinogen and electrocardiographic changes. Subjects with implanted cardioverterdefibrillators also tend to suffer from ventricular arrhythmia and tachycardia due to air particles and NO_2. Ozone is also implemented with alterations in vascular tone and may cause arterial vasoconstriction in healthy adults (Brook, et al., 2004; Kunzli & Tager, 2005; Le Tertre, et al., 2002; Simkhovich, et al., 2008; Zanobetti & Schwartz, 2005).

PM and O_3 impair vascular function and raises diastolic blood pressure but PM is considered to contribute the most to the biological mechanisms. The underlying mechanisms responsible for these symptoms are unclear but Franchini and Mannucci suggest that it may involve activation of pulmonary neural reflex arcs and therefore disrupt the cardiac ion channels and the inflammatory system. Brook et al. (2009) concluded that PM probably instigates acute autonomic imbalance and therefore increasing diastolic blood pressure. A schematic description can be seen in Figure 5 (Brook, et al., 2004; Franchini & Mannucci, 2007).

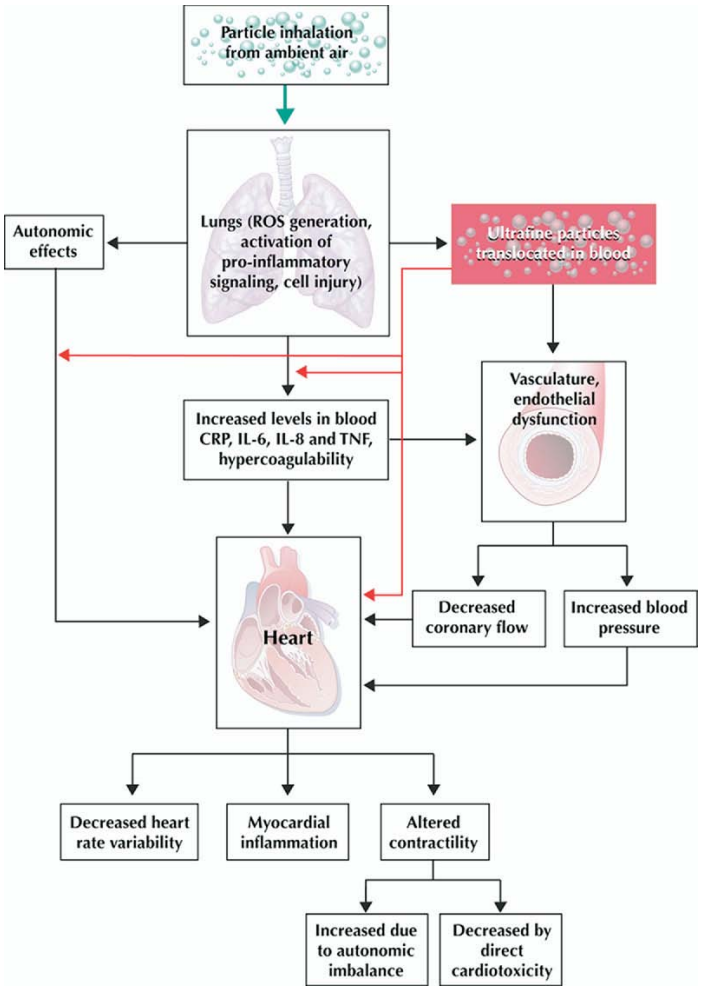

Figure 5. Exposure to $PM_{0.1}$ air pollution and possible pathways of adverse cardiovascular effects. The three main effects that are considered to contribute to cardiovascular failure due to PM exposure (Simkhovich, et al., 2008).

Simkhovich et al. (2008) suggest that since Ultra-Fine Particles ($PM_{0.1}$) can migrate into the blood circulation and be transported through the vascular system to the heart and it can possibly cause cardiac arrhythmias and decrease cardiac contractility and coronary flow. They also suggest that exposure to $PM_{0.1}$ can cause significant changes in many cardiovascular mechanisms and some symptoms such as changes in heart rate, blood pressure and blood coagulation ability develop acutely in response of increased $PM_{0.1}$ exposure. Particulate matter can disrupt the autonomic nervous system and different effects can vary due to the type of PM (PM_{10}, $PM_{2.5}$ or $PM_{0.1}$) and their concentrations (Simkhovich, et al., 2008).

Künzli et al. (2005) studied the association between atherosclerosis and long-term exposure to ambient $PM_{2.5}$ and used data on 798 participants from two clinical trials and concluded that carotid intima-media thickness increased by 2.9% for a cross sectional exposure of 10 $\mu g/m^3$ of $PM_{2.5}$. These results show epidemiologic evidence of an association between atherosclerosis and PM (Künzli, et al., 2005).

Human exposure studies, animal models, and tissue or cellular studies as well as epidemiological studies may provide some explanations of the patho-physiology behind the adverse health effects of air

pollutants but still the subject remains unclear and the studies have inherent limitations (Bernstein 2004). Further studies in these fields are needed.

2.3 Drug Use

Not many studies have been done on the possible adverse health effects of air pollution using drug dispensation as an outcome measure. Such studies on the use of heart drugs have not been found. On the other hand, five studies of adverse effect of air pollution on drug dispenses against respiratory diseases were found in the literature.

One such study has been conducted in Reykjavík, Iceland by Carlsen et al. (2009) and they used the daily number of drug dispensing for obstructive pulmonary disease over the time period of 2006 to the end of September 2008. They found a positive association between the air pollution factors of PM_{10}, O_3, H_2S, and NO_2 and respiratory drug dispensations. When the peak ambient pollution of PM_{10}, O_3, H_2S, and NO_2 was studied they found an increase of 3%, 5%, 2% and 6-7% in drug dispensations, respectively (Carlsen, et al., 2009). The association was strongest with a time lag of 3-5 days for PM_{10}, O_3, and H_2S but the time lag regarding NO_2 concentrations were 12-14 days.

Laurent et al. (2009) used a population of 15,121 individuals, aged 0-39 that bought respiratory drugs in Strasbourg, France and the ambient air pollution of PM_{10}, NO_2, and O_3. They found that an increase of 10 $\mu g/m^3$ of PM_{10}, NO_2, and O_3 resulted in an increase of 7.5%, 8.4%, and 1% of respiratory drug (short-acting beta agonist) sales (Laurent, et al., 2009).

Vegni et al. (2005) also used respiratory drug dispensing as an indicator of the adverse effect of air pollution. They looked at the 84,713 inhabitants of Como and used the weekly count of dispenses and weekly dispensed daily defined doses (DDD) of respiratory drugs which they modeled with the weekly mean air pollution concentration. The ambient air pollution they studied was total suspended particles (TSP) which is a sort of ambient particulate matter. Vegni (2005) found that the RR for weekly mean concentrations of TSP and respiratory drug dispensing to be 1.082 and for DDD it was 1.137 (Vegni, et al., 2005).

Pitard et al. (2004) studied the effect of ambient black smoke (BS), SO_2, and NO_2 on anti-asthmatics, bronchodilators, couch and cold preparation sales for children younger than 16 years. Their results show that with an increase of 10 $\mu g/m^3$ of BS the sales of anti-asthmatics and bronchodilators increased by 6.2%. The same increase of BS, SO_2, and NO_2, was associated with increase of 9.2%, 11.8%, and 13.6% in sales of couch and cold preparation sales, respectively (Pitard, et al., 2004).

And finally, there was a study made by Zeghnoun et al. the year 1999 and they looked the effects of BS, NO_2, and SO_2 on daily respiratory drug sales and found an association between those factors with lags varying from 1 to 9 days (Zeghnoun, et al., 1999).

These five studies were all concordant that drug dispensing for respiratory diseases may be used as an indicator of health effects by air pollutant, and therefore it is possible that the dispense of drugs for heart diseases could also be used in epidemiological surveillance of air pollutant and possible health effects.

2.3.1 Summary

As can be seen, air pollution exposure and exposure to fluctuating levels of ambient air pollution has been associated with an increase in cardiovascular morbidity and mortality. Clearly there are adverse health effects to cardiovascular patients from ambient air pollution as have been indicated in the above mentioned studies.

2.4 Laws and Regulations

Icelandic laws and regulations concerning air quality are mostly drawn from the findings of the European Union of air quality.

The following laws and regulations are considered relevant for air quality and ambient levels of PM, NO_2, O_3, and H_2S in Iceland and fall under the Icelandic legal framework.

Law no.7/1998[1]

The purpose of this law is to provide Icelanders wholesome and unpolluted living conditions.

Emission control surveillance regulation no.786/1999[2]

This regulation applies for emission control surveillance over possible polluting businesses and activity.

Air quality regulation no.787/1999[3]

This regulation applies to air quality and air pollution defense.

Air pollutant defense regulation no.788/1999[4]

This regulation applies for emission permits of pollutants from vehicle exhaust.

Air pollutant regulation no.251/2002[5]

This regulation applies for control, measurements, information flow and alerts to the public about various air pollutants in the atmosphere, including PM and NO_2.

[1] Lög um hollustuhætti og mengunarvarnir nr. 7/1998
[2] Reglugerð um mengunarvarnareftirlit nr. 786/1999
[3] Reglugerð um loftgæði nr. 787/1999
[4] Reglugerð um varnir gegn loftmengun af völdum hreyfanlegra uppsprettna nr. 788/1999
[5] Reglugerð um brennisteinsdíoxíð, köfnunarefnisdíoxíð og köfnunarefnisoxíð, bensen, kolsýring, svifryk og blý í andrúmsloftinu og upplýsingar til almennings nr. 251/2002

Aerosol limit regulation no.817/2002[6]

This regulation applies for ambient aerosol limit.

Ground level ozone regulation no. 745/2003[7]

This regulation applies to monitoring, measuring, environmental and information limits as well as information flow considering ground level O_3 concentrations.

Atmospheric hydrogen sulfide regulation no.514/2010[8]

This regulation was adopted the year 2010 and applies to monitoring, measuring environmental and information limits as well as information flow considering atmospheric H_2S concentrations.

There are some changes already predetermined to the air pollution regulation no.251/2002 and they are considering the guideline limits of PM_{10}. These changes are to the yearly average limit and how often it is permissible to exceed this limit each year.

Regulation standards the year 2005:

Annual mean PM_{10} limit is 40 µg/m^3 and 24 hour limit is 50µg/m^3. Number of permissible days exceeding the 24 hour limit are 35 (Table 2).

Regulation standards adopted the year 2010:

Yearly mean PM_{10} limit was brought down to 20 µg/m^3 and the 24 hour limit stayed the same. The number of days exceeding the 24 hour limit was decreased to 7 days. These changes came into effect the 1st of January 2010 (Table 2).

[6] Reglugerð um mörk fyrir fallryk í andrúmslofti nr. 817/2002
[7] Reglugerð um styrk ósons við yfirborð jarðar nr. 745/2003
[8] Reglugerð um styrk brennisteinsvetnis í andrúmslofti nr. 514/2010

Table 2. 24-hour limit value and annual limit value of PM_{10} over the years 2005 to 2010. Margin of tolerance (MOT) is displayed (EU, 1999).

Year	24-hour Limit (µg/m³)	MOT[a] (days)	No. of Exceedances	Annual Limit (µg/m³)
2005	50	35	9	20
2006	50	29	29	20
2007	50	23	19	20
2008	50	18	28	20
2009	50	12	20	20
2010	50	7	-	20

[a] *Margin of tolerance: Number of days per year that are permissible to exceed the 24-hour limit value. Aimed to avoid, prevent or reduce harmful effects on human health.*

The year 2007 the PM_{10} 24 hour concentration exceeded the 24 hour health limit 19 times and the year 2006 it was 29 times. These violations were within the limit for each year (Böðvarsdóttir, 2007; Reykjavík, 2009). The years 2002 to 2005 the days of PM_{10} concentration exceeding the health limits were within the 24 hour limit. The year 2008 however had 28 days exceeding the 24 hour limit while the number of permissible days was only 18, and the year 2009 had 20 days exceeding the 24 hour limit, as can be seen in Table 2 (Böðvarsdóttir, 2006a, 2006b, 2006c, 2006d, 2007, 2009).

3 Objectives

3.1 Aim and Hypothesis of the Study

The aim was to evaluate whether there is an association between day-by-day ambient air concentration levels of NO_2, O_3, PM_{10}, and H_2S in the Reykjavík area and the dispensation of drugs for angina pectoris among the adults of the population.

Furthermore, the specific aims were to study:

- Whether air pollution concentrations, measured as 1-hour peak, 24-hour mean, and 3-day mean, are associated with the daily dispensing of drugs for heart diseases, the C01DA group (*organic nitrates*) and the C01DA02 sub-group (*glyceryl trinitrate*).
- Whether there is a delay (lag-time) for the dispensing of drugs following increased concentrations levels of air pollution.

4 Material and Methods

In this chapter the material and methods used in the study will be described. The study population, design, exposure and outcome data will be detailed as well as the statistical methods and the hypotheses that were tested.

4.1 Study Data

4.1.1 Pharmaceutical Data

The Directorate of Health in Iceland provided pharmaceutical information from the Icelandic Pharmaceuticals Data Bank. The Icelandic Pharmaceuticals Data Bank holds data on all dispensations of prescription drugs to the total outpatient population in Iceland from January 1st 2003 and onwards. For the current study, information was retrieved from all dispensations of cardiovascular medication, ATC group C01, to people living in the Reykjavík area, and outside the Reykjavík area, during the study period including; date of dispensation, sex, birth year, residential zip code (codes within the Reykjavík capital area) of the patient, number of dispensations per patient, number of defined daily doses (DDD), name of drug and ATC code. The pharmaceutical data record is quite comprehensive with good coverage where 98% of all drug sales are recorded and registered in the Icelandic Pharmaceuticals Data Bank.

The drug data are registered according to the Anatomical Therapeutical Chemical classification system (ATC) which is a classification system that categorizes drugs into groups depending on which organ or biological system they act and on their chemical, pharmacological and therapeutic characteristics. Included in the ATC classification system is the defined daily dose (DDD) which is the “assumed average maintenance dose per day for a drug used for its main indication in adults“ (WHO, 2009) and is only assigned for drugs that have an ATC code. The ATC classification system is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC). Each drug is classified into five different levels (WHO, 2009).

The first level of the code indicates the anatomical main group and consists of one letter. There are 14 main groups coded with letters of the alphabet, where group A (alimentary) refers to medicine that affects the alimentary tract and metabolism, group B (blood) refers to medicine affecting the blood and blood forming organs, group C (cardiovascular) to medicine affecting the cardiovascular system etc. (WHO, 2009).

The second level of the code refers to the therapeutic main group and consists of two digits, for example C01; cardiac therapy. The third level of the code refers to therapeutic or pharmaceutical sub-group and consists of one letter, for example C01A; *cardiac glycosides*. The fourth level refers to the chemical, therapeutic and pharmalogical sub-group and consists of one letter, for example C01AB *scilla glycosides*. The fifth and last code indicates the chemical substance and consists of two digits, for example C01AB01 *proscillaridin* (WHO, 2009).

The drugs in the C01DA group are used as vasodilators, mainly in the treatment of angina pectoris. In this study, the focus was set on two categories of the dispensing data; the entire *organic nitrates* group (C01DA) and the sub-group *glyceryl trinitrate* (C01DA02). Angina pectoris is a disease marked by brief paroxysmal attacks of chest pain precipitated by deficient oxygenation of the heart muscle. Angina pectoris is a disease with abrupt onset painful attacks and it is the *glyceryl trinitrate* which are used against particular attacks. *Glyceryl trinitrate* is always taken sublingually or by chewing the tablet and spreading the material over the buccal mucous membrane and is ineffective if swallowed. An effective dose of *glyceryl trinitrate* administrated sublingually usually acts within two minutes, and the termination of pain is usually sudden and complete. *Glyceryl trinitrate* is used frequently as a treatment or prevention of individual attacks and the patient can avoid attacks by taking it shortly before a period of stress or exercise. Thus the *organic nitrate* group (C01DA), and in particular the *glyceryl trinitrate* (C01DA02) sub-group are appropriate to study in association with air pollution fluctuations, see late in statistical methods.

The daily number of individuals who were dispensed drugs, in ATC group C01DA and sub-group C01DA02, from January 1st 2005 to December 31st 2009 in the Reykjavík area was used to analyze the association between ambient air pollution and drug dispensations, as this was the period where complete data was available from the Icelandic Pharmaceuticals Data Bank. Over this period there was continuous registration data.

4.1.2 Pollution Data

The City of Reykjavík, Department of Environment (Public Health Authority) measured the pollutant levels of Reykjavík until the end of the year 2008 in cooperation with The Environment Agency of Iceland. From the beginning of 2009 The Environment Agency took over the operation and supervises the measurements throughout the study period.

There are three defined measuring locations in the Reykjavík capital area, one by a busy road intersection in Reykjavík (Grensásvegur – Miklabraut) which around 70,000 cars cross daily (Böðvarsdóttir, 2008). The second one is located by Reykjavík's Family Park and Zoo since 2002 and is intended to measure urban background air pollution. The third one is located at Hvaleyrarholt in Hafnarfjörður and is an industrial monitoring station. Finally, there is one portable measurement station which has been located at various sites in Reykjavík from the year 1990 and two in Kópavogur. The data from the station by Reykjavík's Family Park and Zoo, Hvaleyrarholt, and the portable station were not used in the current study since they contain gaps and will therefore not be discussed further.

The Grensásvegur-Miklabraut station measures 15 pollutants and 7 weather factors continuously. The pollutants are: particulate matter smaller than 10 µm (PM_{10}), particulate matter smaller than 2.5 µm ($PM_{2.5}$), nitrogen oxide (NO), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), ozone (O_3), sulfur dioxide (SO_2), hydrogen sulfide (H_2S), carbon oxide (CO), non-methane hydrocarbons (NMHC), total hydrocarbons (THC), benzene, methane (CH_4), toluene, and p-Xylem. The weather factors are: wind direction, wind speed, temperature, relative humidity, air pressure, radiation and rainfall.

For this study pollution data were retrieved for NO_2, PM_{10}, and O_3 over the time period of January 1st 2003 until December 31st 2009 from the Grensásvegur – Miklabraut measuring station. Data for H_2S were available from February 22nd 2006 to December 31st 2009. The total time period contained some gaps in the data due to inactive measuring equipments due to technical reasons. Other measured factors such as $PM_{2.5,}$ CO, CH_4, and SO_2 were considered for this study. However, the Department of Environment and the Environment Agency thought they did not have as a comprehensive data collection for some of these factors and/or the data reliability was questionable for some of them.

The air pollution measurement equipments used for monitoring NO_2, H_2S, and O_3 are of the Horiba type (models APNA 360E, APSA 360ACE, and APOA 360E). The one used to measure PM_{10} is an Andersen EMS IR Thermo (model FH62 I – R). These devices are calibrated twice a year.

4.1.3 Weather Data

The weather dataset, received from The City of Reykjavík, Department of Environment and The Environment Agency of Iceland, contained 7 weather factors. In this study only two were used, temperature (°C) and relative humidity (RH, %) since, according to existing knowledge, they can affect the studied air pollution concentrations. The dataset spanned the time period of January 1st 2003 to December 31st 2009 with 13 missing values and contained 24-hour mean values for each day of the year.

4.1.4 Other Data

The Directorate of Health in Iceland provided influenza data for the study period. They included monthly number of influenza cases which were reported to the Directorate of Health from primary health care centers. The number of influenza cases per month was recalculated into binary variables (0 and 1). If registered number of influenza cases exceeded 300 in a month then every day of that month was considered an influenza day. This is though somewhat crude for the study design.

4.2 Study Methods

4.2.1 Study Population

The study population of this research consisted of 18 years and older of the Reykjavík capital area during the study period of January 1st 2005 to December 31st 2009 as registered in the National Registry by Statistics Iceland (Hagstofan). The inhabitants were at average 136,006 each year over the study period (Hagstofan, 2009). All individuals (18 years and older) who were dispensed drugs for cardiovascular diseases (ATC code C01DA) were subject to this study. An individual who dispensed a drug in the C01DA group or C01DA02 sub-group twice the same day was only counted once (i.e. as one individual dispensing that day). For the *organic nitrate* (C01DA) group there were 3,348 such cases and for the *glyceryl trinitrate* (C01DA02) group there were 97 cases.

4.2.2 Study Period

The study period was defined January 1st 2005 to December 31st 2009 as this was the period where complete data was available from the Icelandic Pharmaceuticals Data Bank. Therefore January 1st 2003 to December 31st 2004 was excluded from the study. The entire dataset contained 1,826 days.

4.2.3 Study Design

Case Crossover Design

A case-crossover analysis was applied in this study. The case-crossover study is a variant of the case-control study frequently used in epidemiological studies. The case control design is used to identify factors, or exposure, that may contribute to a medical condition (e.g. disease). In a case-control study, subjects (cases) who have a specified exposure, and other subjects (controls), who have been sampled from the same background population, are compared in respect to frequency of past exposure. Throughout the years, many variants of case-control studies have been described.

The case-crossover design is thus a correspondent to a case-control design and was developed in the early 1990's to study the effects of temporary, short-term exposures of, air pollution, for example, on health outcomes with an abrupt onset, such as heart attacks. The title of the first description of the method was: "The case-crossover design: A method for studying transient effects on the risk of acute events"(Maclure, 1991). The control series in a case-crossover study do not consist of a different set of individuals but rather a sample of the time experience of the cases before (and after) they developed the outcome (Rothman, 2002). The design allows use of routinely monitored air pollution information to be used as well as having the individual as the unit of observation (case) rather than days (Janes, et al., 2005; Rothman, 2002).

According to Maclure and Mittleman (2000) and Janes et al. (2005) the case-crossover design is suitable if the exposure is discontinuous and brief, such as varying short-term air pollution, and the outcome has an abrupt onset (Janes, et al., 2005; Maclure & Mittleman, 2000). Therefore this method was applied to this study. Here, the exposure variable was air pollution which is intermittent in the Reykjavík area given the nature of fluctuating pollution levels. The outcome variable, the dispensing of *organic nitrates* (C01DA) and the sub-group *glyceryl trinitrate* (C01DA02), was used as the surrogate of a heart disease, angina pectoris, which has an abrupt onset. The air pollution data of this study showed seasonal and weekly fluctuation and therefore a bi-directional case-crossover sampling was used. The dispensation of drugs was also different according to the day of the week, the dispensation were fewer during weekends than other days. Bi-directional control periods i.e. before and after the event (case exposure), were sampled to meet these time trends. The interference for each case (air pollution exposure) was compared to two control periods (air pollution exposure), that is to say the same day of the week before the index day (the day of drug dispensation) and the same day of the week after the index day (Figure 6). Together, the exposure

at the control days and exposure at the index day form a matched case control set. Those sets from different individuals are then analyzed by using conditional logistic regression models. Sets with different levels of exposure are informative and are utilized in the case-crossover design.

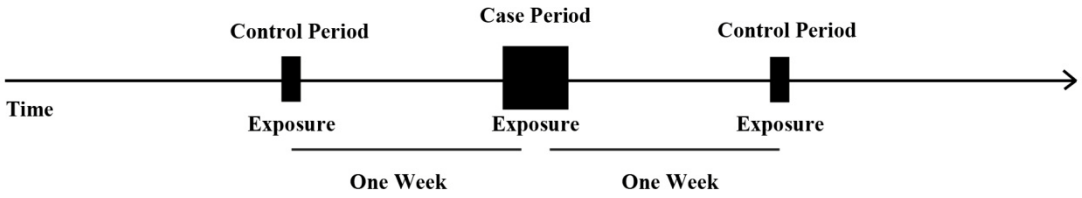

Figure 6. Bi-directional sampling of control exposures in a case-crossover study. Time between case exposure and control period exposures is one week, i.e. case exposure and control exposures are the same day of the week of the corresponding weeks.

Conditional Logistic Regression

The matching was 1:2 since there was one case (index day with exposure) and two control periods; the same day of the week one week before the index day and same day of the week one week following the index day. Conditional logistic regression is useful to describe the correlation between a dependant variable of a binary (or dichotomous) source (dispensation of a drug or not) and a continuous independent variable (pollution exposure).

The odds ratio (OR) is representative for a 10 µg/m^3 change in the concentration of pollutant, which is compatable to measures used in previous studies on similar subjects.

Beginning and Ending the Study Period

In the beginning of the study period, on the first day of drug dispense, there is only available one control period i.e. the same day of the week the week after dispensation. As more dispensation days come gradually into the study the control periods before the day of dispensation come available, for the first time on the eight day of the dispensation in the beginning of the study period. This gradual movement of the analysis though days of the study period also has consequences for the lag analyses. At the end of the study period similarly the only control periods before the dispensation will be available towards the ending of the study period. In the case when exposure data is missing there will be an interruption of the study period for at least one or more days and these interruptions are in the calculation treated as temporary ending of the study period and subsequently new beginning of the study period after the interval of missing data.

4.2.4 Measures

Exposure Variables

The pollution data used in this study contained 30 or 60 minute mean values for the following pollutants: NO_2, PM_{10}, O_3, and H_2S over the time period of January 1st 2005 to December 31st 2009. The mean 1-hour peak concentration value (maximum daily 1-hour mean value) and the 24-hour mean concentration value (from the time 00:00 to 00:00 the next day) were calculated for each pollutant as well as a 3-day mean, i.e. the average for index day and two days prior to the index day for the 3-day mean concentration values.

The weather data were given in 24-hour mean values for temperature and relative humidity (RH) and therefore the mean 1-hour peak levels were not available for these two factors in the study.

Outcome Variables

The pharmaceutical data used in this study contained the date of dispensation, sex, birth year of individuals older than 18 years, residential zip code (codes within the Reykjavík capital area) of the individual, number of dispensations per individual, name of the drug and ATC code.

Delay in Outcome

It is possible that there is a delay (lag time) between exposures of pollutant until an individual is dispensed the drug. Therefore, a lag time up to 5 days was introduced in the analyses. The definition of each lag is as follows; lag 0: air pollution exposure on the day of drug dispensation, lag 1: air pollution exposure the day before the day of drug dispensation etc.

Other Variables

The study period was stratified into the following categories: the entire study period (1st January 2005 to 31st of December 2009), winter months and summer months. The winter months are from November 1st to April 30th each year and summer months are May 1st to October 31st each year.

Adjustments for influenza season were included in the case-crossover analysis.

4.2.5 Missing Values

Pharmaceutical Data

The pharmaceutical data had no missing values in the dataset.

Pollution Data

The pollution data had some missing values over the time period due to inactive measuring equipments. The entire dataset contained 1,826 days but the missing values differ according to different pollution factors, i.e. NO_2 has 143 (7.83%) missing values, O_3 82 (4.49%) days, and PM_{10} 36 (1.97%) days, and therefore 1,683, 1,744, and 1,790 were usable values within each pollutant factor, respectively. H_2S measurements did not start until February 22nd 2006 and therefore the

entire dataset only contained 1,409 days with 219 (15%) missing values and had 1,190 usable days.

Weather Data

The temperature data had 13 missing values as well as the relative humidity (RH) due to downtime of the measurement equipment.

Handling Missing Data

If there were two or more missing values in a matched case control set (one set contains three values) those days were excluded, otherwise they were applicable. This is also explained in chapter 4.2.3, where the procedure in the beginning and ending of the study period is clarified.

4.2.6 Statistical Methods

Pearson's Correlation

Correlation between different air pollutants and exposure factors was studied by using a Pearson's correlation test between two variables. The tests were two-tailed and a 1% and 5% level of significance were applied in all statistical analysis.

The test was developed by Karl Pearson and is used to measure the correlation (linear dependence) between two variables, X and Y, and gives a value between -1 and 1, where -1 is a 100% negative correlation, 1 is a 100% positive correlation and 0 is no correlation at all and the variables are independent.

Case-Crossover

To evaluate the association between ambient pollution and number of dispensations, a time-stratified case-crossover study design was used. In this design, case's exposure before the day of dispensation (case-defining event) is compared with his or her own exposure experience during two control periods. Control periods were chosen the same day of the week in the week before and after the dispensation day. Exposures during the case period were compared with exposures occurring in control periods. The case-crossover approach is to control for confounding, by making within-subject comparisons and then time independent confounders are controlled by design.

Association of pollutant concentrations on each of the six exposure periods, day 0 to 5 before dispensation (lags 0 to 5) was compared, one at a time, with pollution concentration on corresponding control periods. By this design seasonality, time trends, and slowly varying potential confounders were control for. A conditional logistic regression was performed, stratifying on each day, to estimates odds ratios (OR) and 95% confidence intervals (CI). For each pollutant in the model meteorological covariates, daily mean temperatures, and mean relative humidity were controlled for with appropriate lag (0 to 5). Also the model was run with pollutant exposure averaged over three consecutive days. Only one dispensation per individual per day was counted thus repeated dispensation for the same individual within a single day were excluded from the analyses.

Three separate multy pollutant models were considered, one that included all of the four pollutant factors (NO_2, O_3, PM_{10}, and H_2S) as well as the two weather factors (temperature and relative humidity). The second model included only three pollutant factors; NO_2, O_3, and PM_{10} as well as the two weather factors. The third separate model included the pollutant and weather factors as well as the influenza season. Level of significance was set at 0.05 (95% CI).

Statistical Programs

Programs used for this study were Excel 2007, SPSS 16.0 and STATA 11.

4.3 Ethical Approvals

The National Bioethics Committee office issued a permit for this study (reference number VSNb2010030008/03.7), as well as the Data Protection Authority (research study number 2010030263ÞS/-). The Directorate of Health issued a permit for the use of the pharmaceuticals data for the study dated May 5th 2010 (reference number 2010030105/5.2.3.3/SH/sh). Data used in this study were not personally identifiable in any way.

5 Results

In this section the results of the study are presented according to the study objectives. The first section overviews the descriptive statistics of the study data and section two present the results of the main objectives described in section 3.1. The second section will outline the results of the association between ambient air pollution in the Reykjavík area and the dispensation of *organic nitrate* (C01DA) and *glyceryl trinitrate* drugs (C01DA02) among adults (≥18 years). The odds ratio (OR) for individuals being dispensed cardiovascular drugs (C01DA or C01DA02) associated with a 10 μg/m^3 change in the pollutant concentration are demonstrated as well as the lag time of drug dispensing due to air pollution exposure. An estimation on the strength of the association between *organic nitrates* (C01DA) and *glyceryl trinitrate* (C01DA02) with the air pollution in the light of different exposure measure will be presented. Results will be presented both in text and graphics (tables and figures).

5.1 Descriptive Statistics

5.1.1 Ambient Air Pollution Levels and Weather Factors

The five year study period, from January 1st 2005 to December 31st 2009, included 1,826 days. There were some missing data for each exposure variable as can be seen in the time series plot (Figure 7). Missing values measured in days for PM_{10} were 36 (1.97% of total study values), 83 for O_3 (4.49% of total study values), and for NO_2 143 (7.83% of total study values). H_2S measurements did not start until February 22nd 2006 and therefore the entire dataset only contained 1,409 days with 219 (15%) missing values and had 1,190 usable days. This can be seen in Figure 7.

Figure 7 shows that pollutants often have a seasonal pattern over the study period. This is somewhat clear for NO_2 and O_3 but not as clear for PM_{10} and H_2S.

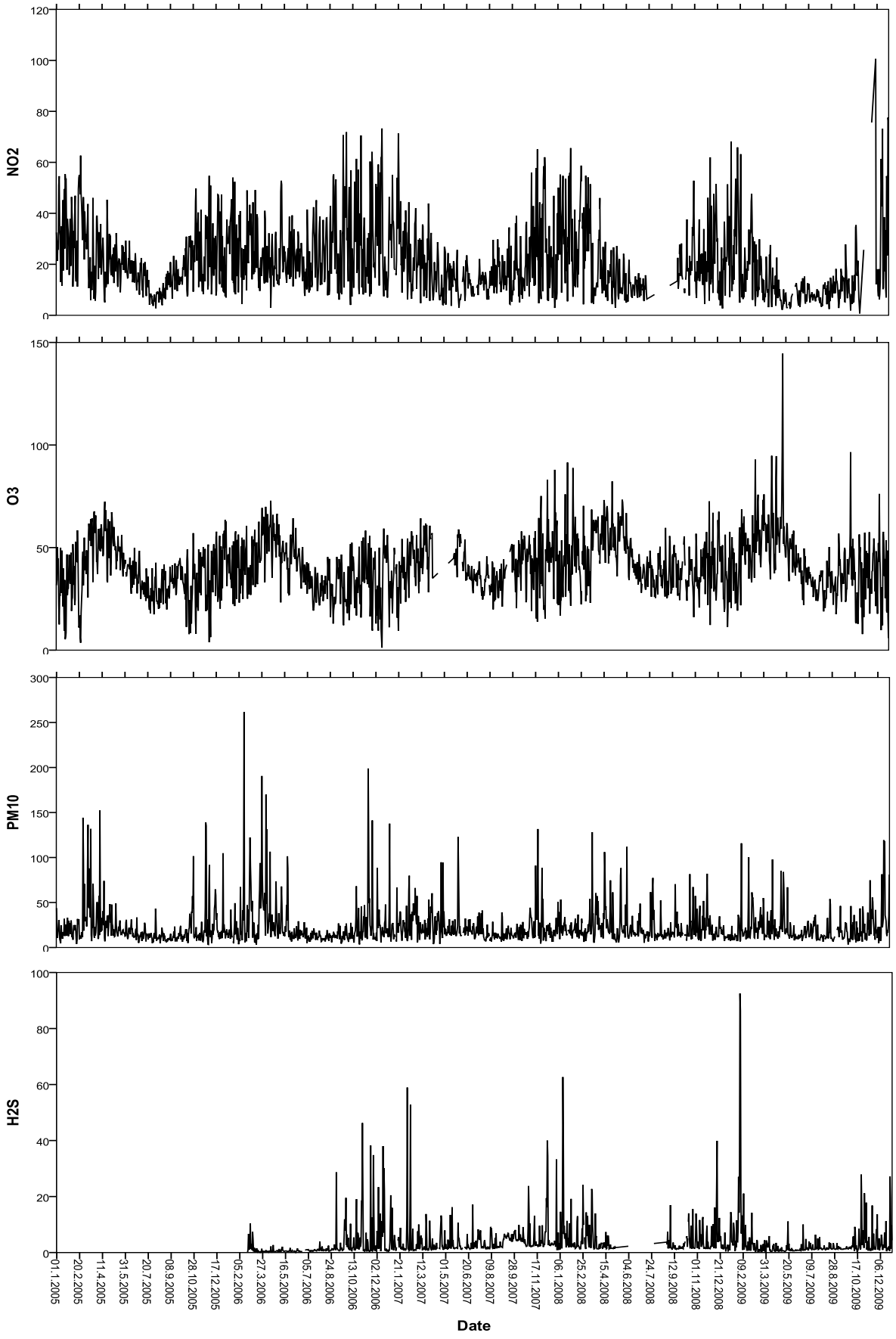

Figure 7. Daily 24-hour mean concentration levels of NO_2, O_3, PM_{10}, and H_2S ($\mu g/m^3$). Measurements of H_2S started in February 2006. Gaps in figures are due to missing data.

Table 3 shows the ambient air pollution concentrations in the Reykjavík area for the whole study period, according to seasons and pollutant metrics. Pollution values and standard deviations were higher over the winter months of November 1st to April 30th than over the summer months of May 1st to October 31st for every variable. This is most obvious for PM_{10}. The mean 1-hour peak concentration values, as well as the standard deviations, were higher than the 24-hour mean values and the 3-day mean values, and their standard deviations, for each pollutant, over the study period for each metric category. Furthermore, the 3-day mean measurement for each pollutant was very similar to, or slightly higher than, the 24-hour mean values. PM_{10} showed the largest range of concentration levels throughout the study period while H_2S had the smallest range of concentration levels as well as the lowest 24-hour mean (Table 3).

Table 3. Descriptive statistics of daily air pollution levels over the study period according to seasons and pollutant metric. Mean 1-hour peak values, 24-hour mean values, and 3-day mean values are shown as well as maximum and minimum values over the same periods.

	Total time period[a]			Winter[b]			Summer[c]		
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Mean (SD)	Min	Max
24-hour mean									
PM_{10} (µg/m^3)	23 (21)	3	262	27 (26)	3	262	18 (13)	3	123
NO_2 (µg/m^3)	21 (13)	1	101	25 (15)	3	101	16 (11)	1	72
O_3 (µg/m^3)	41 (14)	1	145	43 (15)	1	95	38 (12)	8	145
H_2S (µg/m^3)	4 (7)	0	93	5 (8)	0	93	3 (4)	0	46
Maximum mean 1-hour peak									
PM_{10} (µg/m^3)	77 (126)	11	1779	98 (162)	12	1779	56 (67)	11	705
NO_2 (µg/m^3)	48 (28)	1	210	57 (27)	6	166	38 (25)	1	210
O_3 (µg/m^3)	58 (17)	7	195	65 (17)	7	162	52 (14)	7	195
H_2S (µg/m^3)	14 (25)	0	203	19 (29)	0	203	10 (19)	0	170
3-day mean									
PM_{10} (µg/m^3)	21 (15)	5	126	27 (18)	5	126	18 (10)	6	84
NO_2 (µg/m^3)	21 (11)	1	101	25 (11)	5	101	16 (9)	1	53
O_3 (µg/m^3)	41 (11)	6	109	43 (12)	6	81	38 (11)	14	109
H_2S (µg/m^3)	4 (5)	0	69	5 (6)	0	69	3 (3)	0	28

Abbreviations: Mean: mean value over specified time period, Max: maximum value over specified time period, Min: minimum value over specified time period, SD: standard deviation.

[a] Time period: 1st January 2005 to 31st of December 2009. n(total) = 1,826, n(PM_{10}) = 1,744, n(NO_2) = 1,683, n(O_3) = 1,790, n(H_2S) = 1,190.

[b] Winter months: November 1st to April 30th. n(total) = 906, n(PM_{10}) = 894, n(NO_2) = 868, n(O_3) = 873, n(H_2S) = 600.

[c] Summer months: May 1st to October 31st. n(total) = 920, n(PM_{10}) = 896, n(NO_2) = 815, n(O_3) = 871, n(H_2S) = 590.

Table 4 shows the weather factors (relative humidity and temperature) over the whole study period, according to seasons and weather metrics. The 3-day mean was similar to the 24-hour mean concentrations and the temperature was higher over the summer months but the relative humidity was higher over the winter months.

Table 4. Descriptive statistics of daily weather factors over the study period according to seasons and pollutant metric. 24-hour mean values and 3-day mean values are shown as well as maximum and minimum values over the same periods.

	Total time period[a]			Winter[b]			Summer[c]		
	Mean (SD)	**Min**	**Max**	**Mean (SD)**	**Min**	**Max**	**Mean (SD)**	**Min**	**Max**
24-hour mean									
Rel. humidity (%)	78 (11)	39	103[d]	80 (12)	39	103[d]	77 (10)	48	97
Temperature (°C)	6 (5)	-10	21	2 (4)	-10	12	9 (4)	-8	21
3-day mean									
Rel. humidity (%)	78 (9)	43	101[d]	79 (10)	43	101[d]	76 (8)	50	97
Temperature (°C)	6 (5)	-7	18	2 (3)	-7	11	9 (3)	-2	18

Abbreviations: Mean: mean value over specified time period, Max: maximum value over specified time period, Min: minimum value over specified time period, SD: standard deviation, Rel. humidity: relative humidity.

[a] *Time period: 1st January 2005 to 31st of December 2009.*

[b] *Winter months: November 1st to April 30th.*

[c] *Summer months: May 1st to October 31st.*

[d] *The maximum value of relative humidity is 100%. There is a 3% error margin in the measuring equipment.*

Table 5 shows air pollution, temperature, relative humidity, and Pearson's correlation coefficients between exposure terms of the 24-hour mean and 3-day mean. A two-tailed bivariate correlation test was used with a 0.01 and 0.05 level of significance. Most correlation coefficients for temperature were negative and the highest correlation was found between the 24-hour mean and the 3-day mean of the same pollutant. The strongest correlation between pollutants was negative and was between the 24-hour mean concentration levels of NO_2 and O_3. The strongest positive correlation was for the 24-hour means of NO_2 and H_2S. Temperature correlates negatively to each pollutant factor and the relative humidity (RH) correlates negatively to PM_{10}, and O_3.

Correlation coefficients of the exposure factors of the mean 1-hour peak values can be seen in Table 9 in the appendix.

Table 5. Pollution variable correlation matrix.

	NO_2		O_3		PM_{10}		H_2S		Temp		RH	
	24-hr mean	**3-day mean**	**24-hr mean**	**3-day mean**	**24-hr mean**	**3-day mean**	**24-hr mean**	**3-day mean**	**24-hr mean**	**3-day mean**	**24-hr mean**	**3-day mean**
NO_2												
24-hr mean	1.00											
3-day mean	0.78#	1.00										
O_3												
24-hr mean	-0.62#	-0.41#	1.00									
3-day mean	-0.41#	-0.52#	0.81#	1.00								
PM_{10}												
24-hr mean	0.13#	0.06*	0.13#	0.18#	1.00							
3-day mean	0.11#	0.11#	0.17#	0.22#	0.72#	1.00						
H_2S												
24-hr mean	0.34#	0.32#	-0.28#	-0.24#	0.02	-0.01	1.00					
3-day mean	0.31#	0.41#	-0.21#	-0.29#	-0.02	-0.01	0.73#	1.00				
Temp												
24-hr mean	-.043#	-0.45#	-0.04	-0.11#	-0.28#	-0.33#	-0.28#	-0.30#	1.00			
3-day mean	-0.39#	-0.48#	-0.10	-0.12#	-0.24#	-0.34#	-0.27#	-0.34#	0.95#	1.00		
RH												
24-hr mean	0.04	0.03	-0.07*	-0.07*	-0.33#	-0.34#	0.03	0.05	0.15#	0.12#	1.00	
3-day mean	0.02	0.03	-0.05	-0.07*	-0.33#	-0.43#	-0.00	0.03	0.12#	0,14#	0.82#	1.00

Pearson´s Correlation Coefficients (p value): n (NO_2) = 1,683, n(O_3) = 1,744, n(PM_{10}) = 1,790, n(H_2S) = 1,190, n(Temp) = 1,813, n(RH) = 1,813.
Abbreviations: Max: maximum, Temp: temperature, RH: relative humidity, 24-hr mean: 24-hour mean, 3-day mean: 3-day mean.
** Correlation is significant at the 0.05 level.*
 # Correlation is significant at the 0.01 level.

5.1.2 Dispensation of Drugs

The total number of dispensing of *organic nitrates* (C01DA) during the study period January 1st 2005 to December 31st 2009 was 68,099, including 8,604 dispensing of *glyceryl trinitrates* (C01DA02). At average there were 3 individuals that dispensed an *organic nitrate* drug (C01DA) and 4-5 individuals that dispensed a *glyceryl trinitrate* drug (C01DA02) each day. The average number of dispensing of *organic nitrates* (C01DA) per year was 22,952 of which 57.70% were to males and 42.30% to females.

In total 5,246 individuals in Reykjavík's capital area were dispensed *organic nitrate* drugs (C01DA) during the study period, or on average around three individuals per day. Most individuals

were dispensed drugs on week days and then the number declined reaching a minimum on weekends. There were various peaks over the year such as in late December, beginning of January and during summer.

A frequency table for the whole *cardiac therapy* group (C01) category can be seen in Table 10 in the appendix. Drug dispensing from the *glyceryl trinitrate* group (C01DA) accounted for 59.3% of the total dispensing in the C01 group. The most commonly dispensed drugs in the C01DA category are *isosorbide mononitrates* (C01DA14) and consisted of 83.12% of the total number of dispensing within this group (Table 6). The *glyceryl trinitrate* group (C01DA02) accounted for a little less than 13% of the total number of dispensing.

77% of the individuals that were dispensed drugs in the *organic nitrate* group (C01DA) only dispensed a drug four times or less every year (Table 11 in appendix). For the *glyceryl trinitrate* group (C01DA02) around 96% of the individuals dispensed *glyceryl trinitrates* four times or less, every year (Table 12 in appendix).

Table 6. Frequency table for the *organic nitrates* group (C01DA).

C01DA group	Number of Dispensations	Percent (%)	Drug Name
C01DA0201	**1,755**	**2.58**	**Glyceryl Trinitrate, Discotrine**
C01DA0204	**6,824**	**10.02**	**Glyceryl Trinitrate, Nitromex**
C01DA0206	**25**	**0.04**	**Glyceryl Trinitrate, -**
C01DA0801	2,871	4.22	Isosorbide Mononitrate, Sorbangil
C01DA1401	40,374	59.29	Isosorbide Mononitrate, Imdur
C01DA1402	1,674	2.46	Isosorbide Mononitrate, Monit-L
C01DA1403	14,576	21.40	Isosorbide Mononitrate, Ismo
Total	**68,099**	**100**	

5.2 Ambient Air Pollution and Drug Dispensation

5.2.1 Ambient Air Pollution in the Reykjavík Area and Dispensation of *Organic Nitrate* Drugs (C01DA)

The initial analysis on the association between ambient air pollution exposure and the dispensing of *organic nitrate* drugs showed that there was an association between these factors. Table 7 shows the odds ratio (OR) for individuals being dispensed *organic nitrate* drugs (C01DA) associated with 10 μg/m^3 increase in the 24-hour mean for each pollutant.

Table 7. The matched OR and 95% CI for the dispensation of *organic nitrate* drugs (C01DA), associated with NO_2, O_3, and PM_{10} concentrations, 24-hour mean values in 10 µg/m^3 increase in pollution levels, adjusted for temperature and relative humidity.

	NO_2		O_3		PM_{10}	
Lag	**OR***	**(95% CI)**	**OR***	**(95% CI)**	**OR***	**(95% CI)**
0	**1,046**	**(1,031-1,060)**	**1,020**	**(1,006-1,034)**	**1,009**	**(1,003-1,014)**
1	**1,060**	**(1,045-1,076)**	**1,058**	**(1,043-1,073)**	**1,007**	**(1,001-1,012)**
2	1,006	(0,990-1,022)	**0,984**	**(0,970-0,998)**	**1,007**	**(1,001-1,013)**
3	0,994	(0,978-1,009)	0,993	(0,978-1,008)	**0,991**	**(0,985-0,997)**
4	0,996	(0,981-1,012)	1,010	(0,995-1,026)	**0,979**	**(0,974-0,985)**
5	**0,982**	**(0,968-0,997)**	1,009	(0,995-1,023)	0,995	(0,990-1,000)

* *Bolded when statistically significant. Data have been calculated in a unique multivariate analysis separately for each lag, taking into account simultaneously all the variables. Number of observations; lag 0: 162,072, lag 1: 160,177, lag 2: 159,939, lag 3: 161,097, lag 4: 161,405, and lag 5: 160,917.*

When including H_2S in the model (Table 13 in the appendix) the number of observations decreased of around one third due to smaller dataset of H_2S values. The OR for NO_2, O_3, and PM_{10} showed a similar pattern (Table 7) but the OR for H_2S did not follow the same pattern as the other pollutant variables (Figure 12 in appendix).

5.2.2 Ambient Air Pollution in the Reykjavík Area and Dispensation of *Glyceryl Trinitrate* Drugs (C01DA02)

Table 8 shows the OR for individuals being dispensed *glyceryl trinitrate* drugs (C01DA02) associated with an increase of 10 µg/m^3 of the 3-day mean pollutant concentration of each pollutant. The OR for individuals being dispensed *glyceryl trinitrate* drugs (C01DA02) associated with an increase of 10 µg/m^3 of the 24-hour mean pollutant concentration of each pollutant can be seen in Table 14 in appendix. Lag days are 0 to 5 and the confidence interval is 95%.

Table 8. The matched OR and 95% CI for the dispensation of *glyceryl trinitrate* drugs (C01DA02), associated with NO_2, O_3, and PM_{10} concentrations, 3-day mean values in 10 µg/m^3 increase in pollution levels, adjusted for temperature and relative humidity.

	NO_2		O_3		PM_{10}	
Lag	**OR***	**(95% CI)**	**OR***	**(95% CI)**	**OR***	**(95% CI)**
0	**1.116**	**(1.059-1.176)**	**1.090**	**(1.036-1.146)**	1.009	(0.988-1.030)
1	**1.071**	**(1.014-1.130)**	**1.072**	**(1.019-1.129)**	0.998	(0.976-1.021)
2	1.013	(0.957-1.071)	1.018	(0.965-1.073)	0.996	(0.973-1.019)
3	0.977	(0.923-1.034)	0.990	(0.938-1.046)	1.000	(0.978-1.022)
4	0.983	(0.933-1.035)	1.006	(0.956-1.059)	1.005	(0.984-1.027)
5	**0.942**	**(0.895-0.993)**	0.987	(0.938-1.038)	1.004	(0.984-1.025)

* *Bolded when statistically significant. Data have been calculated in a unique multivariate analysis separately for each lag, taking into account simultaneously all the variables. Number of observations; lag 0: 22,436, lag 1: 22,327, lag 2: 22,288, lag 3:22,367, lag 4: 22,406, and lag 5: 22,452.*

The pattern of NO_2 and O_3 was similar (Figure 8 and Figure 9) while PM_{10} was not statistically significant at any time lag (Figure 10). At lag 0 and lag 1 the association was strongest both for NO_2 and O_3 and the 95% CI did not include unity. There was an increase of 11.6% (NO_2) and 9.0% (O_3) at lag 0, and at lag 1 there was a 7.1% (NO_2) and 7.2% (O_3) increase. The OR at lag 2 also showed an increase of 1.3% for NO_2 and 1.8% for O_3 with 95% CI which included unity. For NO_2 at lag 3 to lag 5 the OR was 0.977, 0.983 and 0.942, respectively with the only significant OR at lag 5. For O_3 the OR at lag 3 to lag 5 was 0.990, 1.006 and 0.987 but not statistically significant. This can be seen graphically in Figure 8 and Figure 9.

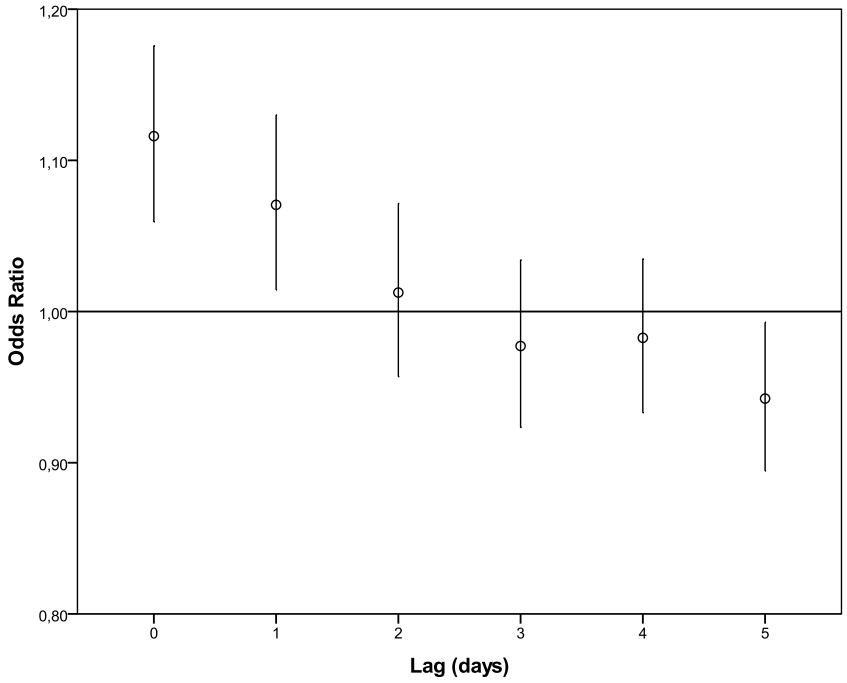

Figure 8. Association of NO_2 exposure (3-day mean) and daily *glyceryl trinitrate* (C01DA02) dispensations with lag 0-5 days, adjusted for PM_{10}, O_3, temperature, and humidity, and matched for day of the week. Bars show 95% confidence interval.

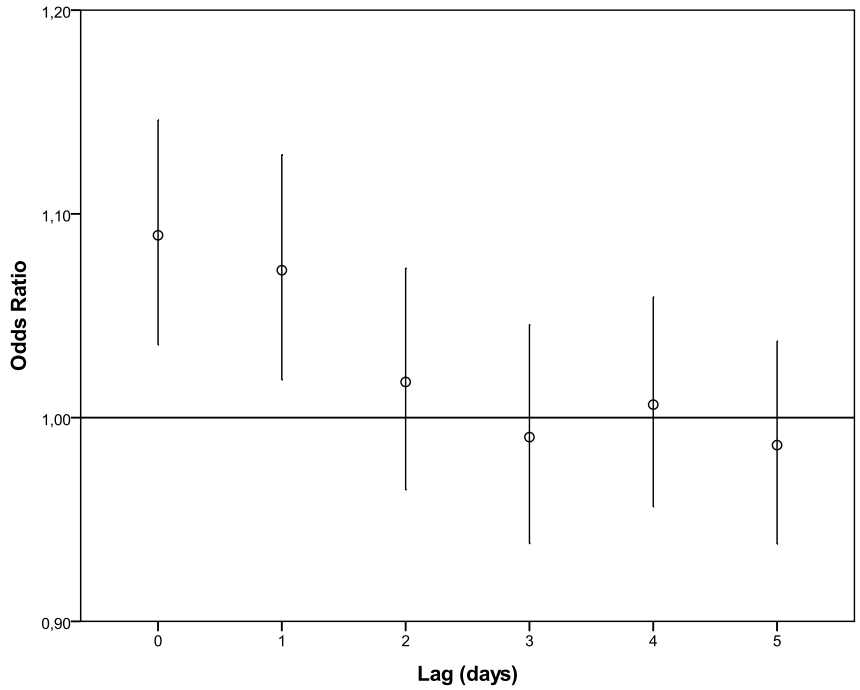

Figure 9. Association of O_3 exposure (3-day mean) and daily *glyceryl trinitrate* (C01DA02) dispensations with lag 0-5 days, adjusted for PM_{10}, NO_2, temperature, and humidity, and matched for day of the week. Bars show 95% confidence interval.

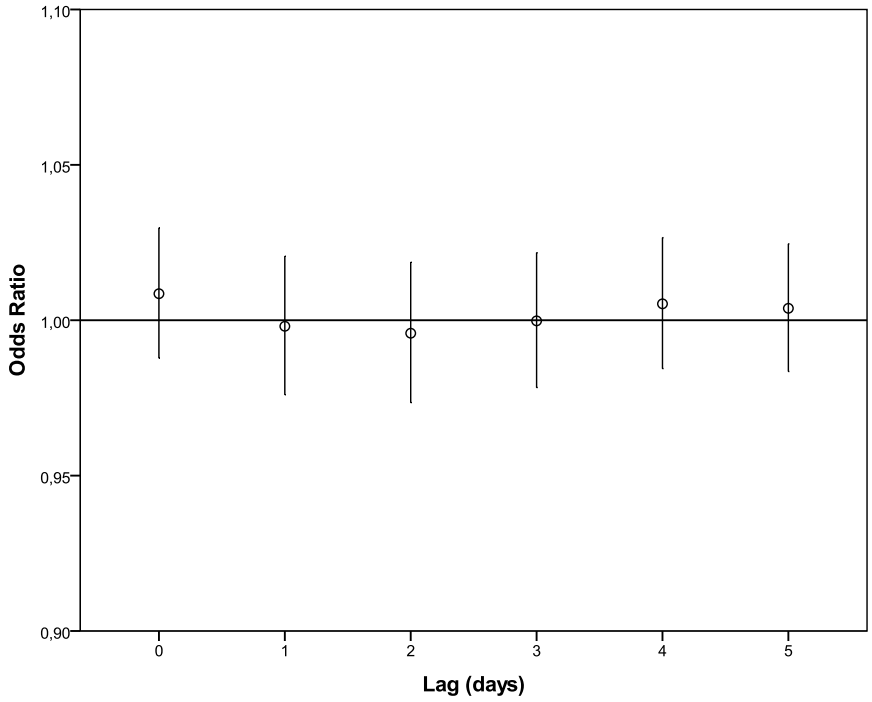

Figure 10. Association of PM_{10} exposure (3-day mean) and daily *glyceryl trinitrate* (C01DA02) dispensations with lag 0-5 days**,** adjusted for O_3, NO_2, temperature, and humidity and matched for day of the week. Bars show 95% confidence interval.

Association of H_2S exposure (3-day mean) and daily *glyceryl trinitrate* (C01DA02) dispensations with lag 0 to 5 days showed a different pattern than the other pollutants (Figure 11). The association between concentrations of NO_2, O_3, PM_{10}, and H_2S (3-day mean values) and the dispensing of *glyceryl trinitrate* drugs (C01DA02) can be seen in Table 15 in the appendix. Introducing H_2S in the regression model did not change the pattern of association of the other exposures. The OR was below one at lag 0 and lag 1 (0.934 and 0.975) and at lag 2 to 5 the odds ratio was 1.003, 1.027, 1.008, and 1.062, respectively, shown in Figure 11.

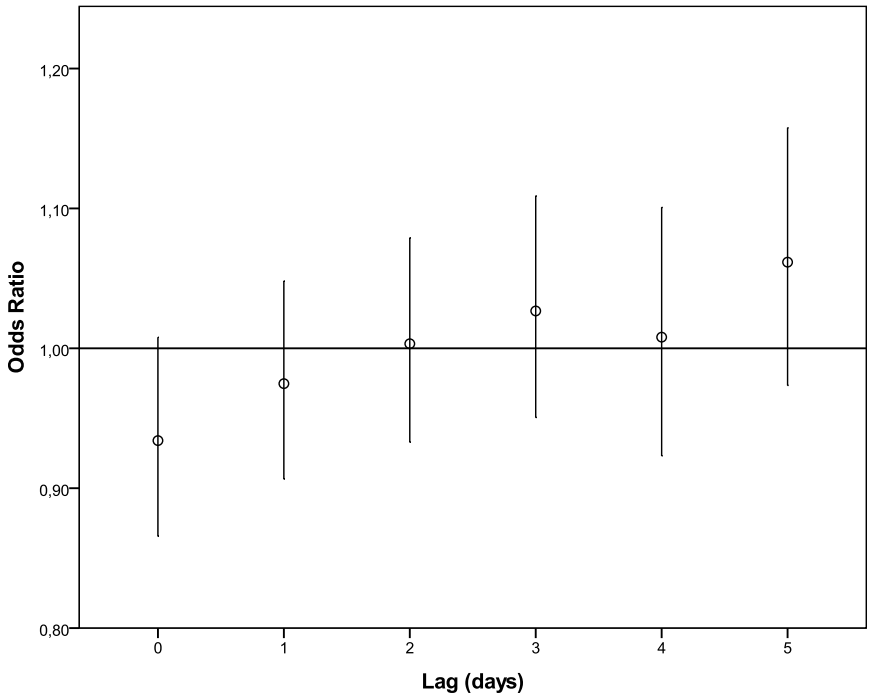

Figure 11. Association of H_2S exposure (3-day mean) and daily *glyceryl trinitrate* (C01DA02) dispensations with lag 0-5 days, adjusted for O_3, NO_2, PM_{10}, temperature, and humidity, and matched for day of the week. Bars show 95% confidence interval.

When considering the pollutant metrics, the mean 1-hour peak concentrations showed small estimates of the OR, most of which were not statistically significant (results are not shown). The 24-hour mean showed some statistically significant outcomes (Table 13 in the appendix) but the 3-day mean yielded the strongest association when using a case-crossover model. Results from using the 24-hour mean as a pollutant metric showed a very similar pattern to the the results from using the 3-day mean as a pollutant metric.

Introducing the influenza season in the regression model did not change the pattern of the association of the exposures NO_2, O_3, PM_{10} and H_2S. The ORs for these exposures were somewhat higher than in the analyses without the variable influenza season. The OR for influenza season was in no instance statistically significant on a 5% level, except in the model when H_2S was not introduced and at lag 0.

6 Discussion

In summary, exposure to urban air pollution was associated with the dispensing of *organic nitrate* drugs (C01DA) among adults. When the *glyceryl trinitrate* group (C01DA02) was considered there was an increase of 11.6% and 7.1% in *glyceryl trinitrate* drug dispensations for every 10 $\mu g/m^3$ increase of NO_2 with a lag of 0 and 1 days and there was an increase of 9.0% and 7.2% in *glyceryl trinitrate* drug dispensations for every 10 $\mu g/m^3$ increase in O_3 with a lag of 0 and 1 days, respectively.

This is the first known study to examine the association between exposure to ambient air pollution and dispensations of *organic nitrate* and *glyceryl trinitrate* drugs.

6.1 Descriptive Statistics

6.1.1 Ambient Air Pollution Levels and Weather Factors

Seasonal pattern is somewhat clear for NO_2 and O_3. The concentration range differs between pollutants and the biggest range of concentration levels is with the PM_{10} pollutant and could be explained by the fact that PM_{10} is not just a traffic related pollutant but also has other sources. H_2S has the smallest range of concentration levels and the lowest 24-hour mean. H_2S is not a traffic related pollutant and its sources are considered to be the geothermal power plant Hellisheiðarvirkjun and Nesjavellir. The mean 1-hour peak is higher than the 24-hour mean and 3-day mean for each pollutant variable over the study period. The 3-day mean is very similar to the 24-hour mean. For weather factors, the relative humidity is slightly higher over the winter months and the temperature is around 7°C lower. Over the winter months of November 1st to April 30th the pollution concentrations are higher for each pollutant variable which concurs with the correlation between pollution and weather factors. There is a moderate significant negative correlation between temperature and each studied pollutant factor which means that when the temperature gets warmer, the air pollution concentrations decrease. There is also a moderate significant negative correlation between PM_{10} and relative humidity which is consistent with other studies that show the relationship between those two factors (Johansson, et al., 2007). If the relative humidity increases the PM_{10} concentration decreases. On the other hand, many previous studies show that O_3 concentrations are generally higher over the summer months of May 1st to October 31st than over the winter months (Gryparis, et al., 2004; Ren, et al., 2009), which is inconsistent with these results. The present 24-hour mean showed the O_3 concentration of 43.20 $\mu g/m^3$ and 38.28 $\mu g/m^3$ over the winter and summer periods, respectively. In this context it is noteworthy that Reykjavík is located on 64° northern latitude. The UV radiation and the warmth that contributes to the generation of O_3 is perhaps not available in enough quantity. It is also notable that there is a fairly high significant negative correlation between NO_2 and O_3 (-0.62) and could perhaps partly be explained with the previous mentioned arguments. An Icelandic study on the association of air pollution in Reykjavík with dispensation of respiratory drugs showed similar results concerning the association between NO_2 and O_3 concentrations (Carlsen, et al., 2009). These inconsistencies call for further studies.

6.1.2 Dispensing of Drugs for Angina Pectoris

The total number of dispensation of the *organic nitrates* group (C01DA) over the study period of January 1st 2005 to December 31st 2009 was 64,751 when excluding the dispensations that occurred two times or more by the same individual. The total number of dispensing of the *glyceryl trinitrate* group (C01DA02) over the same period (excluding multiple dispensing over one day) was 8,507 which account for 13.14% of the total *organic nitrate* drug (C01DA) dispensing. The indication for use of *glyceryl trinitrate* drugs was considered more acute than the use of *organic nitrate* drugs since the *organic nitrate* group (C01DA) includes medication that is prescribed to use continuously, i.e. should be taken in at a regular basis.

6.2 Ambient Air Pollution and Dispensation of Drugs for Angina Pectoris

The association between ambient air pollution in the Reykjavík area and dispensing of *glyceryl trinitrate* drugs (C01DA02) showed a higher OR than the *organic nitrate* group (C01DA). This could be explained with the nature of the drugs. *Glyceryl trinitrate* drugs are used on more acute situations both in treatment and prophylactic purpose and patients take them sublingual at the moment they experience chest pain or expect stress. The 3-day mean pollutant metric yielded the strongest association with dispensing of *glyceryl trinitrate* (C01DA02). For every increase of 10 $\mu g/m^3$ of NO_2 3-day mean concentrations yielded an increase of 11.6% and 7.1% in daily dispensing of *glyceryl trinitrate* (C01DA02) at lag 0 and lag 1, respectively. At lag 5 there was a decrease of 5.8% which was statistically significant. That indicates that the weight of the exposure on the control period (lagged 5 days) was relatively higher than the weight of the exposure on the index day (lagged 5 days). This decrease in ORs begins at lag 3 (not statistically significant) and lasts to lag 5. At lag 0 and lag 1 there was a statistically significant increase of 9.0% and 7.2% for dispensing of *glyceryl trinitrate* (C01DA02) with every 10 $\mu g/m^3$ increase in the O_3 3-day mean concentrations. A decrease seems to occur at lag 3 and 5 (similar to NO_2) even though it is not statistically significant. In these calculations, 3-day mean values of PM_{10} concentrations did not show any statistical significant association with dispensing of *glyceryl trinitrate* (C01DA02) despite showing an association to the *organic nitrate* group (C01DA) at lag 0 to 4.

An experimental study on humans has shown that inhalation of fine particulate air pollution and ozone at concentrations that occur in the urban environment cause acute arterial vasoconstriction (Brook, et al., 2002). Another study has shown that endothelial function was impaired by ordinary levels of air pollution in healthy young males, in an urban area and may be reduced by 50% between the least and the most polluted day (Briet, et al., 2007).

A multicenter study on myocardial infarction survivors in five European cities suggested that ambient air pollution is associated with increased risk of hospital cardiac readmission (von Klot, et al., 2005). The study of von Klot et al. (2005) showed that there was no lag for readmission associated with an increase in air pollution and that readmission because of angina pectoris was

significantly associated with an increase in concentration of NO_2 and O_3. The RR for these air pollutants were 1.032 and 1.044 respectively.

The pattern in the present study concurs with the results from Guo et al. (2009). Guo et al. (2009) conducted a study on the association between daily average pollution concentrations of $PM_{2.5}$, NO_2 and SO_2 and emergency room visits for cardiovascular disease in Beijing. They found similar results using a single pollutant model with a statistically significant OR of 1.014 at lag 0 for NO_2 and 1.005 for $PM_{2.5}$

There are some studies on the association between ambient air pollution with cardiovascular morbidity and mortality. They use as an outcome hospital emergency room visits (Cao, et al., 2009; Guo, et al., 2009), hospital admissions for cardiovascular disease (Dominici, et al., 2006; Symons, et al., 2006; Zanobetti & Schwartz, 2005), and mortality due to cardiovascular causes (Clancy, et al., 2002; Liang, et al., 2009; Samet, et al., 2000). Laurent et al. (2009) maintained that using pharmaceutical dispensing or sales could be more sensitive method to study the association between air pollution exposure and health effects (Laurent, et al., 2009). This could be the reason why the results from this study show a higher risk than other studies. The effect may be reduced with the delay it takes to be admitted to the hospitals.

6.3 Study Strengths and Limitations

6.3.1 Pharmaceutical Data

This is the first known study to examine the association between exposure to ambient air pollution and dispensation of drugs for angina pectoris. Some studies have though been conducted on the association between ambient air pollution and respiratory drug sales and shown some interesting results (Carlsen, et al., 2009; Laurent, et al., 2009; Pitard, et al., 2004; Vegni, et al., 2005; Zeghnoun, et al., 1999). Zeghnoun et al. (1999) was the first to examine the association between exposure to urban air pollution and drug sales and found that drug sales may be a valuable health indicator and a predictor of the risk of emergency department visits and hospitalization particularly for respiratory and cardiovascular disease. Health indicators such as hospital admissions, visits to the emergency room department and mortality due to cardiovascular diseases reflect a limited portion of patients with such diseases.

In the present study those who were dispensed *glyceryl trinitrate* drugs (C01DA02) were either previously known to have angina pectoris or newly diagnosed with angina pectoris at the time of the dispensation. The data do not allow an identification of these two categories of drug users.

The pharmaceutical data used in this study was on number of dispensations per individual, not measured as daily doses, which is difficult to apply as the category C01DA02 is not used on regular basis, but in case of acute event. The most frequent number of drug dispensation (C01DA02) was once in a calendar year, i.e. most individuals only dispensed a drug within the C01DA02 group only once a year, which supports the assumption that an individual was not dispensed a drug on the control periods. The distribution of drug dispensing in the present study

show variation according to day of the week and thus the matching, but no adjustment were made for holidays such as Christmas day, New Years, and Easter when most pharmacies were closed. Therefore (and for other reasons) dispensing is limited and thus may lead to bias, which have not been evaluated here.

6.3.2 Air Pollution Data

There were only used measurements of studied pollutant factors from one air monitoring station in Reykjavík. This is thus an ecological study with the inherent weakness that the exposure concentrations are not on an individual level but cover the whole population of the Reykjavík area or those with angina pectoris of the population. This could lead to difficulties in interpretation of the results, which should be made cautiously.

The Department of Environment and the Environment Agency of Iceland supervised the measurement stations and took care of maintenance which considered the data reliable, however, it is unknown to us how the Department of Environment and the Environment Agency of Iceland validated the measurements and that is not a part of this study.

$PM_{2.5}$ and SO_2 are often considered in other studies when the association between air pollution and population health is examined (Guo, et al., 2009). These factors were not used in the present study as they were not available. PM_{10} levels could be considered as an indicator of $PM_{2.5}$ concentrations since particle size is included in PM_{10} measurements, but $PM_{2.5}$ has more often been linked to the adverse health effects of air pollution in previous studies.

Here, air pollution concentrations were higher during colder months and some previous studies on the adverse health effects of air pollution exposure show that health effects vary between pollutants and season. For O_3 studies have shown a stronger association to cardiovascular morbidity over the summer months (Chang, et al., 2005) but for NO_2 and SO_2 the association is stronger over the winter months (Cao, et al., 2009). Here, it is duly noted that, the nature of the research model used (bi-directional case-crossover) adjust for season and day of the week due to the fact that the control exposure cases (control days) are within the same season and day of week as the case exposure (index day). In order to do further adjustment temperature and relative humidity were put into the model.

The pollutant exposures in this study have four main sources: 1) exhaust gasses and particles from motor vehicles, 2) windblown particles from the surrounding environment (gravel roads, building sites etc), 3) dust storms blowing from the high land deserts and the south shoreline, 4) H_2S emission from the geothermal power plants, and 5) natural background concentrations and long-range air pollution transfer from Europe. Points three and four depend on easterly and south easterly wind blowing from the sources to the Reykjavík area. However, for the first two points, the most important factor is the traffic intensity and the weather conditions, including the frequency of inversion in the Reykjavík area. In the light of this, future studies in this field should include information on the wind direction.

In this study there were some missing data on the measurements of the air pollution and the measurements for H_2S did not start until February 2006 (more than a year after the commence of the study). The missing values in the data were treated as the beginning and end of the study and the missing data diminish the available material for the study, because if there were two or more missing values, from the air pollution measurements, in a matched case control set, those days were excluded. Diminished material may give wider confidence intervals, however other possible consequences have not been evaluated. The fact that the information for H_2S was available for shorter time interval than for NO_2, O_3, and PM_{10} is one of the main reasons why priority was given to the calculation without H_2S in the material. The other main reason is that H_2S has different sources.

6.3.3 Case-Crossover

The case-crossover design might have some limitations and Janes et al. (2005) estimates that the larger number of control exposures used in the case-crossover model would increase the efficiency. Also, control sampling may lead to some bias due to selection and information bias. Janes et al. for example, also estimates that sampling controls too close to the case day will result in a loss of power as a result of autocorrelation in the exposure series and that the conditional logistic regression yields some bias estimations which was though not considered serious in this study.

Here, a bi-directional case-crossover model was used to analyze the association between air pollution exposure and dispensation of drugs for angina pectoris. Time series models are though often used. A case-crossover model is an approach to control for confounders by design and allows for the analyses of several exposure factors simultaneously. The model makes the assumption that there is no time trend in exposure within a matched set of case (exposure) and controls (exposure) periods. Janes et al. (2005) maintained that a case-crossover model has several strengths. First, it does not require a control sample, leading to less bias due to unsuitable control selection. Second, by design and matching, it controls for time-dependant and fixed confounders. The bi-directional control selection also controls for confounding related to stable individual characteristics such as age, sex, smoking, and gender because the case exposure and control exposure effect the same individual thus each subject is their own control. A control selection of a week before and a week after the index day in this study adjust for seasonal, long-term trends, day of the week, and confounding. Such a selection was also used by Chang et al. (2005) (Chang, et al., 2005; Jaakkola, 2003).

7 Conclusions and Implications of Causality

In conclusion, this study provides evidence concerning the effects of air pollution on dispensation of drugs for angina pectoris. A positive association was observed between ambient air pollution in the Reykjavík area and the dispensation of drugs for angina pectoris (ATC C01DA). *Glyceryl trinitrates,* (ATC C01DA02) yielded a stronger association with air pollution exposure than the *organic nitrate* group (C01DA) using a 3-day mean of pollutant concentration. The strongest OR was observed at lag 0 and lag 1 which supports that air pollution has adverse effects on patients with angina pectoris.

To our knowledge this is the first study on the association between air pollution and dispensation of drugs for angina pectoris as an outcome. The results suggest that NO_2, O_3, and PM_{10} ambient air concentrations may adversely affect cardiovascular health and that dispensation of drugs for angina pectoris could be used as a health indicator. As in similar studies the outcome, dispensing of drugs for angina pectoris, have not been used previously. Further studies are needed to confirm or refute these findings.

In future studies it would be preferable to take into account seasons, $PM_{2.5,}$ SO_2, and the wind direction. The final conclusion on the possible causal association of air pollution and dispensation of drugs for angina pectoris will in the future be harvested from intervention studies.

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Appendix

Table 9. Pollution variable correlation matrix.

		NO_2	O_3	PM_{10}	H_2S	Temp	RH
		24-hr max	24-hr max	24-hr max	24-hr max	24-hr mean	24-hr mean
NO_2							
	24-hr max	1.00					
O_3							
	24-hr max	-0.13#	1.00				
PM_{10}							
	24-hr max	0.04	0.15#	1.00			
H_2S							
	24-hr max	0.33#	-0.07*	0.05	1.00		
Temp							
	24-hr mean	-0.46#	-0.26#	-0.22#	-0.30#	1.00	
RH							
	24-hr mean	-0.00	0.03	-0.22#	-0.19	-0.16#	1.00

Pearson´s Correlation Coefficients (p value): n (NO_2) = 1,683, n(O_3) = 1,744, n(PM_{10}) = 1,790, n(H_2S) = 1,260, n(Temp) = 1,813, n(RH) = 1,813.
Abbreviations: Max: maximum, Temp: temperature, RH: relative humidity, 24-hr mean: 24-hour mean, 24-hr max: maximum daily 1- hour mean.
** Correlation is significant at the 0.05 level.*
 # Correlation is significant at the 0.01 level.

Table 10. Frequency table for drugs in the *cardiac therapy* (C01) group. *Organic nitrates* (C01DA) account for 59.3% of the total dispensations over the study period.

C01 group	Number of Dispensations	Percent (%)	Drug Name
Digitalis glycosides			
C01AA0503	7,178	6.25	Digoxin, Lanoxin
C01AA0504	16,673	14.53	Digoxin, Lanoxin mite
Antiarrhythmics. class Ia			
C01BA0302	2,651	2.31	Disopyramide, Durbis Retard
Antiarrhythmics. class Ib			
C01BB0201	34	0.03	Mexiletine, Mexitil
C01BB0203	25	0.02	Mexiletine, Mexitil
Antiarrhythmics. class Ic			
C01BC0301	177	0.15	Propafenone, Rytmonorm
C01BC0401	3,261	2.84	Prindine, Tambocor
Antiarrhythmics. class III			
C01BD0101	12,705	11.07	Amiodarone, Cordarone
C01BD0102	129	0.11	Amiodarone, Trangorex
C01BD0103	862	0.75	Amiodarone, Cordarone
C01BD0104	362	0.32	Amiodarone, Cordarone
Adrenergic and dopaminergic agents			
C01CA0101	39	0.03	Etilefrine, -
C01CA0102	4	0	Etilefrine, -
C01CA0103	96	0.08	Etilefrine, -
C01CA0104	6	0.01	Etilefrine, -
C01CA1701	944	0.82	Midodrine, Gutron
C01CA2403	29	0.03	Epinephrine, -
C01CA2404	1,428	1.24	Epinephrine, EpiPen
C01CA2405	21	0.02	Epinephrine, EpiPen Junio
C01CA2406	2	0	Epinephrine, Adrenalin Mylan
Phosphodiesterase inhibitors			
C01CE0001	9	0.01	-
Organic nitrates			
C01DA0201	1,755	1.53	Glyceryl Trinitrate, Discotrine
C01DA0204	6,824	5.95	Glyceryl Trinitrate, Nitromex
C01DA0206	25	0.02	Glyceryl Trinitrate, -
C01DA0801	2,871	2.5	Isosorbide Mononitrate, Sorbangil
C01DA1401	40,374	35.18	Isosorbide Mononitrate, Imdur
C01DA1402	1,674	1.46	Isosorbide Mononitrate, Monit-L
C01DA1403	14,576	12.7	Isosorbide Mononitrate, Ismo
Other vasodilators used in cardiac diseases			
C01DX1601	27	0.02	Nicorandil, -
Total	**114,761**	**100**	

Table 11. Number of individuals per year and dispensation frequency (C01DA).

Number of individuals						
	Year					
Number of dispensations	2005	2006	2007	2008	2009	Total
1	879	769	734	686	640	3,708
2	375	293	315	312	363	1,658
3	482	495	493	483	494	2,447
4	673	643	641	622	641	3,220
5	191	170	187	185	135	868
6	84	72	58	87	65	366
7	39	53	38	49	43	222
8	27	50	24	33	31	165
9	20	43	23	20	25	131
10	14	13	18	11	24	80
11	3	21	17	15	18	74
12	6	24	24	26	36	116
13	12	67	91	88	110	368
14	7	23	56	55	58	199
15	4	18	21	26	29	98
16	1	18	15	12	13	59
17	5	13	9	13	17	57
18	4	5	9	15	16	49
19	2	11	11	4	9	37
20	2	9	11	9	4	35
21	3	9	9	10	15	46
22	2	5	10	9	9	35
23	5	2	8	6	9	30
24	4	3	11	6	17	41
25	4	10	11	17	11	53
26	4	23	19	27	33	106
27	6	5	18	25	10	64
28	3	4	7	5	7	26
29	0	1	1	3	0	5
30	1	4	1	1	0	7
31	1	0	2	2	0	5
32	0	0	1	0	0	1
33	0	1	0	0	0	1
34	0	0	1	0	1	2
41	0	0	0	1	0	1
42	0	1	0	0	0	1
Total	**2,863**	**2,878**	**2,894**	**2,863**	**2,883**	**14,381**

Table 12. Number of individuals per year and dispensation frequency (C01DA02).

Number of individuals						
	Year					
Number of dispensations	**2005**	**2006**	**2007**	**2008**	**2009**	**Total**
1	977	854	816	712	639	3,998
2	164	146	167	140	124	741
3	75	74	46	48	48	291
4	57	44	48	44	26	219
5	20	19	18	14	8	79
6	19	13	7	11	10	60
7	5	7	5	6	6	29
8	4	2	3	2	3	14
9	0	1	1	0	1	3
10	3	0	2	0	1	6
11	0	2	0	0	1	3
12	2	0	0	0	0	2
14	0	0	1	0	0	1
16	0	1	0	1	0	2
18	0	1	0	0	0	1
Total	**1,326**	**1,164**	**1,114**	**978**	**867**	**5,449**

Table 13. The matched OR and 95% CI for the dispensation of *organic nitrate* drugs (C01DA), associated with NO_2, O_3, and PM_{10} concentrations, 24-hour mean values in 10 µg/m^3 increase in pollution levels, adjusted for temperature and relative humidity.

	NO_2		**O_3**		**PM_{10}**		**H_2S**	
Lag	**OR***	**(95% CI)**	**OR***	**(95% CI)**	**OR***	**(95% CI)**	**OR***	**(95% CI)**
0	**1,048**	**(1,032-1,064)**	**1,019**	**(1,003-1,035)**	1,005	(0,998-1,011)	**1,045**	**(1,027-1,063)**
1	**1,068**	**(1,051-1,086)**	**1,070**	**(1,052-1,087)**	1,005	(0,998-1,011)	0,985	(0,968-1,003)
2	1,015	(0,998-1,033)	0,992	(0,976-1,009)	**1,010**	**(1,003-1,017)**	1,010	(0,992-1,028)
3	1,001	(0,983-1,019)	0,999	(0,982-1,016)	**0,989**	**(0,982-0,996)**	**1,025**	**(1,008-1,043)**
4	1,005	(0,988-1,023)	**1,027**	**(1,009-1,045)**	**0,974**	**(0,967-0,981)**	**1,043**	**(1,022-1,064)**
5	**0,972**	**(0,968-0,988)**	1,006	(0,990-1,021)	0,999	(0,992-1,006)	1,001	(0,977-1,025)

* *Bolded when statistically significant. Data have been calculated in a unique multivariate analysis separately for each lag, taking into account simultaneously all the variables. Number of observations; lag 0: 118,088, lag 1: 116,586, lag 2: 116,670, lag 3: 117,270, lag 4: 117784, and lag 5: 116,927.*

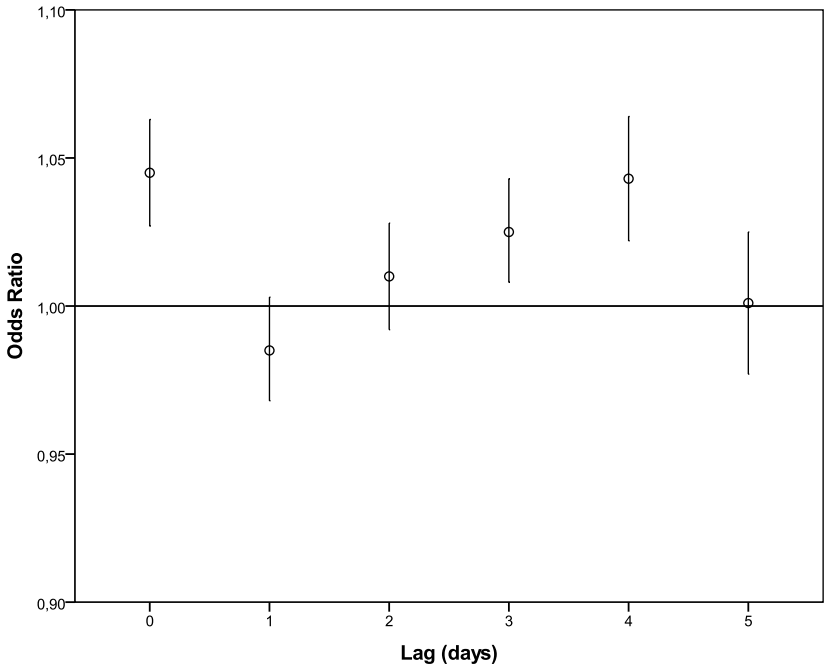

Figure 12. Association of H_2S exposure (24-hour mean) and daily *organic nitrate* (C01DA) dispensations with lag 0-5 days, adjusted for O_3, NO_2, PM_{10}, temperature, and humidity and matched for day of the week. Bars show 95% confidence interval.

Table 14. The matched OR and 95% CI for the dispensation of *glyceryl trinitrate* drugs (C01DA02), associated with NO_2, O_3, and PM_{10} concentrations, 24-hour mean values in 10 µg/m^3 increase in pollution levels, adjusted for temperature and relative humidity.

	NO_2		**O_3**		**PM_{10}**	
Lag	**OR***	**(95% CI)**	**OR***	**(95% CI)**	**OR***	**(95% CI)**
0	**1.069**	**(1.028-1.112)**	**1.036**	**(0.995-1.078)**	1.005	(0.991-1.018)
1	**1.081**	**(1.038-1.125)**	**1.088**	**(1.045-1.133)**	0.999	(0.985-1.014)
2	1.037	(0.994-1.083)	1.036	(0.995-1.080)	1.003	(0.988-1.019)
3	1.027	(0.983-1.074)	1.020	(0.978-1.064)	0.988	(0.971-1.004)
4	0.986	(0.945-1.029)	0.992	(0.951-1.035)	0.995	(0.981-1.010)
5	**0.953**	**(0.914-0.993)**	0.973	(0.935-1.013)	1.009	(0.995-1.024)

* *Bolded when statistically significant. Data have been calculated in a unique multivariate analysis separately for each lag, taking into account simultaneously all the variables. Number of observations; lag 0: 21,913, lag 1: 21,755, lag 2: 21,617, lag 3: 21,682, lag 4: 21,663, and lag 5: 21,646.*

Table 15. The matched OR and 95% CI for the dispensation of *glyceryl trinitrate* drugs (C01DA02), associated with concentrations of NO_2, O_3, PM_{10}, and H_2S, 3-day mean values in 10 µg/m^3 increase in pollution levels, adjusted for temperature and relative humidity.

	NO_2		**O_3**		**PM_{10}**		**H_2S**	
Lag	**OR***	**(95% CI)**	**OR***	**(95% CI)**	**OR***	**(95% CI)**	**OR***	**(95% CI)**
0	**1.136**	**(1.069-1.207)**	**1.094**	**(1.029-1.163)**	0.998	(0.972-1.024)	0.934	(0.866-1.008)
1	**1.096**	**(1.029-1.168)**	**1.094**	**(1.028-1.166)**	0.988	(0.961-1.015)	0.975	(0.906-1.048)
2	1.045	(0.978-1.117)	1.038	(0.972-1.108)	0.983	(0.956-1.012)	1.003	(0.933-1.079)
3	0.993	(0.929-1.061)	0.997	(0.933-1.065)	0.985	(0.958-1.013)	1.027	(0.951-1.109)
4	1.000	(0.942-1.060)	1.007	(0.948-1.070)	0.995	(0.969-1.022)	1.008	(0.923-1.101)
5	**0.937**	**(0.882-0.994)**	0.983	(0.926-1.044)	0.995	(0.969-1.021)	1.062	(0.973-1.158)

* *Bolded when statistically significant. Data have been calculated in a unique multivariate analysis separately for each lag, taking into account simultaneously all the variables. Number of observations; lag 0: 13,816, lag 1: 13,686, lag 2: 13,598, lag 3: 13,650, lag 4: 13,625, and lag 5: 13,616.*