PREFACE

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CONTENTS

SUMMARY

Several epidemiological studies were reported world wide on the association between ambient air pollution and acute health problems such as mortality or respiratory and cardiovascular emergency hospital admissions. Differences in susceptibility among sub-groups of the population to the effects of ambient air pollution exposure on health were also reported. However, the interaction effects of air pollutants on acute health problems remain unclear. Given the fact that, in real life, people are not exposed to single pollutants but to a mixture of pollutants, studying the interaction effects between pollutants on health is very relevant. Findings of animal and human experimental studies indicate the interaction effect of air pollutants especially on pulmonary toxicological responses. Therefore, this study aims to investigate the epidemiologic interaction effects of air pollutants on respiratory and cardiovascular emergency hospital admissions. The investigation was carried out on 1,020,575 respiratory, asthma, COPD and cardiovascular emergency hospital admissions during the winter and summer seasons of the years 1992-1999 in The Netherlands. For the investigation we used a case-crossover study design. The case-crossover study design is similar to a case-control study whereby each person who had an event is matched with his/herself on a nearby time period where he or she did not have the event. Conditional logistic regression is used for single and multi-pollutant modelling. Our investigation indicates more admissions during winter than summer. The level of concentration of PM10, BS, SO_2 and NO_2 was higher during winter while the level of concentration of O_3 is higher during summer. We found positive associations between PM10, BS, SO_2 and NO_2 with respiratory and cardiovascular admissions during winter and between O_3 and admissions during summer. The investigation for interaction of pollutants indicates synergistic and antagonistic effects. The synergistic effect was mainly evident with O_3 and SO_2 on all cause-specific admissions. For respiratory admissions we found synergistic effects between O_3 and SO_2 during both winter (RR=1.032(95%CI, 1.015, 1.050)) and summer (RR=1.026(95%CI, 1.020, 1.031)) and for cardiovascular admissions a synergistic effect between O_3 and SO_2 was seen during the summer season (RR=1.010 (95%CI, 1.006, 1.014)). The synergistic effects of BS and SO_2 with O_3 were more pronounced with asthma admissions during summer and for COPD admissions synergistic effects of NO_2 and SO_2 with O_3 were observed during winter. The synergistic effects of these pollutants are consistent with prior animal and human experimental studies although disease-specific findings are lacking in those studies. In contrast, antagonistic interaction effects were observed between PM10 and O_3 on respiratory and cardiovascular admissions. Pollutants with smaller size and chemically reactive undergo positive interaction with O_3 and therefore we recommend the reconsideration of interaction effects of air pollutants in air pollution regulation and standardization from a public health perspectives.

CHAPTER 1

1.1 Introduction

Several epidemiological studies were reported world wide on the association between ambient air pollution and acute health problems such as mortality or respiratory and cardiovascular hospital admissions(Anderson et al., 1997; Boezen et al., 1999; Host et al., 2008; Le Tertre et al., 2002; Linn et al., 2000; Sunyer et al., 2003a; Sunyer et al., 2003b). Differences in susceptibility among sub-groups of the population to the effects of ambient air pollution exposure on health were also reported. Females, children and older people are more prone to the effects of exposure to ambient air pollution on health. Physiological differences were suggested to explain the differences in susceptibility among these subgroups(Boezen et al., 2005; Sunyer et al., 2002). However, the focus of monitoring and research was on the individual pollutant rather than on the interaction of air pollutants that can be inhaled as a complex mixture. In real life air pollutants occur and are inhaled as a mixture. Furthermore, the mix of pollutants is not always the same, it differs by season. During winter season, the relative concentration of particulate matter with an aerodynamic diameter of 10 µm (PM10), black smoke (BS), NO_2, and SO_2 is high whereas the relative concentration of O_3 is dominant during summer season. Therefore, the seasonal variation of pollutants concentration may affect subsequent interaction effects on health. Thus, separate analysis according to season is relevant to investigate the health impact of interaction effects of air pollutants.

The epidemiologic association between ambient air pollution and pulmonary response is well known from numerous epidemiological studies. However, the interaction effects of air pollutants on acute health problems remain unclear. Nevertheless, studies show that air pollutants interact inside and/or outside the human body which subsequently has negative health effects. This is evident from studies on O_3 and other oxidant gases (SO_2 and NO_2). O_3 reacts with cell membranes and other air pollutants to produce highly potent toxic free radicals (reactive oxygen species) which subsequently trigger pulmonary responses and oxidative stress. O_3 also undergoes photochemical reactions in the atmosphere with other air pollutants which may entail the production of potent toxic compounds. Thus, O_3 is claimed to be potent enough to induce inflammatory responses and oxidative stress alone or in combination with other pollutants which would be manifested with different respiratory and cardiovascular outputs(Bosson et al., 2007; Gilmour, 1995; Pryor, 1994; Sandstrom, 1995; Valavanidis et al., 2009; Wang et al., 2006).

Mauderly and Samet (2009(Mauderly & Samet, 2009)) reviewed and confirmed the existence of synergistic effects of O_3 with other air pollutants on pulmonary responses from animal and human experimental studies. According to animal experimental studies, O_3 interacts with BS and NO_2 to cause pulmonary allergic responses and suppress phagocytosis and the action of mucociliary escalators in rats(Gilmour et al., 1991; Gilmour, 1995; Jakab & Hemenway, 1994). O_3 also has a synergistic effect with respirable acidic aerosols (from oxides of SO_2 and NO_2). Under ambient conditions, sulfur and nitrogen oxides can react with photochemical products and airborne particles to form acidic aerosols. It was evident that the simultaneous exposure to these aerosols and O_3 induces inflammatory responses in rat lung parenchyma which were greater than the effects of exposure to these pollutants alone or which were not seen when rats were exposed to only one of these pollutants(Kleinman et al., 1989; Last et al., 1986).

The synergistic effects of O_3 with other air pollutants are also evident from human and in vitro experimental studies. A more pronounced effect on lung function was reported from healthy and asthmatic subjects who were exposed to the combination of O_3 with NO_2 and SO_2 than when they were exposed to the individual pollutants alone. O_3 was also synergistic in causing lung inflammation with acid aerosols (H_2SO_4 and HNO_3) and particulate matter. More effects were observed when the exposure was in combination than when it was to a single pollutant alone (Bosson et al., 2008; Sandstrom, 1995).

There are a limited number of epidemiological studies that addressed the effects of the interaction of air pollutants on acute health problems(Medina-Ramon et al., 2006) . However, the evidence of animal, human and in vitro experimental studies is sufficient to indicate the presence of synergistic effects of air pollutants on health. Although these experimental studies are evidence for the presence of synergism, it may or may not be realistic in real life situation, and therefore, epidemiological studies should be conducted along with the experimental studies. Therefore, we undertook an epidemiological study to address the synergistic effects of air pollutants on real life health problems. Hence, we investigated the interaction effects of O_3 with PM10, NO_2, SO_2 and BS on respiratory and cardiovascular hospital admissions in the Netherlands from 1992-1999. The investigations were also performed on different sub-groups to identify groups that are most susceptible to the effects of air pollution. The findings of this study may give insight to policy makers and air pollution regulators to reconsider the allowable concentration level of individual air pollutants. Furthermore, it may initiate further investigation into the magnitude and mechanisms underlying the synergistic effects of air pollutants on health.

1.2 Definition and mechanisms of interaction

Definition

According to this study, interaction is the simultaneous exposure to two or more air pollutants in which the biological response differs from the response to the same pollutants inhaled separately. The interaction is called synergistic if the combined effect of the air pollutants is greater than the sum of the effects of the single pollutants or antagonistic if the combined effect is less than the sum.

Mechanisms of interaction

The mechanisms underlying the health effects of specific interactions between air pollutants are not always clear. However, the following mechanisms are suggested.

1. **Physical adsorption**. Physical adsorption refers to the presence (interaction) of gaseous pollutants on the surface of a particle and subsequent transport within the respiratory tract to more sensitive sites. This was evident from animal experimental studies with exposure to highly water soluble and reactive gases (NO_2, SO_2 and O_3) alone or in combination with particulate matter. Most of these gases are naturally taken up by the upper respiratory tract due to their high water solubility and reactivity. Therefore, they did not induce pronounced pulmonary responses when mice were exposed to gaseous pollutants alone but in combination with particulate matter pulmonary responses were high(Schlesinger, 1995). This indicates that particulate matter mediates as an adsorbent and carryon to the target site.

2. **Chemical reaction between pollutants**. This mechanism can be synergistic or antagonistic depending upon the type of chemical reaction involved. It can be synergistic if the interaction of pollutants results in the formation of new potent toxic compounds and carried on the surface of the particles to the target site within the respiratory tract and induce pronounced pulmonary responses. This was observed from experimental studies of combined exposure of particulate matter and O_3 in which more pronounced effects were observed from combined exposure of these pollutants than from exposure to the pollutants alone.(Aam & Fonnum, 2007; Churg, 2003; Valavanidis et al., 2009). On the contrary, an antagonistic effect was reported from the reaction of H_2SO_4 and ammonia where less toxic ammonium sulphate was produced in the interaction than the initial more toxic H_2SO_4 (Schlesinger, 1995).

3. **Alteration of the pulmonary environment.** Some pollutants may change the pulmonary environment and make the lungs more susceptible to the health effects of other pollutants. This may involve an air pollutant which itself has toxic potentials. This was evident from animal experimental studies with the exposure to acidic sulphate particles or basic sulphate alone or in combination with O_3. The most pronounced effect was observed with the combined exposure of acidic sulphate and O_3 which was explained by a change in acidity of the pulmonary fluid

caused by the acidic sulphate. This resulted in a pulmonary environment that was more susceptible to the effect of O_3(Last et al., 1986; Warren et al., 1988)

1.3 Aim of the study

This study aims to investigate the interaction effects of O_3 with PM10, NO_2, SO_2, and BS on emergency hospital admissions due to respiratory diseases, asthma, chronic obstructive pulmonary diseases (COPD) and cardiovascular diseases in the Netherlands during 1992-1999, in different age and gender groups.

1.4 Research questions

1. Are there synergistic effects between O_3 and PM10, NO_2, SO_2, and BS, on total respiratory, asthma, COPD and cardiovascular hospital admissions?
2. Which age or gender group is most susceptible to the acute effects of air pollution exposure?

CHAPTER 2: MATERIALS AND METHODS

2.1 Hospital admissions data

The data on hospital admissions was collected from the morbidity database of Prismant (SIG/LMR) in which all hospital admissions in The Netherlands are registered. The data is available according to age and sex-categories. For the present analysis, only emergency hospital admissions were retrieved. The main diagnosis at discharge was coded and stratified into different files according to their main diagnosis (ICD-9) for each year of admissions in order to restructure the data in the right format for analysis. The stratification for each disease is performed as: respiratory (ICD-9:460-519), asthma (ICD-9:493), COPD (ICD-9: 490-492, 494, and 496), and cardiovascular (ICD-9: 393-414, 428, 430-438).

2.2 Air pollution and weather data

Data regarding air pollution was collected from the RIVM measurement stations in the Netherlands. These stations measure the daily air pollution concentration of O_3, PM10, SO_2, NO_2 and black smoke (BS). The weather data on temperature and relative humidity was taken from the Dutch Meteorological Institute (KNMI) weather stations in the Netherlands.

2.3 Study design

We used a case-crossover study design for the analysis(Bateson & Schwartz, 2001; Schwartz, 2004). The case-crossover study design is similar to a case-control study whereby each person who had an event is matched with his/herself on a nearby time period where he or she did not have the event. The exposure at the day of the event is compared with the exposure in the control period in which the event did not occur. Thus, it avoids the confounding effect due to weather and seasonal variation and individual characteristics (such as smoking behaviour, age, sex or body mass index). We applied time-stratified bidirectional control periods i.e. control days were 14 and 7 days before and after the event day. By this, confounding due to day of the week was also taken into account.

2.4 Statistical analysis

The data analyses were performed using conditional logistic regression. In SPSS, conditional logistic regression is not directly available and therefore we used Cox regression. In Cox regression model, the mean pollutant concentration of the same day (0) and previous days (1, 2 and 3) was entered with the assumption of linearity between pollutant concentration and hospital admissions. The models were adjusted for the mean temperature, relative humidity and public holidays including the long time summer holidays. For each diagnosis, age- and sex-group we performed a separate analysis.

The resulting relative risk (RR) and its 95% confidence interval (CI) refer to the likelihood of being admitted to hospital due to some specific disease when the exposure to the studied air pollutant increases by 10 $\mu g/m^3$. The relative risks were considered to be significantly increased with increasing levels of air pollution if the lower limit of the 95% CI was above the value of 1 and indicated in bold in the results. The analyses were performed separately for winter (November to March) and summer (May to September) seasons. The months of October and April with fluctuating temperature were excluded from the analyses.
First single pollutant models were fitted: the pollutants (PM10, BS, O_3, NO_2 and SO_2) were entered separately into the models.

To investigate interactions between O_3 and the other pollutants we fitted two pollutant models. Because of difficulties in interpreting interactions between two continuous variables we categorized pollutant concentrations into high or low based on the median concentration for each season (table 4). Interactions between a continuous concentration of one pollutant and this high/low variable of the other pollutant were investigated (i.e. is the effect of the pollutant on the outcome different for days with a low or a high concentration of the other pollutant). The resulting relative risk (high vs low) indicates the difference in the effect of the continuous pollutant (p1) between days with a high and days with a low concentration of the other pollutant (p2) (i.e. the interaction effect).

Since, during the summer, O_3 is the predominant pollutant, we investigated interactions between O_3 as a continuous variable and PM10, BS, SO_2 and NO_2 as high/low variables during the summer (i.e. is the effect of O_3 modified by the levels of the other pollutants). During the winter season, we used high/low concentration of O_3 against the continuous concentrations of PM10, BS, NO_2 and SO_2 (i.e. is the effect of PM10, BS, SO_2, and NO_2 modified by the level of O_3).

Everybody exposed to a certain concentration of pollutants will not end up with the same effect. Given the fact that the level of exposure and degree of severity of disease differ between males and females and between younger and older adults, we investigated whether there are differences in susceptibility to the health effects of pollution between certain sub-groups of the population. We performed in-depth analysis for some specific population subgroups to investigate whether the relative risks differ by sex (male vs female) and age (younger adults (15-44) vs elderly (75 and above)). Interaction terms between the subgroups and the pollutants were entered into the model. The differences in the relative risk between female and male as well as between older and younger were compared to predict the most susceptible subgroup to the specific exposure. The in-depth analyses were carried out only for respiratory and cardiovascular admissions, and not for asthma and COPD, to optimise the statistical power.

CHAPTER 3: RESULTS

3.1 Descriptive analysis

Retrieved data with emergency hospital admission were stratified as respiratory, asthma, COPD, and cardiovascular admissions. The mean daily number of admissions and the total number of admissions for the whole study period (1992-1999) are displayed according to their strata in table 1-3. The mean daily measured air pollution and weather condition data are presented in table 4.

3.1.1 Hospital admissions

We have analysed 1,020,575 respiratory, asthma, COPD and cardiovascular emergency hospital admissions during the winter and summer seasons of the years 1992-1999 in all of the Netherlands. Patients with cardiovascular admissions constitute 63% (n=643,368) of the total number of admissions whereas all total respiratory admissions including asthma and COPD account for 37% (n=377,207) of the total number of admissions during the entire study period. Asthma constitutes 8.2% (n=31052) and COPD constitutes 27% (n=102075) of the respiratory admissions (table 1). Differences between winter and summer in the number of admissions were observed for respiratory admissions with winter admissions of 59.6% (n=225,027) and summer season admissions of 40.4% (n=152180) of the total respiratory admissions. The number of admissions for cardiovascular admissions for winter and summer seasons was more or less similar with 51.6% (n=332301) and 48.4% (n=311067) respectively for the entire study period.

Table 1: Distribution of the mean daily admissions, total admissions and percentage of the total cause-specific hospital admissions during the during the winter and summer seasons of 1992-1999 in the Netherlands

admissions	winter season			summer season			overall admissions			
	mean	SD	admission	mean	SD	admission	mean	SD	admission	%
Respiratory	185.97	54.91	225027	124.33	32.87	152180	154.5	43.89	377207	37
Asthma	13.35	4.75	16156*	12.19	5.76	14896*	12.77	5.26	31052*	8.2*
COPD	55.15	22.76	58406*	40.77	15.88	43669*	47.97	19.32	102075*	27*
Cardiovascular	313.79	88.82	332301	290.45	82.72	311067	302.12	85.77	643368	63
Total			557328			453,247			1,020,575	100

**part of respiratory admissions*

There were also prominent differences between male and female cause-specific hospital admissions during winter and summer seasons (table 2). For all investigated causes, except asthma, the mean daily number of male admissions outweighs its female counterpart. The mean daily numbers of winter season hospital admissions with respiratory cases were 108.17 for males and 77.80 for females. The summer season differences in mean daily hospital admissions with respiratory cases were also apparent with 74.61 for males and 49.72 for females. More males admissions were also observed with cardiovascular and COPD admissions. The mean daily number of asthma admissions during both seasons did not show significant differences between males and females. Although the mean daily numbers of admissions during the winter season were higher for both sexes, the general trends of differences between males and females were similar for both seasons (e.g. the percentage of male admissions during winter is more or less similar with the summer season male admissions).

Table 2: The mean daily distribution of male and female emergency hospital admissions during the winter and summer seasons of 1992-1999 in the Netherlands

category	admissions	winter		summer		overall	
		mean	SD	mean	SD	mean	SD
Male	Respiratory	108.17	30.88	74.61	19.81	91.39	25.35
	Asthma	6.66	3.00	6.35	3.53	6.50	3.26
	COPD	33.08	13.43	24.63	9.62	28.85	11.34
	Cardiovascular	180.67	50.46	167.41	47.29	174.04	48.87
Female	Respiratory	77.80	25.85	49.72	14.86	63.76	20.35
	Asthma	6.75	2.90	5.95	3.11	6.35	3.00
	COPD	22.09	10.51	16.16	7.55	19.12	9.03
	Cardiovascular	133.12	40.12	123.03	37.31	128.07	38.71

Apparent differences between hospital admissions in older (75+ years) and younger (15-44 years) subjects were observed in both seasons and with all investigated causes of admissions (table 3). Older people dominate hospital admissions with respiratory, COPD and cardiovascular cases while younger ones experience more admissions with asthma during both seasons. Prominent differences between older and younger admissions were observed mainly with COPD and cardiovascular diseases. The mean daily number of admissions with COPD for male and female for winter season were 18.02 and 3.01 while for summer season 12.41 and 2.69 respectively. The prevalence of admissions due to cardiovascular problems was high for older (87%) subjects compared to their younger counterparts 13% for both winter and summer seasons. The mean daily numbers of admissions for older and younger adults with cardiovascular problems during the winter were 111.59 and 16.31, while for summer it was 100.52 and 15.49 respectively. In contrast to other admissions, the mean daily number of asthma admissions was relatively high for younger adults than older ones during the two seasons.

Table 3: Distribution of daily younger and older emergency hospital admissions during the winter and summer seasons of 1992-1999 in the Netherlands

category	admissions	winter		summer		overall	
		mean	SD	mean	SD	mean	SD
Younger	Respiratory	22.70	6.96	19.42	5.84	21.06	6.4
	Asthma	3.40	1.93	3.25	1.90	3.32	1.91
	COPD	3.01	2.18	2.69	1.75	2.85	1.96
	Cardiovascular	16.31	9.30	15.49	8.67	15.90	8.98
Older	Respiratory	43.91	18.16	28.49	10.00	36.20	14.08
	Asthma	1.44	0.70	1.26	0.53	1.35	0.61
	COPD	18.02	8.88	12.41	6.15	15.21	7.51
	Cardiovascular	111.59	32.04	100.52	29.64	106.05	30.84

3.1.2 Air pollution and weather conditions

The mean daily measured concentration of Particulate matter with an aerodynamic diameter of 10 µm (PM10), black smoke (BS), SO_2, NO_2 and Ozone (O_3) are presented in table 4. The mean daily measured concentrations of PM10, BS, SO_2 and NO_2 were relatively high during winter season while O_3 was high during summer season. The daily mean concentration of BS and SO_2 during the winter was almost two fold relative to their daily mean concentration during the summer season. In contrast the mean daily concentration of O_3 was more than twice its winter season daily mean concentration. Annex 1 & 2 show Pearson correlations between air pollutants and weather conditions. Positive correlations were observed between PM10, BS, SO_2 and NO_2 during the winter season except for O_3 which correlated negatively. The correlations between PM10, BS, SO_2 and NO_2 during summer season were more or less similar with those of the winter season. In contrast to winter season, O_3 correlated positively with PM10, BS, SO_2 and NO_2 during summer season. During winter season PM10, BS, SO_2 and NO_2 correlate negatively with temperature but O_3 correlates positively with temperature. During summer season PM10, BS, O_3, SO_2 and NO_2 correlated positively with temperature but negatively with relative humidity.

Table 4: The distribution of daily measured air pollutants emission and weather variables during the winter and summer seasons of 1992-1999 in the Netherlands.

	winter season				summer season			
	mean	SD	median	min-max	mean	SD	median	min-max
PM10	43.93	26.14	36.10	8.67-251.67	36.86	12.64	33.70	14.59-103.54
BS	15.06	13.29	11.06	0.44-116.33	6.94	3.53	6.16	1.47-34.54
O_3	28.89	19.00	25.84	1.18-106.27	71.07	24.83	66.48	16.11-168.29
NO_2	34.81	12.58	34.43	6.73-93.31	24.13	6.36	23.37	11.85-51.89
SO_2	9.88	7.85	7.71	0.94-60.75	5.17	2.44	4.79	1.34-16.62
Temperature	4.31	4.35	5.00	-13.23-15.27	15.39	3.36	15.31	4.46-24.17
R. humidity	86.99	8.65	88.54	44.00-99.95	79.39	7.61	80.63	48.06-95.40

3.2 Association between air pollution and emergency hospital admissions

We investigated the associations between PM10, BS, O_3, SO_2 and NO_2 and respiratory, asthma, COPD and cardiovascular emergency hospital admissions for winter and summer seasons. The investigations were carried out for all admissions, and for male and female admissions using single pollutant and multi-pollutant modelling. In-depth analyses to identify susceptible sub-groups of the population to air pollution exposure were also performed. The in-depth analyses were carried out on respiratory and cardiovascular hospital admissions for males and females as well as for the age group of 15-44 and 75+ years. The results of the investigation are displayed according to exposure effects (single or multi-pollutants effect) under each title of cause-specific admissions. All the effect estimates are presented as RR (relative risk) unless stated as a percentage.

3.2.1 Respiratory admissions

3.2.1.1 Single pollutant exposure

All respiratory admissions

The results of the association of air pollutants with emergency respiratory hospital admissions are presented in table 5 and 6. During winter season all pollutants except O_3 were positively associated with all respiratory admissions. Nevertheless, the relative risks of PM10, BS and NO_2 were very marginal (less than 1%) except SO_2 exposure for which its effect was 3.3%. In contrast, the effect of O_3 on all respiratory admissions was negative which could be attributed to its lower concentration during winter season. The effects of PM10, BS, O_3, SO_2 and NO_2 for summer season on all respiratory admissions were the inverse of their winter season effects. Thus, only O_3 showed a significant positive association during summer season (RR=1.022 (95%CI, 1.017-1.028)).

Sex specific respiratory admissions

The results of the association of air pollutants with male and female respiratory admissions for winter and summer seasons were compared. Despite the difference in absolute number of daily admissions between males and females, their relative risk of exposure to PM10 did not show any significant differences during winter season. The RRs were 1.007(95%CI, 1.003-1.010) and 1.007(95%CI, 1.003-

1.011) for males and females admissions respectively. BS and SO_2 did not show any effect differences as well when compared with their effects on all respiratory admissions. NO_2 showed a non-significant positive association with males and females respiratory admissions during winter season. The summer season association of pollutants (PM10, BS, O_3, SO_2 and NO_2) with males and females respiratory admissions were consistent with the association of all respiratory admissions (table 6).

Table 5: The association of PM10, BS, O_3, NO_2 and SO_2 ($10\mu g/m^3$) with all, males and females emergency respiratory hospital admissions during winter season of 1992-1999 in the Netherlands

Pollutants	winter season respiratory admissions		
	all admissions	male admissions	female admissions
	RR(95% CI)	RR(95% CI)	RR(95% CI)
PM10	**1.007(1.004-1.009)**	**1.007(1.003,1.010)**	**1.007(1.003,1.011)**
BS	**1.008(1.003-1.014)**	**1.008(1.001,1.015)**	**1.009(1.001,1.017)**
SO_2	**1.033(1.023-1.043)**	**1.035(1.021,1.048)**	**1.030(1.015,1.046)**
NO_2	**1.006(1.000-1.011)**	1.005(0.998,1.013)	1.006(0.997,1.014)
O_3	**0.963(0.958-0.968)**	**0.963(0.956,0.969)**	**0.964(0.956,0.971)**

**bold highlighted= statistically significant at 95% CI*

Table 6: The association of PM10, BS, O_3, NO_2 and SO_2 ($10\mu g/m^3$) with all, males and females emergency respiratory hospital admissions during summer season of 1992-1999 in the Netherlands

Pollutants	summer season respiratory admissions		
	all admissions	male admissions	female admissions
	RR(95% CI)	RR(95% CI)	RR(95% CI)
PM10	**0.978(0.971-0.984)**	**0.976(0.968,0.984)**	**0.980(0.970,0.989)**
BS	**0.874(0.856-0.893)**	**0.875(0.851,0.899)**	**0.873(0.844,0.903)**
SO_2	**0.740(0.714-0.766)**	**0.751(0.718,0.786)**	**0.723(0.684,0.764)**
NO_2	**0.918(0.907-0.929)**	**0.925(0.911,0.939)**	**0.908(0.891,0.926)**
O_3	**1.022(1.017-1.028)**	**1.022(1.015,1.029)**	**1.023(1.015,1.032)**

**bold highlighted= statistically significant at 95% CI*

The in-depth analysis did not show any statistically significant differences between males and females in the effect of exposure on respiratory admissions in both seasons (Annex 3 & 4, and fig.1). Annex 5 & 6 shows the exposure effect differences between younger and older subjects on respiratory admissions during winter and summer seasons. Statistically significant differences of the effect of PM10, BS, O_3, SO_2 and NO_2 were observed between younger (15-44 years) and older subjects (75 and above) during summer season (fig.2). Higher exposure effect differences were observed with BS and SO_2 exposures signifying that older subjects are more susceptible to the risk of BS and SO_2 than the younger adults. There were also significant differences in the effect of exposure to PM10, NO_2 and O_3. In contrast, no pollutant showed any significant effect difference between older and younger subjects during winter season.

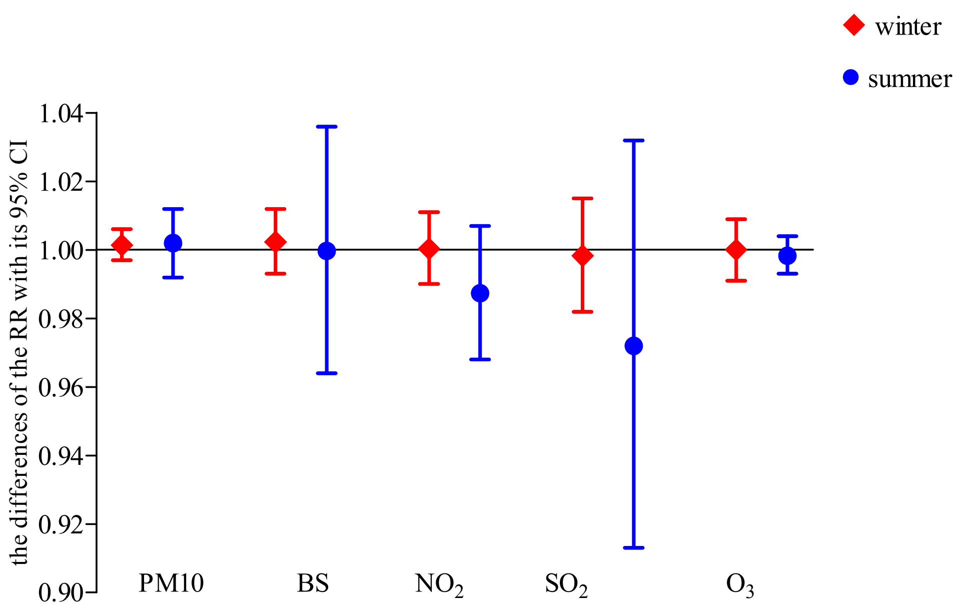

Fig.1 The association of air pollutants and respiratory admissions relative risk differences between male and female (female versus male) during winter and summer seasons of 1992-1999 in the Netherlands

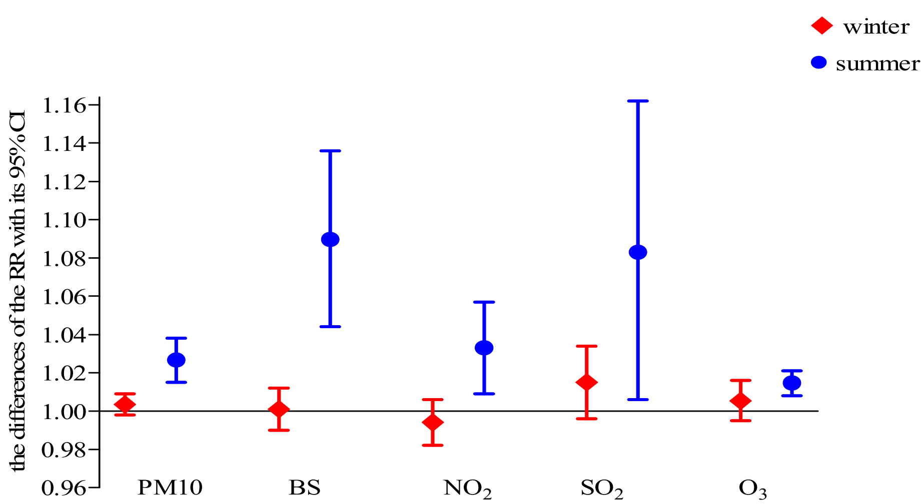

Fig.2 The association of air pollutants and respiratory admissions relative risk diffrences between young and old (old versus young) during winter and summer seasons of 1992-1999 in the Netherlands

3.2.1.2 Multi-pollutants exposure

The winter and summer season interaction effects of pollutants on respiratory admissions are shown in table 7 and 8. More detailed results are presented in annexes 8 to 13, in which the effect of the continuous pollutant on days when the interacting pollutant is relatively low and on days when the interacting pollutant is relatively high, as well as the difference between these effects (i.e. the interaction) is given (i.e. low, high and high versus low concentration effects).

All respiratory admissions

The investigation of interaction effects of PM10, BS, SO_2 and NO_2 on all respiratory admissions during winter season was carried out with high versus low concentration of O_3. The effect of SO_2 was increased by co-exposure to O_3. On days when O_3 levels were low, a 10 μg/m^3 increase in SO_2 resulted in a 1.6% increased risk of being admitted to hospital due to a respiratory disease. However, on days with relatively high O_3 levels, a 10 μg/m^3 increase in SO_2 was associated with a 4.9 % increased risk to be admitted to a hospital. The difference between these estimates is statistically significant (RR=1.032(95%CI, 1.015-1.050)). The effect of PM10 was decreased by co-exposure to O_3 and BS and NO_2 did not show synergy with O_3 on all respiratory admissions except for a borderline and statistically non-significant synergistic effect of NO_2 with O_3 (RR=1.006 (95%CI, 0.994-1.018)).

In the summer season we investigated the synergistic effect of O_3 with high versus low concentrations of PM10, BS, SO_2 and NO_2. The level of concentration of O_3 during summer season was more than double relative to its winter season concentration and its single exposure effect was also positive while the single exposure effects of PM10, BS, SO_2 and NO_2 were negative. However, the O_3 positive association on respiratory admissions is diminished during co-exposure to PM10 but increased during co-exposure to BS, SO_2 and NO_2. Thus, O_3 showed antagonistic effects with PM10 and synergistic effect with BS, SO_2 and NO_2 on all respiratory admissions. Slightly higher synergistic effects of O_3 were observed with SO_2 (RR=1.026 (95%CI, 1.020-1.031)). The synergistic effects of O_3 with BS (RR=1.007 (95%CI, 1.000-1.014)) and NO_2 (RR=1.007 (95%CI, 1.001-1.013)) on all respiratory admissions were more or less similar.

Sex specific respiratory admissions

The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 on males and females respiratory admissions during winter season is consistent with that of all respiratory admissions. But the synergistic effect of SO_2 with O_3 is slightly higher in males (3.5%) than in females (2.9%). The synergistic effects of O_3 with SO_2 also show slight effect-differences between males and females during summer season with RRs of 1.027(95%CI, 1.020-1.034) and 1.024(95%CI, 1.015-1.033) for males and females respectively. During summer, statistically non-significant synergistic effects of O_3 with BS and NO_2 were evident in both sexes as well as the antagonistic effect of O_3 with PM10.

Table 7: The interaction effects of PM10, BS, SO_2 and NO_2 with high versus low concentration of O_3 on all, males and females emergency respiratory hospital admissions during winter season of 1992-1999 in the Netherlands

	admissions								
Pollutants	all respiratory admissions			males respiratory admissions			females respiratory admissions		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.993**	**0.988**	**0.998**	**0.992**	**0.985**	**0.999**	0.995	0.987	1.003
Bs	0.997	0.985	1.010	0.996	0.980	1.013	0.998	0.979	1.018
SO_2	**1.032**	**1.015**	**1.050**	**1.035**	**1.012**	**1.058**	**1.029**	**1.002**	**1.056**
NO_2	1.006	0.994	1.018	1.006	0.990	1.022	1.005	0.987	1.024

Table 8: The interaction effects of O_3 with high versus low concentrations of PM10, BS, SO_2 and NO_2 on all, males and females emergency respiratory hospital admissions during the summer season of 1992-1999 in the Netherlands

admissions									
Pollutants	all respiratory admissions			males respiratory admissions			females respiratory admissions		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.973**	**0.967**	**0.980**	**0.972**	**0.964**	**0.980**	**0.975**	**0.965**	**0.986**
Bs	**1.007**	**1.000**	**1.014**	1.006	0.998	1.015	1.008	0.997	1.019
SO_2	**1.026**	**1.020**	**1.031**	**1.027**	**1.020**	**1.034**	**1.024**	**1.015**	**1.033**
NO_2	**1.007**	**1.001**	**1.013**	**1.008**	**1.000**	**1.015**	1.006	0.998	1.015

3.2.2 Asthma admissions

3.2.2.1 Single pollutant exposure

The results of the single pollutant association with all asthma admissions, males and females asthma admissions for both winter and summer seasons are shown in table 9 and 10.

All asthma admissions

PM10, SO_2, BS and NO_2 show mixed positive and negative statistically non-significant associations during winter except O_3 which associated with significant negative effect. PM10 and BS show positive statistically non-significant association during winter season while NO_2 and SO_2 show negative non-statistically significant association. In contrast, the effects of PM10, SO_2, BS and NO_2 during summer season were significantly negative with all asthma admissions. During this season O_3 presented statistically non-significant borderline positive association with all asthma admission (RR=1.008 (95%CI, 0.992-1.026)).

Sex specific asthma admissions

PM10, SO_2, BS and NO_2 show mixed positive and negative non-significant associations with male and female asthma admissions. During winter PM10, SO_2 and NO_2 show negative non-significant association while BS presents positive non-significant association with male admissions. In contrast, all of them (PM10, BS, SO_2 and NO_2) showed positive non-significant association with female admissions except O_3 for which its effect with both males and females is significantly negative. The difference in relative risks between males and females was statistically non-significant (the result not shown).

The effects of PM10, BS, SO_2 and NO_2 during summer season show negative significant association with both males and females. The effects of O_3 is non-significantly positive with both males and females with higher positive effects on male admissions (male, RR=1.012(95%CI, 0.989-1.036) versus females, RR=1.004(95%CI, 0.980-1.029)).

Table 9: The association of PM10, BS, O_3, NO_2 and SO_2 (10µg/m^3) with all, males and females emergency asthma hospital admissions during winter season of 1992-1999 in the Netherlands

Pollutants	winter season asthma admissions		
	all admissions	male admissions	female admissions
	RR(95% CI)	RR(95% CI)	RR(95% CI)
PM10	1.001(0.992-1.011)	0.998(0.985,1.012)	1.004(0.990,1.017)
BS	1.005(0.984-1.025)	1.003(0.974,1.032)	1.007(0.978,1.036)
SO_2	0.996(0.959-1.035)	0.979(0.928,1.034)	1.013(0.960,1.068)
NO_2	0.997(0.977-1.019)	0.991(0.962,1.021)	1.004(0.974,1.034)
O_3	**0.966(0.947-0.985)**	**0.969(0.943,0.996)**	**0.963(0.937,0.990)**

Table 10: The association of PM10, BS, O_3, NO_2 and SO_2 (10µg/m^3) with all, males and females emergency asthma hospital admissions during summer season of 1992-1999 in the Netherlands

Pollutants	summer season asthma admissions		
	all admissions	male admissions	female admissions
	RR(95% CI)	RR(95% CI)	RR(95% CI)
PM10	**0.936(0.918-0.955)**	**0.941(0.916,0.966)**	**0.932(0.906,0.958)**
BS	**0.778(0.729-0.831)**	**0.808(0.739,0.884)**	**0.747(0.679,0.822)**
SO_2	**0.677(0.605-0.759)**	**0.680(0.582,0.795)**	**0.677(0.574,0.797)**
NO_2	**0.886(0.853-0.920)**	**0.917(0.870,0.966)**	**0.855(0.810,0.903)**
O_3	1.008(0.992-1.026)	1.012(0.989,1.036)	1.004(0.980,1.029)

3.2.2.2 Multi-pollutants exposure

The results of interaction effects of pollutants on all, male and female asthma admissions for winter and summer seasons are presented in table 11 and 12. Annexes 14 to 19 show more detailed results.

All asthma admissions

The results for the winter season did not show any positive interaction effects of PM10, BS and NO_2 with O_3 on all asthma admissions, but a statistically non-significant synergistic effect was evident when SO_2 interacted with O_3 (RR=1.016(95%CI, 0.949-1.087). In contrast, the summer result indicates mixed significant and non-significant synergistic effects of O_3 with PM10, BS, SO_2 and NO_2 on all asthma admissions. O_3 shows significant synergism with BS, SO_2 and NO_2 and non-significant synergism with PM10. More pronounced synergistic effects were evident with BS and SO_2 (BS, RR=1.052(95%CI, 1.030-1.076) and SO_2, RR=1.050(95%CI, 1.031-1.069)). The synergistic effect of O_3 with NO_2 is somewhat lower (NO_2, RR=1.036(95%CI, 1.018-1.055)).

Sex specific asthma admissions

The gender specific analysis of the interaction effects of PM10, BS, SO_2 and NO_2 with O_3 on males and females asthma admissions for winter season is not different from the interaction effects observed on all asthma admissions. None of the pollutants show significant synergistic effects with O_3 on males and females admissions. NO_2 and SO_2 show very low non-significant synergism on male admissions whereas only SO_2 presents the same non-significant synergistic effect on female admissions. The summer result indicates mixed significant and non-significant synergistic effects of O_3 with PM10, BS, SO_2 and NO_2 on both males and females admissions. However, more pronounced significant synergistic effects were observed on male admissions. Only the interaction effect of O_3 with SO_2 is significantly synergistic on female admission. The synergistic effect of O_3 with BS and NO_2 is also evident on female admissions but statistically non-significant.

Table 11: The interaction effect of PM10, BS, SO_2 and NO_2 with high versus low concentration of O_3 on all, males and females emergency asthma hospital admissions during winter season of 1992-1999 in the Netherlands

Winter season admissions									
pollutants	all asthma admission			male asthma admission			female asthma admission		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	0.986	0.967	1.006	0.992	0.964	1.020	0.981	0.954	1.009
Bs	0.970	0.925	1.018	0.984	0.920	1.052	0.956	0.893	1.022
SO_2	1.016	0.949	1.087	1.015	0.924	1.116	1.016	0.922	1.118
NO_2	0.977	0.932	1.023	1.002	0.938	1.070	0.953	0.893	1.017

Table 12: The interaction effect of O3 with high versus low concentrations of PM10, BS, SO_2 and NO_2 on all, males and females emergency asthma hospital admissions during summer season of 1992-1999 in the Netherlands

Summer season admissions									
pollutants	all asthma admission			male asthma admission			female asthma admission		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	1.008	0.987	1.030	1.023	0.993	1.053	0.994	0.964	1.025
Bs	**1.052**	**1.030**	**1.076**	**1.075**	**1.043**	**1.109**	1.030	0.998	1.062
SO_2	**1.050**	**1.031**	**1.069**	**1.056**	**1.029**	**1.083**	**1.044**	**1.018**	**1.072**
NO_2	**1.036**	**1.018**	**1.055**	**1.052**	**1.026**	**1.079**	1.021	0.995	1.047

3.2.3 Chronic obstructive pulmonary diseases (COPD) admissions

3.2.3.1 Single pollutant exposure

The results of the association of PM10, BS, O_3, SO_2 and NO_2 with all, males and females admissions for winter and summer seasons are displayed in tables 13 and 14.

All COPD admissions

PM10, BS, SO_2 and NO_2 show positive significant associations with COPD admissions with a more pronounced effect estimate for SO_2 during winter season while O_3 shows significant negative association. The reverse of the winter association is observed for summer season with all pollutants. PM10, BS, SO_2 and NO_2 present a negative significant association while O_3 shows a positive significant association.

Sex specific COPD admissions

The association of PM10, BS, O_3, SO_2 and NO_2 with male and female COPD admissions for winter and summer seasons are not different from the associations with all COPD admissions in both seasons. Hence, the winter season association of PM10, BS, SO_2 and NO_2 shows positive association while significant negative association is observed with O_3. During summer, COPD admissions for males and females show negative associations with PM10, BS, SO_2 and NO_2 and O_3 shows positive significant association with both male and female admissions. The effect estimates of pollutants during both winter and summer seasons are more or less similar between males and females admissions with a slight tilt to female admissions. Females with COPD are slightly more at risk than males with COPD to the effects of air pollution exposure (table 13).

Table 13: The association of PM10, BS, O_3, NO_2 and SO_2 ($10\mu g/m^3$) with all, males and females emergency COPD hospital admissions during winter season of 1992-1999 in the Netherlands

Pollutants	Winter season COPD admissions		
	All admission	Male admission	Female admission
	RR(95% CI)	RR(95% CI)	RR(95% CI)
PM10	**1.014(1.009, 1.019)**	**1.013(1.007,1.019)**	**1.015(1.007,1.022)**
BS	**1.021(1.011, 1.031)**	**1.019(1.006,1.033)**	**1.024(1.008,1.040)**
SO_2	**1.049(1.031, 1.069)**	**1.049(1.024,1.073)**	**1.051(1.022,1.081)**
NO_2	**1.024(1.014, 1.035)**	**1.023(1.010,1.037)**	**1.026(1.010,1.043)**
O_3	**0.950(0.941, 0.960)**	**0.951(0.938,0.963)**	**0.949(0.934,0.964)**

Table 14: The association of PM10, BS, O_3, NO_2 and SO_2 ($10\mu g/m^3$) with all, males and females emergency COPD hospital admissions during summer season of 1992-1999 in the Netherlands

Pollutants	Summer season COPD admissions		
	All admission	Male admission	Female admission
	RR(95% CI)	RR(95% CI)	RR(95% CI)
PM10	**0.988(0.976, 0.999)**	**0.984(0.969,0.998)**	0.993(0.975,1.012)
BS	**0.901(0.866, 0.936)**	**0.890(0.846,0.936)**	**0.916(0.861,0.974)**
SO_2	**0.734(0.688, 0.784)**	**0.758(0.698,0.824)**	**0.697(0.628,0.774)**
NO_2	**0.924(0.904, 0.944)**	**0.924(0.898,0.950)**	**0.924(0.893,0.956)**
O_3	**1.030(1.020, 1.040)**	**1.028(1.016,1.041)**	**1.033(1.018,1.049)**

3.2.3.2 Multi-pollutants exposure

The results of interaction effects of pollutants on all, male and female COPD admissions for winter and summer seasons are presented in table 15 and 16. Annexes 20 to 25 show more detailed results.

All COPD admissions

The winter season investigation of synergistic effects of PM10, BS, SO_2 and NO_2 with O_3 shows mixed significant and non-significant relative risks on all COPD admissions. SO_2 and NO_2 present positive significant interaction effects with O_3 while PM10 and BS with O_3 show insignificant synergistic effects. Unlike winter season, the summer season interaction effect of O_3 with PM10 is significantly negative (i.e. the effect of O_3 on COPD admission is reduced on days when PM10 is relatively high compared to days with low PM10). The combined effect of O_3 and BS shows negative insignificant association whereas positive significant association is evident with simultaneous exposure of O_3 and SO_2 like that of the winter season. In both seasons O_3 and SO_2 showed marked positive interaction effects.

Sex specific COPD admissions

The sex specific analysis for winter season presents different interaction effects on male and female COPD admissions. These effect-differences between males and females occurred specifically with the interaction effects of BS and SO_2 (both separately with O_3) for which the effects of these pollutants were significantly higher in males. In contrast, statistically non-significant synergistic effects of BS and SO_2 with O_3 were evident for female COPD admissions. The summer analysis shows different interaction effects when it is investigated for O_3. Unlike that of winter, the interaction effect of O_3 with PM10, BS, SO_2 and NO_2 for the summer season did not show any interaction effect differences between males and females. The interaction effect of O_3 with PM10 on both male and female admissions shows negative significant association. This implies that the effect of O_3 on COPD admissions is lower on days with relatively high PM10 levels in both males and females. In contrast, the effects of O_3 were found to be synergistic with SO_2 with no significant effect-differences between males and females. The interaction effects of O_3 with BS and NO_2 on male COPD admissions show statistically non-significant negative association while a statistically non-significant positive association is observed on female admissions.

Table 15: The interaction effect of PM10, BS, SO_2 and NO_2 with high versus low concentration of O_3 on all, males and females emergency COPD hospital admissions during the winter season of 1992-1999 in the Netherlands

COPD admissions									
pollutants	all COPD admission			male COPD admission			female COPD admission		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	1.002	0.992	1.012	1.005	0.992	1.017	0.998	0.982	1.013
Bs	1.021	0.997	1.045	**1.033**	**1.002**	**1.064**	1.003	0.965	1.041
SO_2	**1.047**	**1.014**	**1.081**	**1.063**	**1.020**	**1.108**	1.023	0.972	1.077
NO_2	**1.023**	**1.000**	**1.047**	1.024	0.994	1.054	1.023	0.987	1.060

Table 16: The interaction effect of O_3 with high versus low concentrations of PM10, BS, SO_2 and NO_2 on all, male and female emergency COPD hospital admissions during the summer season of 1992-1999 in the Netherlands

COPD admissions									
pollutants	all COPD admission			male COPD admission			female COPD admission		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.955**	**0.943**	**0.968**	**0.944**	**0.929**	**0.960**	**0.973**	**0.953**	**0.993**
Bs	0.994	0.982	1.008	0.987	0.970	1.003	1.006	0.986	1.028
SO_2	**1.019**	**1.008**	**1.030**	**1.017**	**1.003**	**1.031**	**1.022**	**1.004**	**1.039**
NO_2	1.000	0.989	1.010	0.990	0.977	1.003	1.014	0.998	1.031

3.2.4 Cardiovascular admissions

3.2.4.1 Single pollutant exposure

The associations of pollutants with all, male and female cardiovascular admissions for both winter and summer seasons are presented in table 17 and 18.

All cardiovascular admissions

Like other cause-specific admissions in this study the effect of pollutants on all cardiovascular admission also investigated with an increase of pollutants concentration by 10µg/m^3 during winter and summer seasons. During winter season the level of concentration of PM10, BS, SO_2 and NO_2 were high relative to their winter season level of concentration. It is observed that pollutants with higher level of concentration linearly associated with increased level of all cardiovascular admission. Hence, an increase of 10 µg/m^3 of PM10 is associated with a 0.8% increase in cardiovascular admissions (RR=1.008(95%CI, 1.006-1.010). In the same manner 10 µg/m^3 increases in BS and SO_2 are associated with 1% and 3% increases in cardiovascular admissions respectively. In addition, NO_2 presents a statistically non-significant positive association with all cardiovascular admissions with RR=

1.003(95%CI, 0.999-1.008). In contrast, a statistically significant negative association was observed between O_3 and all cardiovascular admissions (RR=0.957(95%CI, 0.953-0.961). However, during summer season, all pollutants (PM10, BS, SO_2 and NO_2) except O_3 associated negatively with all cardiovascular admissions. Only a positive significant association was evident with O_3 (RR=1.016(95%CI, 1.012-1.019)).

Sex specific cardiovascular admissions

The association of PM10, BS, O_3, NO_2 and SO_2 with male and female cardiovascular admissions were investigated and the results show no effect-differences between male and female cardiovascular admissions irrespective of the varied daily number of admissions between male and female in both winter and summer. Thus, PM10, BS, and SO_2 exposure show more or less similar significant positive association with male and female cardiovascular admissions during winter season. The association of NO_2 with male and female admissions was also positive but statistically non-significant. The effect of O_3 is significantly negative with both sexes.

The summer result for male and female cardiovascular admissions is more or less consistent with that of all cardiovascular admissions. All pollutants except O_3 show negative significant association with both male and female admissions.

Table 17: The association of PM10, BS, O_3, NO_2 and SO_2 (10µg/m^3) with all, male and female emergency cardiovascular hospital admission during winter season of 1992-1999 in the Netherlands

Pollutants	Winter season cardiovascular admissions		
	All admissions	Male admissions	Female admissions
	RR(95% CI)	RR(95% CI)	RR(95% CI)
PM10	**1.008(1.006, 1.010)**	**1.009(1.007,1.012)**	**1.007(1.004,1.010)**
BS	**1.011(1.006, 1.015)**	**1.012(1.006,1.017)**	**1.010(1.003,1.016)**
SO_2	**1.029(1.021, 1.037)**	**1.033(1.022,1.043)**	**1.023(1.011,1.036)**
NO_2	1.003(0.999, 1.008)	1.004(0.998,1.010)	1.002(0.995,1.009)
O_3	**0.957(0.953, 0.961)**	**0.957(0.952,0.963)**	**0.955(0.949,0.961)**

Table 18: The association of PM10, BS, O_3, NO_2 and SO_2 (10µg/m^3) with all, male and female emergency cardiovascular hospital admission during summer season of 1992-1999 in the Netherlands

Pollutants	Summer season cardiovascular admissions		
	All admissions	Male admissions	Female admissions
	RR(95% CI)	RR(95% CI)	RR(95% CI)
PM10	**0.967 (0.963, 0.971)**	**0.967(0.961,0.972)**	**0.967(0.961,0.974)**
BS	**0.853 (0.841, 0.866)**	**0.851(0.834,0.868)**	**0.855(0.835,0.874)**
SO_2	**0.695 (0.678, 0.712)**	**0.693(0.671,0.716)**	**0.697(0.671,0.724)**
NO_2	**0.905 (0.898, 0.913)**	**0.905(0.895,0.914)**	**0.905(0.894,0.917)**
O_3	**1.016 (1.012, 1.019)**	**1.019(1.014,1.023)**	**1.012(1.006,1.017)**

The in-depth analysis results for the identification of susceptible group between male and female cardiovascular admissions are displayed in annexes 26 & 27. Hence, the results indicate no statistically significant effect estimate differences between male and female cardiovascular admissions regardless of the differences in daily number of hospital admissions with this case. We also showed the results in fig. 3 to compare the risk of air pollution differences between male and female admissions.

We observed a difference in the mean daily numbers of cardiovascular admissions between younger and older subjects. However, there is no significant difference in the effect of air pollution exposure between these age groups (annexes 28 & 29 but also see fig. 4).

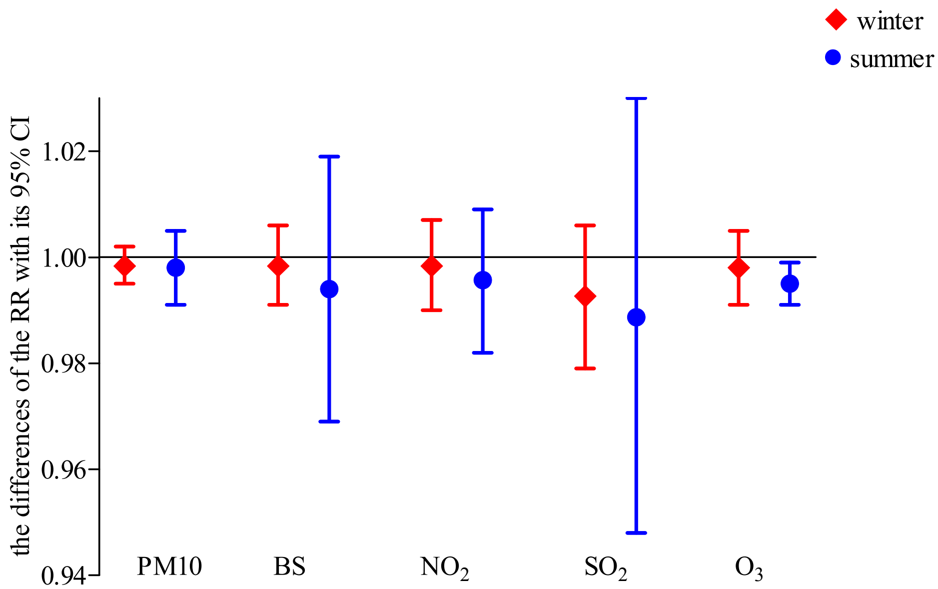

Fig.3 The air pollution exposure effects differences between male and female (female versus male) cardiovascular admissions during winter and summer seasons of 1992-1999 in the Netherlands

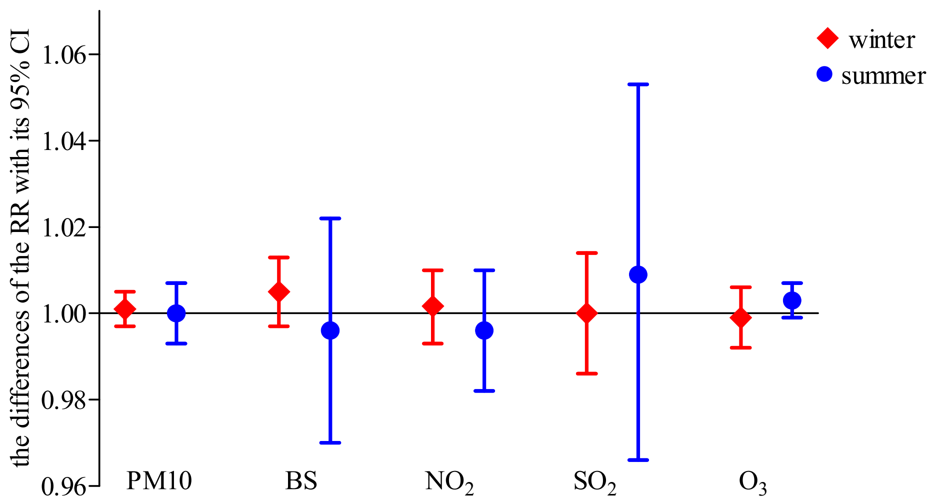

Fig.4 The air pollution exposure effect differences between younger and older (older versus younger) cardiovascular admissions during winter and summer seasons of 1992-1999 in the Netherlands

3.2.4.2 Multi-pollutants exposure

The results of the interaction effects of pollutants on cardiovascular admission during winter and summer seasons are presented in table 19 to 20. In addition, detailed results are given in annexes 30 to 35.

All cardiovascular admissions

During both seasons the interaction effect of PM10 with O_3 shows significant antagonistic effect on all cardiovascular admissions. This implies that the combined exposure of PM10 and O_3 does not impose negative health effects but it reduces the likelihood of ill response. During winter season BS showed statistically significantly negative interaction effects on all cardiovascular admissions whereas SO_2 showed a statistically non-significant synergistic effect with O_3 (RR=1.008(95%CI, 0.994-1.021)).

During summer season O_3 shows significant synergy only with SO_2 (RR=1.010(95%CI, 1.006-1.014). In contrast, the interaction effects of O_3 with PM10 and NO_2 were antagonistic on all cardiovascular hospital admissions. Particularly, the interaction effect of O_3 with PM10 was dramatic due to the fact that the effect of O_3 with low concentration of PM10 reduced from 7% to 1.6% when it interacted with high concentrations of PM10. The reduction in interaction effect of O_3 with NO_2 was also apparent from 2.6% to 1.8% (low to high concentration of NO_2).

Sex specific cardiovascular admissions

The interaction effects of PM10, BS, NO_2 and SO_2 with high versus low concentration of O_3 were also investigated separately for male and female cardiovascular admissions for both winter and summer seasons. Hence we found similar results for the interaction effects that we observed on all cardiovascular admissions for winter season. However, we did find statistically non-significant synergistic effect of SO_2 with O_3 on male (RR=1.006(95%CI, 0.988-1.024) and female (RR=1.010(95%CI, 0.990-1.032) admissions (table 19). The summer season analysis for male and female cardiovascular admissions for synergistic effect of O_3 with PM10, BS, NO_2 and SO_2 shows more or less similar results with those of all cardiovascular admissions. Thus, O_3 only shows synergy with SO_2 with marginally statistically significant effects on male (RR=1.012(95%CI, 1.006-1.017)) and female (RR=1.006(1.000-1.013)) admissions (table 20).

Table 19: The interaction effect of PM10, BS, SO_2 and NO_2 with high versus low concentration of O_3 on all, males and females emergency cardiovascular hospital admissions during the winter season of 1992-1999 in the Netherlands

	admissions								
pollutants	all cardiovascular admission			male cardiovascular admission			female cardiovascular admission		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.992**	**0.988**	**0.996**	**0.993**	**0.988**	**0.998**	**0.990**	**0.984**	**0.996**
Bs	**0.986**	**0.976**	**0.996**	0.988	0.975	1.001	**0.983**	**0.968**	**0.998**
SO_2	1.008	0.994	1.021	1.006	0.988	1.024	1.010	0.990	1.032
NO_2	0.990	0.980	1.000	0.992	0.979	1.005	0.987	0.972	1.002

Table 20: The interaction effect of O_3 with high versus low concentrations of PM10, BS, SO_2 and NO_2 on all, males and females emergency cardiovascular hospital admissions during summer season of 1992-1999 in the Netherlands

	admissions								
pollutants	all cardiovascular admission			male cardiovascular admission			female cardiovascular admission		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.949**	**0.944**	**0.954**	**0.947**	**0.941**	**0.953**	**0.952**	**0.945**	**0.959**
Bs	0.997	0.992	1.002	0.996	0.990	1.003	0.997	0.989	1.004
SO_2	**1.010**	**1.006**	**1.014**	**1.012**	**1.006**	**1.017**	**1.006**	**1.000**	**1.013**
NO_2	**0.992**	**0.989**	**0.996**	**0.993**	**0.988**	**0.998**	**0.992**	**0.986**	**0.998**

CHAPTER 4: DISCUSSION

4.1 Validity of the study

The current study investigates the interaction effects of O_3 with PM10, BS, NO_2 and SO_2 on respiratory, asthma, COPD and cardiovascular emergency hospital admissions during 8 years (from 1992-1999) in all of the Netherlands. Our findings need to be interpreted with the consideration of the strength of our study design, data size and stratification we performed with respect to season of the year and population category. The investigation covers a huge dataset of 1,020,575 emergency hospital admissions with the above mentioned specified disease categories. To analyse this huge dataset we used a case-crossover study design. The case-crossover study design is very suitable to investigate the short term health effects of air pollution exposure with time patterns matching with individual cases(Bateson & Schwartz, 2001; Schwartz, 2004). In case-crossover study design the person him/herself is used both as a control and a case within a given referent time interval. Hence it avoids confounding biases due to personal characteristics and seasonal variations by matching and design. This can be attained by selecting symmetrical referent time periods nearer to the event day(Janes et al., 2005). Therefore, we selected two symmetrical bidirectional control periods before and after the event day. Furthermore, we also did season specific analysis for winter and summer with the exclusion of months with unstable weather conditions. Therefore, the correlation between daily numbers of admission and level of concentration of pollutants due to variation of pollutants concentration during winter and summer cannot be compromised. Furthermore, the tool we used (conditional logistic regression) also allows us to control unforeseen confounders through matching. Conditional logistic regression was suggested as a good tool to control for additional confounders that are not used in the matching (Janes et al., 2005).To validate the predictors we did not restrict confounding control only by matching but also we adjusted for all the possible confounders (weather conditions and public holidays) according to season. Therefore, the regression coefficient of the pollutants (β) is unlikely to be confounded by seasonal variation or other possible confounders. Therefore, in our view our findings signify valid associations between the pollutants and emergency hospital admissions.

Another issue in validity: is personal exposure comparable to the concentrations measured by the fixed air pollution stations. Thus, the exposure is different between seasons because in summer windows are open and people are more outside and during winter the ground level concentration of pollutants are high due to heavily moisturized air but also indoor air circulation is limited that windows are close during winter. Therefore, stratification of the analyses according season is another method for the validity of the findings.

4.2 Direction of interpretation

To the best of our knowledge our study is the first to investigate acute effects of air pollutants and their interaction on respiratory and cardiovascular hospital admissions covering such a long study period and over 1 million admissions. Therefore, we are not able to compare our findings with prior epidemiological findings and thus we prefer to use several lines of evidence to interpret our findings. Hence, the following three lines of evidence will be used. 1) The findings of animal and human experimental studies that addressed the interaction effects of air pollutants especially synergistic toxicological effects on pulmonary responses. Most of them lack disease-specific analysis unlike epidemiological studies and may limit us to compare them directly but they are very indicative from a synergistic toxicological point of view on pulmonary responses. 2) The mechanisms by which pollutants interact in the environment and in living organism and the way they enhance or suppress the effects of each other along with their physical and chemical nature. 3) The current finding on single pollutant association with each cause-specific admission gives us relevant information about each specific pollutant association which could indicate the existence of interaction in co-pollutants exposure if the value is deviated from its single pollutant effect. In our view these combinations can validate the interpretation of the current finding on the existence of interaction effects of pollutants regardless of epidemiological evidence. The discussion will be outlined with regard to each specific cause of admission.

4.3.1 Respiratory admissions

PM10 and O_3 show antagonistic interaction effects on all respiratory admissions in both winter and summer seasons (fig. 5). This implies that the presence of these pollutants together in inhaled air reduces the likelihood of developing ill health. The results of the winter season single pollutant exposure indicate that PM10 associated positively with respiratory admissions whereas O_3 shows a relatively strong association during summer season (table 5 & 6). This single association is consistent with prior findings (Peng et al., 2008). However, both pollutants (PM10 and O_3) show antagonistic interaction effects in all cause-specific admissions. Studies show that O_3 uses particulate matter as an adsorbent to penetrate down to air spaces especially where it can induce pulmonary responses (Schlesinger, 1995). This mechanism may not be realistic with PM10 with relatively higher aerodynamic diameter to facilitate the movement of O_3 in a respiratory way deep to air space. Rather they may be liable to mucociliary clearances before reaching the target site at which they can induce pulmonary responses, because particles with respirable size (less than 2.5 µm aerodynamic diameters) can penetrate the respiratory way and arrive at air space (alveoli). Thus, particles with relatively smaller size (less than 2.5 µm aerodynamic diameters) have higher surface area and porosity to facilitate the attachment of oxidant gases which subsequently increases the level of synergistic interaction (Last et al., 1986; Oberdorster, 2001; Valavanidis et al., 2008).

In contrast, we found similar interaction effects of O_3 and SO_2 on all respiratory admissions in both seasons. Positive association of SO_2 with respiratory admission was evident during winter season while O_3 shows strong association during summer season from the single pollutant exposure analysis. This is consistent with the prior epidemiological studies (Medina-Ramon et al., 2006; Sunyer et al., 2003a). The mechanisms by which O_3 and SO_2 interact to induce pulmonary response are still not well identified, but indirect evidence confirms their interaction. SO_2 is one of the highly water soluble gaseous air pollutants by which up to 98% can be absorbed in naso-pharynx during nasal breathing in sedentary subjects, whereas the rest can go deep into air space or be absorbed in mucus and epithelial fluids forming sulphuric acid and bisulphates (Sandstrom, 1995). The increased pulmonary acidity due to exposure of SO_2 increases the effects of O_3 as an interaction that is triggered by change in acidity of pulmonary environment (Last et al., 1986). G.Hoek (1999) also indicated the epidemiologic interaction effect of O_3 and SO_2 indirectly with sulphate aerosols, because SO_2 reacts with photochemical products and airborne particles to form acidic vapour and aerosols(Kleinman et al., 1989).

The sex specific analysis on the synergistic effect of O_3 and SO_2 shows no differences between male and female respiratory admissions during both seasons (fig. 6 & 7).

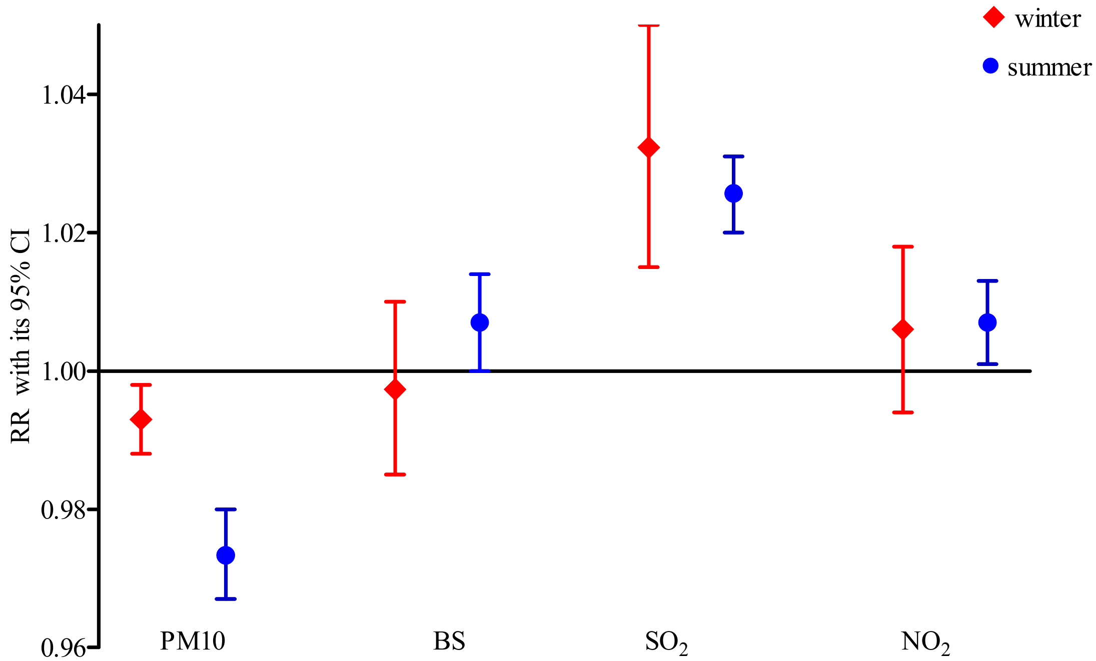

Fig.5 The interaction effects of pollutants on all respiratory admissions during winter and summer seasons of 1992-1999 in the Netherlands

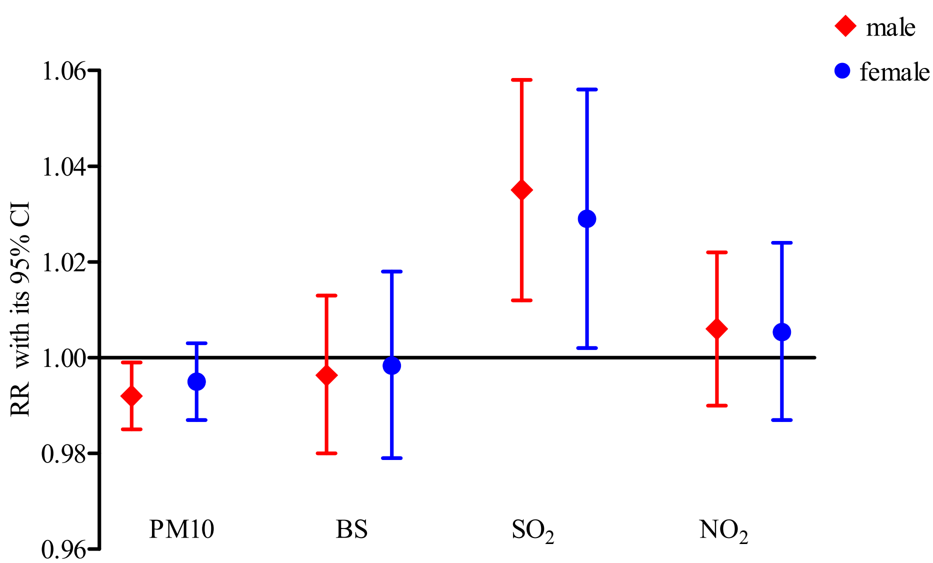

Fig.6 The interaction effects of pollutants on male and female respiratory admissions during winter season of 1992-1999 in the Netherlands

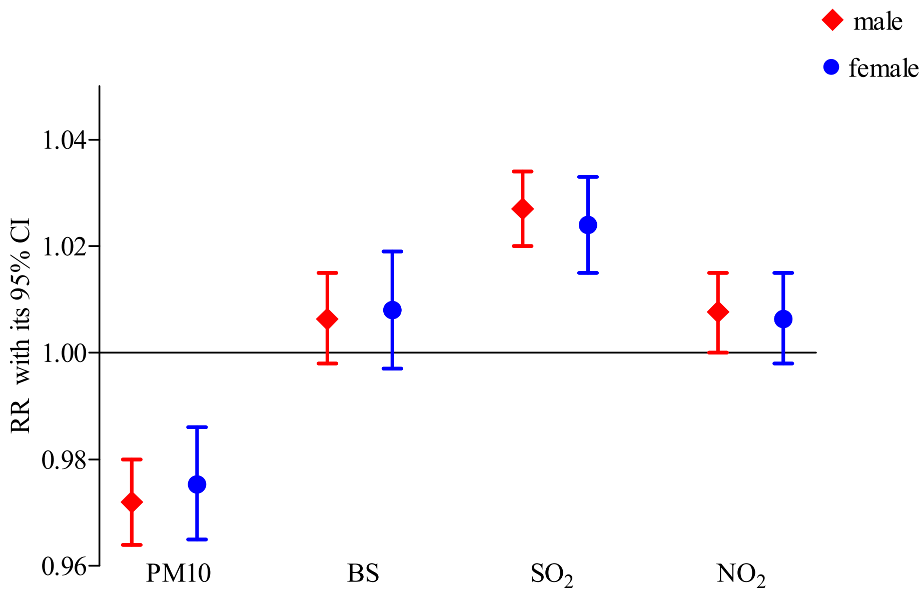

Fig.7 The interaction effects of pollutants on male and female respiratory admissions during summer season of 1992-1999 in the Netherlands

4.3.2 Asthma admissions

The single pollutant analysis indicates a negative significant association of BS, NO_2 and SO_2 with asthma admissions during summer season while O_3 shows positive statistically non-significant border-line association. However, their co-pollutant analysis indicates significant positive interaction effects of these pollutants (BS, NO_2 and SO_2) with O_3 (Fig.8). Especially the synergistic effects with BS and SO_2 are prominently high relative to NO_2 on all asthma admissions. These results are consistent with the animal and human experimental studies of synergistic effects of O_3 with BS, SO_2 and NO_2 (Mauderly & Samet, 2009) in which pronounced pulmonary inflammation was observed. Bosson (2007)(Bosson et al., 2007) indicates the synergistic effects of O_3 and diesel based PM (the main source of BS, SO_2 and NO_2) from sixteen healthy non-smoking subjects who were exposed to a com-bination of these pollutants. The synergistic effects of O_3 with SO_2 and NO_2 can be also explained indirectly with sulphate and nitrate aerosols. Oxidation of SO_2 and NO_2 produce sulphuric acid and nitric acid in the atmosphere which are subsequently inhaled as aerosols. It was shown that the com-bined exposure of O_3 with these aerosols elicits pulmonary responses in rat (Enami et al., 2008; Schlesinger et al., 1992)

During winter, we did not find any significant interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (fig.8).

The differences between male and female susceptibility to synergistic effects of SO_2 and NO_2 with O_3 are more or less similar to those of respiratory admissions. In general, the interaction effects of O_3 with BS and NO_2 in males are more than twice those in females (fig. 9). An interaction effect of O_3 with SO_2 was slightly more pronounced among male than female asthma admissions. The possible explana-tion for this difference in susceptibility could be due to relatively high exposure of males to traffic emissions and occupational related risks.

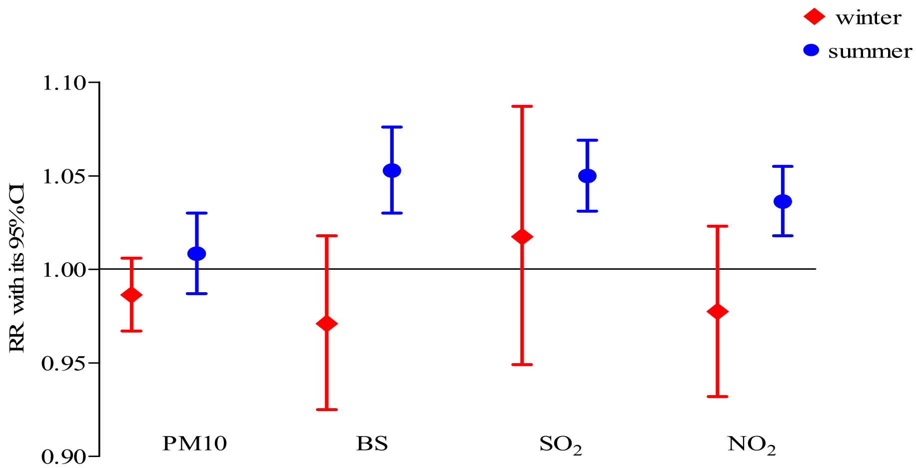

Fig.8 The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 on all asthma admissions during winter and summer seasons of 1992-1999 in the Netherlands

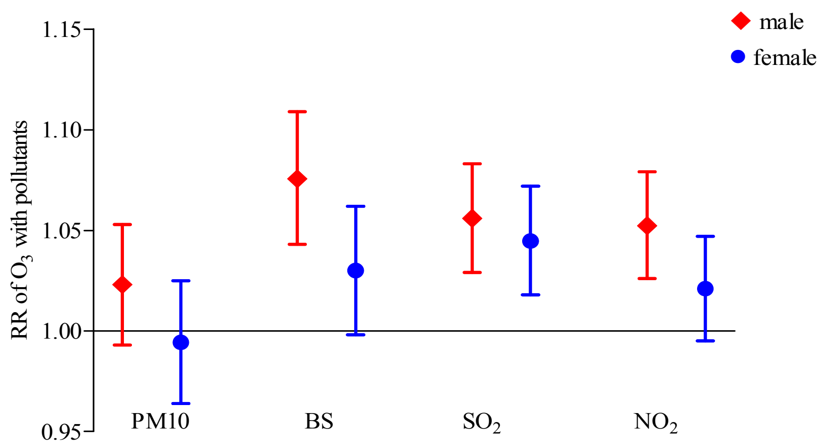

Fig. 9 The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 on all, male and female asthma admissions during summer season of 1992-1999 in the Netherlands

4.3.3 COPD admissions

The general trend of the interaction effects of PM10, BS, SO_2 and NO_2 with O_3 on COPD admissions as such is not different from respiratory and asthma admissions (table 15 & 16 and fig.10). However, the relative risk of the synergistic effect and the level of significance varies. NO_2 and SO_2 show a significant synergistic effect with O_3 on COPD admissions during winter season. The synergistic effects of these two pollutants are consistent with the two specific causes of admissions (i.e. respiratory and asthma admissions) discussed above. Therefore, we opt not to repeat the discussion here, because COPD is part of the respiratory admissions. However, one important point we would like to emphasize is the strong synergistic effect of SO_2 with O_3 during winter season, because these two pollutants present negative associations during winter season with COPD admission when they investigated for their single pollutant effect association. During winter season the concentration level of O_3 is relatively low due to the low photochemical activity which is ineffective in initiating the formation of O_3. In contrast, the concentration level of SO_2 is relatively high during winter season, but short-lived due to its high water solubility that SO_x is subsequently washed away with rain in the form of H_2SO_4. However, their combined effects present pronounced synergistic effects on all COPD admissions. The possible explanation could be the inhalation of atmospheric sulphate aerosols with O_3 and/or the subsequent change in acidity of the pulmonary environment that can boost the effects of O_3. (Last et al., 1986) and

(Schlesinger et al., 1992) clearly indicated how SO_2 interact with O_3 to induce pronounced effects on pulmonary responses. The high interaction effects of SO_2 with O_3 during winter relative to the interaction effects of O_3 with SO_2 during summer is another indication to effects of acidity in enhancing the effects of interaction between SO_2 and O_3 (fig.10). This supports the suggestion forwarded by Last (1986) that the effect of synergism of SO_2 with O_3 mainly results from the formation of acid and not from the sulphate component.

During summer season O_3 presents strong antagonistic effects with PM10 on all, male and female COPD admissions. Our possible explanation is not different from that we have suggested earlier with regard to respiratory admissions. The differences in interaction effects of SO_2 and BS with O_3 between males and females are high in winter season with males showing higher interaction effects. In contrast females show slightly higher interaction effects during summer season in all pollutants except with SO_2 (fig.11 & 12). This disparity may need further investigation as to why males and females show differences in susceptibility to a mix of air pollution depending on the season.

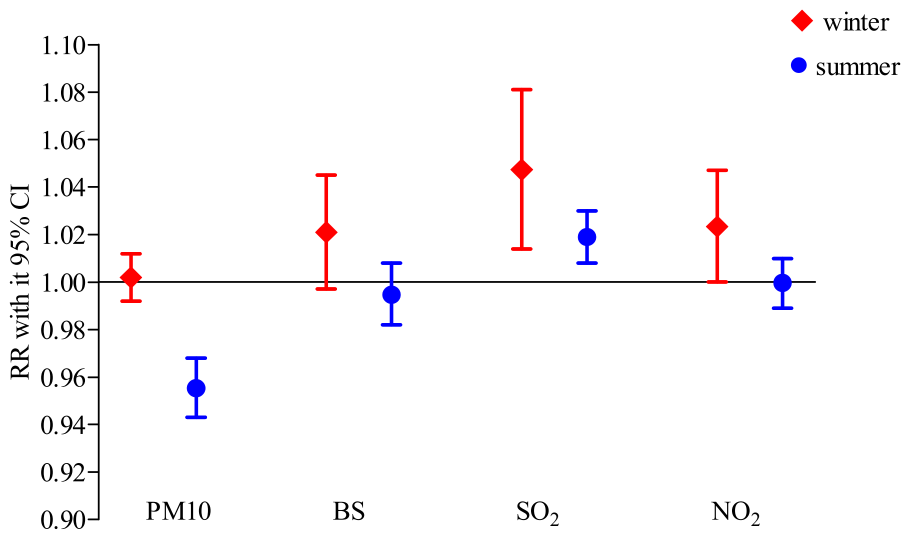

Fig. 10 The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 on all COPD admissions during winter and summer season of 1992-1999 in the Netherlands

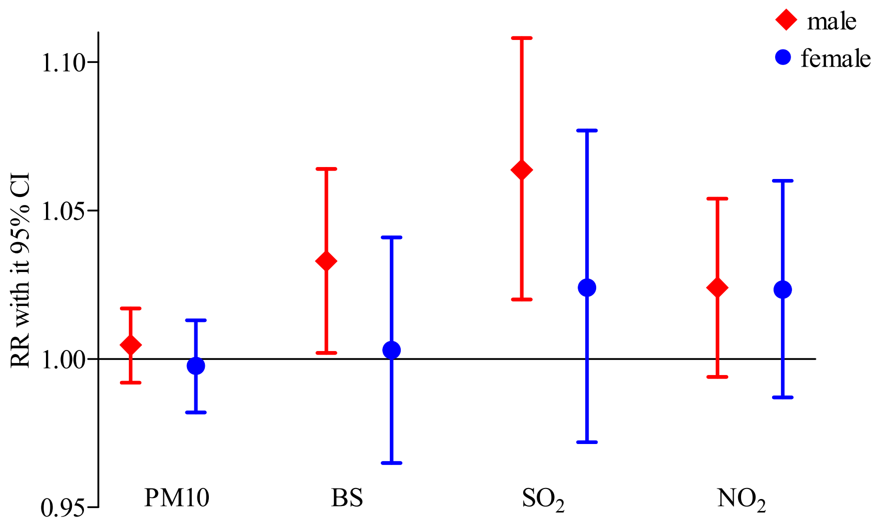

Fig. 11 The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 on male and female COPD admissions during the winter season of 1992-1999 in the Netherlands

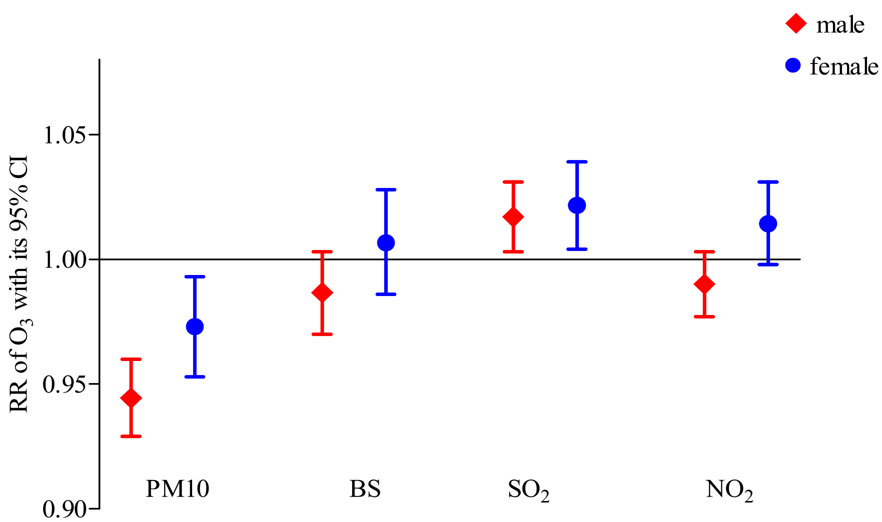

Fig. 12 The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 on male and female COPD admissions during the summer season of 1992-1999 in the Netherlands

4.3.4 Cardiovascular admissions

SO_2 presented a relatively strong association with all, male and female cardiovascular admissions during winter season. The association of SO_2 with cardiovascular admission is consistent with the Aphea-II study in which the association of SO_2 remains significant even after adjusting for PM10 especially with ischemic admissions (Sunyer et al., 2003b). The SO_2 positive association with cardiovascular is also reflected as an interaction with O_3 in both seasons (table 19 & 20 and fig.13). Further characteristics of O_3 and SO_2 and the way in which both interact on cardiovascular admission will be suggested in the following paragraph.

O_3 is a highly reactive oxidant gas which penetrates into the lung and causes lung injury. The alveolar epithelial cells are among the lung cells that are liable to O_3 exposure. O_3 induces oxidative stress through its cellular reaction products and by activated respiratory tract inflammatory processes. O_3 induces epithelial cytotoxicity, DNA damage and injury through oxidative stress which ultimately produces necroses and epithelial permeability (Valavanidis et al., 2009). O_3 reacts with cell membranes with the production of oxygen radicals which further induce oxidative stress as a result of accumulation of these free radicals in blood vessels(Pryor, 1994; Valavanidis et al., 2008). The excess accumulation of these free radicals and incapability of the cell to avoid them cause atherosclerosis which further hinder blood supply to heart and brain. This was evident from animal study causing oxidative stress in rat alveolar cells (Wang et al., 2006). O_3 also suppresses phagocytes action and increases alveolar permeability which further allows ultrafine particles to be deposited in distant sites (Gilmour, 1995). The reaction of O_3 and resulting accumulation of free radicals at distant site together with deep site deposition of SO_2 and its aqua acidity evidence their synergistic interaction on cardiovascular admissions in both seasons.

PM10 presented a marginally significant association with cardiovascular admissions when investigated for its single pollutant effect estimate during winter season. This is consistent with the study of Peng et al., 2008(Peng et al., 2008) in which PM10 presented significant association with cardiovascular admissions without adjusting for PM2.5, but after adjusting for PM2.5 its association turned out to be statistically insignificant. From this association it can be predicted that the particle size and composition of PM10 could play an important role in the association with cardiovascular admissions. Since particles smaller than 2.5 μm aerodynamic diameter can penetrate deep to distant site (air spaces) and induce pulmonary responses (Dominici et al., 2006). The toxicological mechanism and importance of size and composition of particles for oxidative stress is well known (Valavanidis et al., 2008).That could be the possible explanation why PM10 showed antagonistic effect as an interaction with O_3 on cardiovascular admissions in both seasons. Similarly we did not find any statistically significant association of NO_2 when we investigated for its single association with cardiovascular admissions during both seasons. This contradicts with the study conducted in APHEA project in which NO_2 presented a strong association with cardiovascular mortality (Samoli et al., 2006). There is evidence that up to 90% of the inhaled NO_2 is taken up within the upper respiratory tract (Schlesinger et al., 1992) and is thus unable to penetrate deeper to distant site. In addition both NO_2 and O_3 have an inverse relationship in the atmosphere. NO reacts with O_3 to form NO_2 through photochemical reactions(Kley et al., 1999) and therefore the possibility to act synergistically is minimal.

The interaction effects of O_3 with all pollutants (PM10, BS, SO_2 and NO_2) did not show any significant effect differences between male and female cardiovascular admissions (fig.14&15).

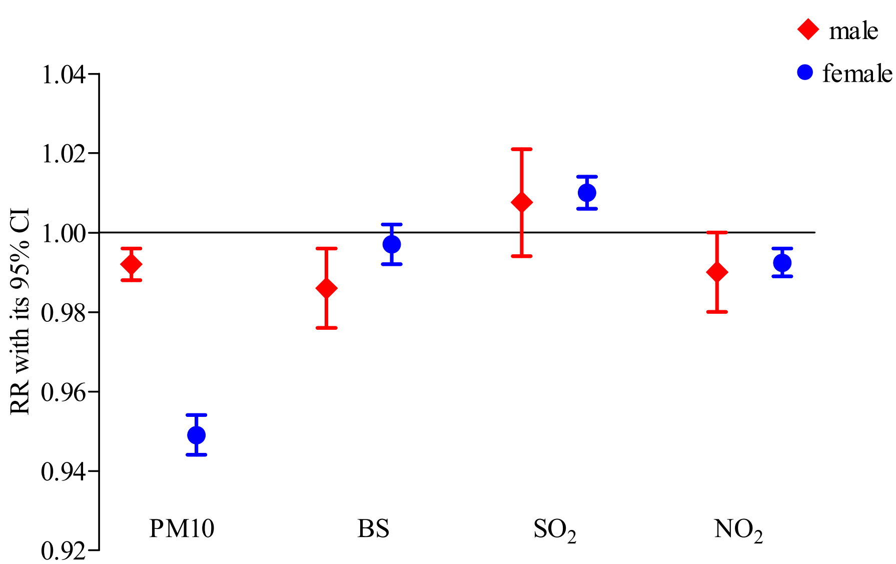

Fig.13 The interaction effects of pollutants and O_3 on all cardiovascular admissions during winter and summer seasons of 1992-1999 in the Netherlands

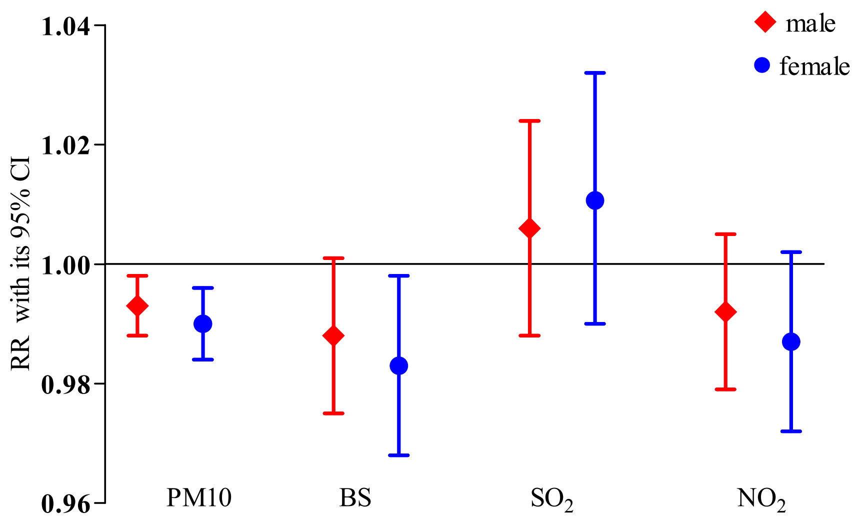

Fig.14 The interaction effects of O3 with PM10, BS, SO_2 and NO_2 on male and female cardiovascular admissions during winter seasons of 1992-1999 in the Netherlands

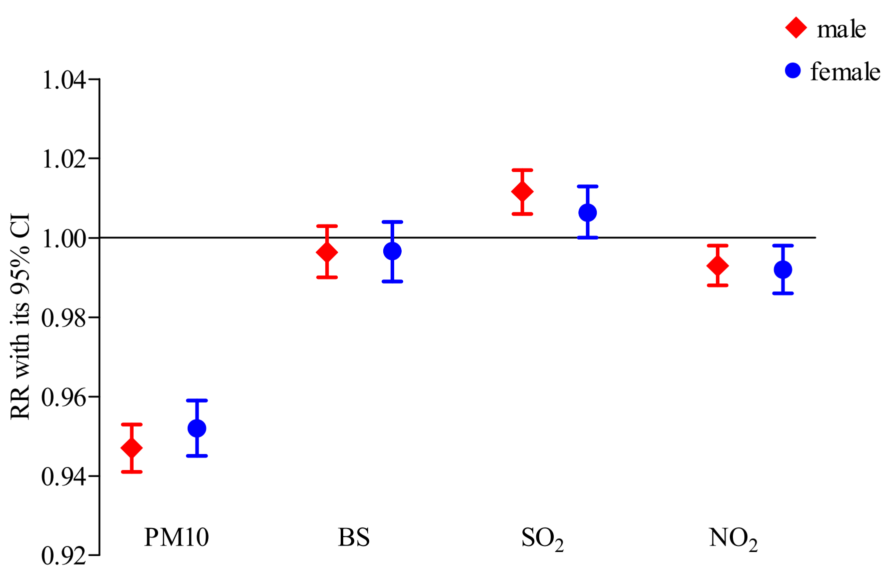

Fig.15 The interaction of pollutants effects on male and female cardiovascular admissions during summer seasons of 1992-1999 in the Netherlands

CHAPTER 5: CONCLUSION

Our analyses of all the cause-specific admissions for both winter and summer season indicate the presence of synergistic and antagonistic interaction effects among some pollutants. The synergistic effect was mainly evident with O_3 and SO_2 on all cause-specific admissions and with BS and NO_2 on some cause-specific admissions. In contrast, antagonistic interaction effects were observed between PM10 and O_3 on almost all cause-specific admissions. Our study did not address the physical and chemical nature of air pollutants, but it underlines the importance of the physical and chemical nature of air pollutants. Pollutants with particle size of greater than 2.5 µm aerodynamic diameter did show antagonistic interaction whereas pollutants less than 2.5 µm aerodynamic diameter showed synergistic interaction. Therefore, it is evident that pollutants with smaller size and chemically reactive showed a positive interaction with O_3 in all cause-specific admissions even when either of them were at lowest concentration level. Therefore the air pollution regulation and standardization should reconsider the physical (particle size and composition) and chemical nature of air pollutants and their fate in the environment and living tissue with due attention to the consequence of interaction effects from public health point of view. Although the current study indicates the interaction effects of air pollutants on respiratory and cardiovascular emergency hospital admissions we urge further investigation with different methodology which can corroborate the current findings.

CHAPTER 6: LITERATURE

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CHAPTER 7: ANNEXES

Annex 1: The Pearson correlation of mean day 0 and days 1-3 pollutants concentration and weather conditions during the winter season of 1992-1999 in the Netherlands

	PM10	BS	O_3	NO_2	SO_2	Temp.	humidity
PM10	1.000	0.895	-0.353	0.691	0.675	-0.405	-0.131
BS		1.000	-0.577	0.745	0.700	-0.545	-0.024
O_3			1.000	-0.586	-0.290	0.324	-0.527
NO_2				1.000	0.514	-0.328	0.089
SO_2					1.000	-0.477	-0.302
Temperature						1.000	0.148
R. humidity							1.000

Annex 2: The Pearson correlation of mean day 0 and days 1-3 pollutants concentration and weather conditions during the summer season of 1992-1999 in the Netherlands

	PM10	BS	O_3	NO_2	SO_2	Temp.	humidity
PM10	1.000	0.822	0.566	0.695	0.549	0.589	-0.394
BS		1.000	0.324	0.864	0.489	0.375	-0.250
O_3			1.000	0.239	0.313	0.582	-0.798
NO_2				1.000	0.589	0.293	-0.198
SO_2					1.000	0.263	-0.331
Temp.						1.000	-0.403
R.humidity							1.000

Annex 3: The differences in relative risk of exposure to Pollutants (10µg/m^3) between males and females (female vs male) respiratory admissions during the winter season of 1992-1999 in the Netherlands (single pollutant exposure)

respiratory risks									
pollutants	male			female			female vs male		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.006**	**1.003**	**1.009**	**1.008**	**1.004**	**1.011**	1.001	0.997	1.006
Bs	**1.007**	**1.001**	**1.014**	**1.010**	**1.002**	**1.018**	1.002	0.993	1.012
NO_2	1.005	0.998	1.013	1.006	0.998	1.014	1.000	0.990	1.011
SO_2	**1.033**	**1.021**	**1.046**	**1.032**	**1.018**	**1.046**	0.998	0.982	1.015
O_3	**0.963**	**0.957**	**0.969**	**0.963**	**0.956**	**0.970**	1.000	0.991	1.009

Annex 4: The differences in relative risk of exposure to Pollutants (10µg/m^3) between males and females (female vs male) respiratory admissions during the summer season of 1992-1999 in the Netherlands (single pollutant exposure)

respiratory risks									
pollutants	male			female			female vs male		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.977**	**0.970**	**0.984**	**0.979**	**0.970**	**0.987**	1.002	0.992	1.012
BS	**0.875**	**0.852**	**0.897**	**0.874**	**0.847**	**0.901**	0.999	0.964	1.036
NO_2	**0.923**	**0.910**	**0.936**	**0.911**	**0.896**	**0.927**	0.987	0.968	1.007
SO_2	**0.748**	**0.717**	**0.781**	**0.727**	**0.690**	**0.765**	0.971	0.913	1.032
O_3	**1.023**	**1.017**	**1.030**	**1.022**	**1.016**	**1.028**	0.998	0.993	1.004

Annex 5: The differences in relative risk of exposure to Pollutants (10µg/m^3) between older and younger (older vs younger) respiratory admissions during winter season of 1992-1999 in the Netherland (single pollutant exposure)

respiratory risks									
pollutants	younger (15-44 yrs)			older (75+ yrs)			older vs younger		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.006**	**1.003**	**1.009**	**1.007**	**1.005**	**1.010**	1.003	0.998	1.009
Bs	**1.008**	**1.002**	**1.014**	**1.010**	**1.004**	**1.016**	1.001	0.990	1.012
NO_2	**1.007**	**1.001**	**1.013**	**1.007**	**1.001**	**1.012**	0.994	0.982	1.006
SO_2	**1.029**	**1.018**	**1.040**	**1.035**	**1.025**	**1.046**	1.015	0.996	1.034
O_3	**0.962**	**0.957**	**0.968**	**0.962**	**0.957**	**0.968**	1.005	0.995	1.016

Annex 6: The differences in relative risk of exposure to Pollutants (10µg/m^3) between older and younger (older vs younger) respiratory admissions during summer season of 1992-1999 in the Netherland (single pollutant exposure)

respiratory risks									
pollutants	younger (15-44 yrs)			older (75+ yrs)			older vs younger		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.972**	**0.965**	**0.978**	**0.980**	**0.973**	**0.986**	**1.027**	**1.015**	**1.038**
BS	**0.858**	**0.838**	**0.878**	**0.881**	**0.861**	**0.901**	**1.089**	**1.044**	**1.136**
NO_2	**0.912**	**0.900**	**0.923**	**0.920**	**0.909**	**0.932**	**1.033**	**1.009**	**1.057**
SO_2	**0.727**	**0.699**	**0.756**	**0.748**	**0.720**	**0.776**	**1.081**	**1.006**	**1.162**
O_3	**1.019**	**1.014**	**1.024**	**1.024**	**1.018**	**1.029**	**1.015**	**1.008**	**1.021**

Annex 8: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on all respiratory emergency hospital admissions during winter season of 1992-1999 in the Netherlands

all admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.007**	**1.004**	**1.010**	1.000	0.996	1.004	**0.993**	**0.988**	**0.998**
Bs	1.002	0.996	1.009	0.999	0.988	1.011	0.997	0.985	1.010
NO_2	0.993	0.985	1.002	0.999	0.990	1.008	1.006	0.994	1.018
SO_2	**1.016**	**1.005**	**1.028**	**1.049**	**1.033**	**1.066**	**1.032**	**1.015**	**1.050**

Annex 9: The interaction effects of O_3 with high vs low concentrations of pm10, BS, SO_2 and NO_2 on all respiratory emergency hospital admissions during the summer season of 1992-1999 in the Netherlands

all admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	**1.050**	**1.042**	**1.059**	**1.022**	**1.017**	**1.027**	**0.973**	**0.967**	**0.980**
High vs low BS	**1.022**	**1.013**	**1.030**	**1.029**	**1.024**	**1.034**	**1.007**	**1.000**	**1.014**
High vs low SO_2	1.001	0.994	1.008	**1.026**	**1.021**	**1.032**	**1.026**	**1.020**	**1.031**
High vs low NO_2	**1.019**	**1.012**	**1.026**	**1.026**	**1.021**	**1.032**	**1.007**	**1.001**	**1.013**

Annex 10: The interaction effects of high vs low concentrations of O_3 with pm10, BS, SO_2 and NO_2 on male respiratory emergency hospital admissions during the winter season of 1992-1999 in the Netherlands

male admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.007**	**1.003**	**1.011**	0.999	0.993	1.005	**0.992**	**0.985**	**0.999**
Bs	1.003	0.994	1.011	0.999	0.984	1.014	0.996	0.980	1.013
NO_2	0.994	0.983	1.005	0.999	0.988	1.011	1.006	0.990	1.022
SO_2	**1.019**	**1.004**	**1.034**	**1.054**	**1.032**	**1.076**	**1.035**	**1.012**	**1.058**

Annex 11: The interaction effects of high vs low concentrations of O_3 with pm10, BS, SO_2 and NO_2 on female respiratory emergency hospital admissions during the winter season of 1992-1999 in the Netherlands

female admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.006**	**1.001**	**1.011**	1.001	0.994	1.008	0.995	0.987	1.003
Bs	1.001	0.991	1.011	1.000	0.982	1.018	0.998	0.979	1.018
NO_2	0.992	0.979	1.005	0.998	0.984	1.012	1.005	0.987	1.024
SO_2	1.014	0.996	1.031	**1.043**	**1.017**	**1.069**	**1.029**	**1.002**	**1.056**

Annex 12: The interaction effects of high vs low concentrations of O_3 with pm10, BS, SO_2 and NO_2 on male respiratory emergency hospital admissions during summer season of 1992-1999 in the Netherlands

male admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	**1.051**	**1.040**	**1.062**	**1.021**	**1.015**	**1.028**	**0.972**	**0.964**	**0.980**
High vs low BS	**1.021**	**1.011**	**1.032**	**1.028**	**1.021**	**1.035**	1.006	0.998	1.015
High vs low SO_2	0.999	0.990	1.008	**1.026**	**1.019**	**1.033**	**1.027**	**1.020**	**1.034**
High vs low NO_2	**1.018**	**1.009**	**1.027**	**1.025**	**1.019**	**1.032**	**1.008**	**1.000**	**1.015**

Annex 13: The interaction effects of high vs low concentrations of O_3 with pm10, BS, SO_2 and NO_2 on female respiratory emergency hospital admissions during summer season of 1992-1999 in the Netherlands

female admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	**1.049**	**1.036**	**1.063**	**1.023**	**1.015**	**1.032**	**0.975**	**0.965**	**0.986**
High vs low BS	**1.022**	**1.009**	**1.035**	**1.030**	**1.022**	**1.039**	1.008	0.997	1.019
High vs low SO_2	1.003	0.992	1.014	**1.027**	**1.019**	**1.036**	**1.024**	**1.015**	**1.033**
High vs low NO_2	**1.021**	**1.010**	**1.033**	**1.028**	**1.019**	**1.036**	1.006	0.998	1.015

Annex 14: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on all asthma emergency hospital admissions during winter season of 1992-1999 in the Netherlands

all admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	1.004	0.992	1.016	0.990	0.974	1.006	0.986	0.967	1.006
Bs	1.006	0.982	1.031	0.976	0.935	1.020	0.970	0.925	1.018
NO_2	1.000	0.967	1.034	0.977	0.945	1.010	0.977	0.932	1.023
SO_2	0.984	0.941	1.028	0.999	0.939	1.064	1.016	0.949	1.087

Annex 15: The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on all asthma emergency hospital admissions during summer season of 1992-1999 in the Netherlands

all admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
Pm10	1.004	0.978	1.030	1.012	0.995	1.029	1.008	0.987	1.030
BS	**0.966**	**0.941**	**0.992**	**1.017**	**1.000**	**1.034**	**1.052**	**1.030**	**1.076**
SO_2	**0.967**	**0.946**	**0.989**	1.016	0.998	1.033	**1.050**	**1.031**	**1.069**
NO_2	0.980	0.958	1.003	1.016	0.998	1.033	**1.036**	**1.018**	**1.055**

Annex 16: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on male asthma emergency hospital admissions during winter season of 1992-1999 in the Netherlands

male admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	1.001	0.984	1.018	0.993	0.970	1.016	0.992	0.964	1.020
Bs	1.007	0.972	1.043	0.991	0.932	1.053	0.984	0.920	1.052
NO_2	0.987	0.941	1.036	0.989	0.943	1.037	1.002	0.938	1.070
SO_2	0.973	0.913	1.037	0.988	0.905	1.079	1.015	0.924	1.116

Annex 17: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on female asthma emergency hospital admissions during winter season of 1992-1999 in the Netherlands

female admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	1.006	0.989	1.023	0.987	0.965	1.011	0.981	0.954	1.009
Bs	1.006	0.972	1.041	0.961	0.904	1.023	0.956	0.893	1.022
NO_2	1.013	0.966	1.062	0.965	0.921	1.012	0.953	0.893	1.017
SO_2	0.995	0.935	1.058	1.010	0.923	1.105	1.016	0.922	1.118

Annex 18: The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on male asthma emergency hospital admissions during summer season of 1992-1999 in the Netherlands

male admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	0.994	0.959	1.031	1.017	0.993	1.041	1.023	0.993	1.053
High vs low BS	**0.949**	**0.915**	**0.985**	1.021	0.997	1.045	**1.075**	**1.043**	**1.109**
High vs low SO_2	**0.966**	**0.936**	**0.997**	1.020	0.996	1.044	**1.056**	**1.029**	**1.083**
High vs low NO_2	0.969	0.939	1.001	1.020	0.996	1.044	**1.052**	**1.026**	**1.079**

Annex 19: The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on female asthma emergency hospital admissions during summer season of 1992-1999 in the Netherlands

female admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	1.013	0.976	1.052	1.007	0.983	1.032	0.994	0.964	1.025
High vs low BS	0.983	0.946	1.021	1.012	0.988	1.037	1.030	0.998	1.062
High vs low SO_2	0.968	0.937	1.000	1.011	0.986	1.036	**1.044**	**1.018**	**1.072**
High vs low NO_2	0.990	0.958	1.023	1.010	0.986	1.036	1.021	0.995	1.047

Annex 20: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on total COPD emergency hospital admissions during winter season of 1992-1999 in the Netherlands

all admissions									
pollutants	low O_3			high O_3			High vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.010**	**1.004**	**1.016**	**1.012**	**1.004**	**1.021**	1.002	0.992	1.012
Bs	1.008	0.996	1.020	**1.029**	**1.007**	**1.051**	1.021	0.997	1.045
NO_2	1.004	0.988	1.020	**1.027**	**1.010**	**1.044**	**1.023**	**1.000**	**1.047**
SO_2	**1.026**	**1.005**	**1.047**	**1.074**	**1.042**	**1.106**	**1.047**	**1.014**	**1.081**

Annex 21: The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on total COPD emergency hospital admissions during summer season of 1992-1999 in the Netherlands

all admissions									
pollutants	low concentration			high concentration			High vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
Pm10	**1.079**	**1.062**	**1.097**	**1.031**	**1.021**	**1.041**	**0.955**	**0.943**	**0.968**
BS	**1.042**	**1.026**	**1.059**	**1.037**	**1.027**	**1.047**	0.994	0.982	1.008
SO_2	1.013	0.999	1.026	**1.032**	**1.022**	**1.041**	**1.019**	**1.008**	**1.030**
NO_2	**1.034**	**1.020**	**1.047**	**1.033**	**1.023**	**1.043**	1.000	0.989	1.010

Annex 22: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on male COPD emergency hospital admissions during winter season of 1992-1999 in the Netherlands

male admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	1.009	1.001	1.017	**1.013**	**1.003**	**1.024**	1.005	0.992	1.017
Bs	1.004	0.988	1.020	**1.036**	**1.008**	**1.065**	**1.033**	**1.002**	**1.064**
NO_2	1.002	0.982	1.023	**1.026**	**1.004**	**1.049**	1.024	0.994	1.054
SO_2	1.021	0.994	1.049	**1.085**	**1.044**	**1.127**	**1.063**	**1.020**	**1.108**

Annex 23: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on female COPD emergency hospital admissions during winter season of 1992-1999 in the Netherlands

female admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.013**	**1.003**	**1.022**	1.010	0.997	1.024	0.998	0.982	1.013
Bs	1.014	0.995	1.034	1.017	0.982	1.053	1.003	0.965	1.041
NO_2	1.005	0.980	1.030	**1.028**	**1.001**	**1.056**	1.023	0.987	1.060
SO_2	**1.033**	**1.000**	**1.067**	**1.057**	**1.008**	**1.109**	1.023	0.972	1.077

Annex 24: The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on male COPD emergency hospital admissions during summer season of 1992-1999 in the Netherlands

male admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	**1.091**	**1.068**	**1.113**	**1.029**	**1.017**	**1.042**	**0.944**	**0.929**	**0.960**
High vs low BS	**1.049**	**1.028**	**1.071**	**1.035**	**1.022**	**1.048**	0.987	0.970	1.003
High vs low SO_2	1.013	0.995	1.030	1.030	1.017	1.042	**1.017**	**1.003**	**1.031**
High vs low NO_2	**1.041**	**1.024**	**1.059**	**1.031**	**1.018**	**1.044**	0.990	0.977	1.003

Annex 25: The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on female COPD emergency hospital admissions during summer season of 1992-1999 in the Netherlands

female admissions									
pollutants	low concentration			high concentration			High vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	**1.062**	**1.036**	**1.090**	**1.033**	**1.018**	**1.049**	**0.973**	**0.953**	**0.993**
High vs low BS	**1.033**	**1.007**	**1.059**	**1.039**	**1.024**	**1.055**	1.006	0.986	1.028
High vs low SO_2	1.013	0.991	**1.035**	**1.035**	**1.019**	**1.050**	**1.022**	**1.004**	**1.039**
High vs low NO_2	**1.022**	**1.000**	**1.044**	**1.036**	**1.021**	**1.052**	1.014	0.998	1.031

Annex 26: The differences in relative risk of exposure to Pollutants (10µg/m^3) between males and females (female vs male) cardiovascular admissions during winter season of 1992-1999 in the Netherlands (single pollutant exposure)

cardiovascular risks									
pollutants	male			female			female vs male		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.009**	**1.007**	**1.012**	**1.007**	**1.004**	**1.010**	0.998	0.995	1.002
Bs	**1.012**	**1.006**	**1.017**	**1.010**	**1.003**	**1.016**	0.998	0.991	1.006
NO_2	1.004	0.998	1.010	1.002	0.996	1.009	0.998	0.990	1.007
SO_2	**1.032**	**1.022**	**1.042**	**1.024**	**1.013**	**1.036**	0.993	0.979	1.006
O_3	**0.958**	**0.953**	**0.963**	**0.956**	**0.951**	**0.962**	0.998	0.991	1.005

Annex 27: The differences in relative risk of exposure to Pollutants (10µg/m^3) between males and females (female vs male) cardiovascular admissions during summer season of 1992-1999 in the Netherlands (single pollutant exposure)

cardiovascular risks									
pollutants	male			female			female vs male		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.968**	**0.963**	**0.973**	**0.966**	**0.960**	**0.972**	0.998	0.991	1.005
BS	**0.855**	**0.840**	**0.871**	**0.850**	**0.833**	**0.868**	0.994	0.969	1.019
NO_2	**0.907**	**0.898**	**0.916**	**0.903**	**0.893**	**0.913**	0.996	0.982	1.009
SO_2	**0.699**	**0.678**	**0.720**	**0.690**	**0.667**	**0.715**	0.988	0.948	1.030
O_3	**1.018**	**1.014**	**1.022**	**1.013**	**1.009**	**1.017**	**0.995**	**0.991**	**0.999**

Annex 28: The differences in relative risk of exposure to Pollutants (10µg/m^3) between older and younger (older vs younger) cardiovascular admissions during winter season of 1992-1999 in the Netherlands (single pollutant exposure)

cardiovascular risks									
pollutants	younger (15-44 yrs)			older (75+ yrs)			older vs younger		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.008**	**1.005**	**1.010**	**1.008**	**1.006**	**1.010**	1.001	0.997	1.005
Bs	**1.009**	**1.004**	**1.014**	**1.011**	**1.006**	**1.015**	1.005	0.997	1.013
NO_2	1.003	0.997	1.008	1.003	0.998	1.007	1.002	0.993	1.010
SO_2	**1.029**	**1.019**	**1.038**	**1.028**	**1.020**	**1.037**	1.000	0.986	1.014
O_3	**0.957**	**0.953**	**0.962**	**0.957**	**0.952**	**0.961**	0.999	0.992	1.006

Annex 29: The differences in relative risk of exposure to Pollutants (10μg/m^3) between older and younger (older vs younger) cardiovascular admissions during winter season of 1992-1999 in the Netherlands (single pollutant exposure)

cardiovascular risks									
pollutants	younger (15-44 yrs)			older (75+ yrs)			older vs younger		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**0.967**	**0.962**	**0.972**	**0.967**	**0.962**	**0.971**	1.000	0.993	1.007
BS	**0.854**	**0.840**	**0.869**	**0.852**	**0.840**	**0.865**	0.996	0.970	1.022
NO_2	**0.907**	**0.898**	**0.915**	**0.904**	**0.897**	**0.912**	0.996	0.982	1.010
SO_2	**0.693**	**0.673**	**0.713**	**0.695**	**0.678**	**0.712**	1.008	0.966	1.053
O_3	**1.014**	**1.011**	**1.018**	**1.015**	**1.012**	**1.019**	1.003	0.999	1.007

Annex 30: The interaction effect of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on all cardiovascular emergency hospital admissions during winter season of 1992-1999 in the Netherlands

all admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.009**	**1.007**	**1.012**	1.001	0.997	1.004	**0.992**	**0.988**	**0.996**
Bs	**1.007**	**1.002**	**1.012**	**0.993**	**0.984**	**1.002**	**0.986**	**0.976**	**0.996**
NO_2	0.996	0.989	1.003	**0.986**	**0.979**	**0.993**	0.990	0.980	1.000
SO_2	**1.018**	**1.009**	**1.027**	**1.026**	**1.013**	**1.039**	1.008	0.994	1.021

Annex 31: The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on all cardiovascular emergency hospital admissions during summer season of 1992-1999 in the Netherlands

all admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
Pm10	**1.071**	**1.065**	**1.077**	**1.016**	**1.013**	**1.020**	**0.949**	**0.944**	**0.954**
BS	**1.026**	**1.020**	**1.032**	**1.023**	**1.019**	**1.026**	0.997	0.992	1.002
SO_2	**1.007**	**1.002**	**1.012**	**1.016**	**1.013**	**1.020**	**1.010**	**1.006**	**1.014**
NO_2	**1.026**	**1.021**	**1.031**	**1.018**	**1.014**	**1.022**	**0.992**	**0.989**	**0.996**

Annex 32: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on male cardiovascular emergency hospital admissions during winter season of 1992-1999 in the Netherlands

male admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.010**	**1.006**	**1.013**	1.003	0.998	1.007	**0.993**	**0.988**	**0.998**
Bs	**1.008**	**1.001**	**1.015**	0.996	0.984	1.008	0.988	0.975	1.001
NO_2	0.997	0.988	1.006	**0.989**	**0.980**	**0.998**	0.992	0.979	1.005
SO_2	**1.023**	**1.011**	**1.035**	**1.029**	**1.012**	**1.046**	1.006	0.988	1.024

Annex 33: The interaction effects of PM10, BS, SO_2 and NO_2 with O_3 (high/low O_3) on female cardiovascular emergency hospital admissions during winter season of 1992-1999 in the Netherlands

female admissions									
pollutants	low O_3			high O_3			high vs low O_3		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
PM10	**1.008**	**1.005**	**1.012**	0.998	0.993	1.004	**0.990**	**0.984**	**0.996**
Bs	1.006	0.998	1.014	0.989	0.975	1.003	**0.983**	**0.968**	**0.998**
NO_2	0.996	0.985	1.007	0.983	0.972	0.994	0.987	0.972	1.002
SO_2	1.011	0.997	1.025	1.021	1.002	1.041	1.010	0.990	1.032

Annex 34: The interaction effects of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on male cardiovascular emergency hospital admissions during summer season of 1992-1999 in the Netherlands

male admissions									
pollutants	low concentration			high concentration			high vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	**1.077**	**1.069**	**1.085**	**1.020**	**1.015**	**1.025**	**0.947**	**0.941**	**0.953**
High vs low BS	**1.030**	**1.022**	**1.038**	**1.026**	**1.021**	**1.031**	0.996	0.990	1.003
High vs low SO_2	**1.008**	**1.001**	**1.014**	**1.019**	**1.015**	**1.024**	**1.012**	**1.006**	**1.017**
High vs low NO_2	**1.028**	**1.022**	**1.035**	**1.021**	**1.016**	**1.026**	**0.993**	**0.988**	**0.998**

Annex 35: The interaction effect of O_3 with PM10, BS, SO_2 and NO_2 (high/low) on female cardiovascular emergency hospital admissions during summer season of 1992-1999 in the Netherlands

female admissions									
pollutants	low concentration			high concentration			High vs low conc.		
	RR	CI-low	CI-high	RR	CI-low	CI-high	RR	CI-low	CI-high
High vs low Pm10	**1.064**	**1.054**	**1.073**	**1.012**	**1.006**	**1.018**	**0.952**	**0.945**	**0.959**
High vs low BS	**1.022**	**1.012**	**1.031**	**1.018**	**1.013**	**1.024**	0.997	0.989	1.004
High vs low SO_2	1.005	0.997	1.013	**1.012**	**1.006**	**1.017**	**1.006**	**1.000**	**1.013**
High vs low NO_2	**1.023**	**1.015**	**1.030**	**1.014**	**1.008**	**1.020**	**0.992**	**0.986**	**0.998**