A new global Air Quality Health Index based on the 2021 WHO Air Quality Guideline Values

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DEDICATION

I would like to dedicate this PhD thesis to my Late Grandma, Mrs. Rufina Aina Ojo. I wish you were here to see me being one of your deepest and wildest dreams.

Granma, I did it!

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LIST OF ABBREVIATIONS

AQA	Air Quality Act
AQHI	Air Quality Health Index
AQG	Air Quality Guideline
AQI	Air Quality Index
AQMP	Air Quality Management Plan
CI	Confidence Interval
CVD	Cardiovascular Diseases
CT	Cape Town
DLNM	Distributed lag non-linear model
DFFE	Depart of Forestry, Fisheries and the Environment
EPA	Environmental Protection Agency
GBD	Global Burden of Disease
GDP	Gross Domestic Product
IQR	Interquartile Range
LMIC	Low- and middle-income country
NAAQS	National Ambient Air Quality Standards
NCD	Non-Communicable Diseases
NO_2	Nitrogen dioxide
O_3	Ozone
PM	Particulate matter
$PM_{2.5}$	PM with aerodynamic less than or equal to 2.5 micrometers
PM_{10}	PM with aerodynamic less than or equal to 10 micrometers
RD	Respiratory Diseases
RR	Relative risk
SA	South Africa
SAAQIS	South Africa Air Quality Information Systems
SAWS	South Africa Weather Services
SDG	Sustainable Development Goals
SES	Socio-Economic Status

SSA	sub-Saharan Africa
SO_2	Sulfur dioxide
Tapp	Apparent temperature
WHO	World Health Organization

SUMMARY

As Africa continues to grow with rapid urbanization and industrialization, the downside is that air pollution is the second leading cause of death on the continent; yet its health effects remain largely unquantified. This is evidenced by global systematic reviews and multi-city studies in which South Africa was the only country included. This thesis addressed two major research gaps in South Africa. First, it examined the short-term effects of multiple ambient air pollutants on cardiorespiratory hospitalizations and mortality. Second, it proposed a revised methodology for the Air Quality Health Index (AQHI) that references the long-term WHO 2021 Air Quality Guideline values. This would allow the scientific evidence to be properly reflected in the interpretation of short-term concentrations. The constructed index was applied using air pollution data from Cape Town.

The study used daily air pollution, temperature, relative humidity data from the City of Cape Town, with hospital admissions (2011-2016) and mortality (2006 – 2015) data collected from six private hospitals and the South African Department of Statistics, respectively. For both hospital admissions and mortality due to cardiovascular and respiratory diseases, time-series analyses of daily health outcomes and air pollution were conducted using generalized additive quasi-Poisson models within a distributed lag non-linear modelling framework to estimate the cumulative effects. In addition, independent effects of multi-pollutant were examined and analyses were stratified by age group, sex, and season. The AQHI was constructed using effect estimates from two global systematic reviews and meta-analyses. Excess risks (ER) were derived for $PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3. Single pollutant AQHIs were developed and scaled using the ERs at the WHO 2021 long-term Air Quality Guideline (AQG) values to define the "low risk". The daily total AQHI is the weighted average of the single AQHIs.

In the first part, we found a robust association between air pollution and cardiorespiratory health outcomes, with stronger effects among the female group and the elderly, with evidence of mortality displacement among the elderly. The second part of the thesis showed that the daily air quality posed "low risk" to the Cape Town population on 11% of the days within our study period. In addition, there was inconsistent improvement in the daily air quality over the decade, with the last year (2015) having the highest number of "low risk" days (28%).

This thesis adds to the growing body of evidence on the cardiorespiratory health effects of short-term exposure to air pollution and proposes a new tool for communicating air quality.

CHAPTER 1:

Background

1. Air pollution: the single biggest environmental threat to human health

The short-term (acute) and long-term (chronic) health effects of air pollution are well documented as shown in Figure 1.(1) As of 2019, the global burden of disease (GBD) attributable to ambient particulate matter (PM) pollution was estimated at 105 (95% Uncertainty interval: 95.9 – 138 million) million years of life lost and 4.14 (3.45 – 4.80) million premature deaths of which 95% occurred in low- and middle-income countries – making it the 6th leading risk factor for global deaths.(2) This is a conservative estimate as it does not consider the contribution from other ambient air pollutants such as gases. High-income countries have made significant efforts to reduce emissions and the disease burden associated with ambient air pollution, resulting in improved air quality, in contrast to most low- and middle-income countries (LMIC) where the air quality has generally worsened.(3) According to the State of Global Air report, air pollution is the second leading risk factor for death after malnutrition in Africa where it contributed to 1.1 million deaths in 2019, of which 37% were related to ambient air pollution. The continent is also home to half of the world's 10 most polluted countries with high levels of ambient $PM_{2.5}$.(4) Increasing levels of air pollution and its health impacts may partly explain the region's the ongoing epidemiological transition from communicable disease to non-communicable diseases (NCDs), with a 67% increase in the prevalence of NCDs between 1990 and 2017.(5)

A World Bank economic assessment of the global costs of air pollution and its health burden found that air pollution and its related diseases impose a significant economic burden, equivalent to an average of 6.5% of gross domestic product (GDP) across Africa. The combined annual cost of these damages from $PM_{2.5}$ exposure for countries such as the Democratic Republic of the Congo, Egypt, Ghana, Kenya, and South Africa is over 5.4 billion U.S. dollars.(6) The upward trend of air pollution in sub-Saharan Africa (SSA) driven by large-scale urbanization, economic development, and heavy reliance on the burning of fossil fuels is preventing the region from improving its air quality.

In South Africa, approximately 50 million of the population (95%) were exposed to harmful concentrations of ambient PM with aerodynamic diameter <2.5 µm ($PM_{2.5}$) and ozone (O_3) with measurements above the National Ambient Air Quality Standards (NAAQS) of 10 µg/m^3

and 120 µg/m^3, respectively.(7) Mpumalanga, SA, is the world's largest nitrogen dioxide (NO_2) and Sulphur dioxide (SO_2) hotspot and home to a cluster of 12 coal-fired power plants with a total of 32 gigawatts.(8) According to the 2022 Ember report, SA generated at least 87% of its electricity from coal burning which accounts for 42% of the country's total emission.(9, 10) SA's Department of Mineral Resources and Energy, announced that coal production, and its use will continue for the next 20 years as there is a lack of suitable clean energy alternatives.(11) In 2017, renewable energy power producers provided 3162 MW (megawatt) of electricity which was connected to the national electricity grid.(11) Other sources of pollution in SA include traffic, metallurgic, mining, industry, domestic fuel burning, and agriculture.

1.1 Epidemiological evidence of short-term effects of air pollution in South Africa.

Majority of the studies that examined the influence of air pollution on health outcomes, mainly self-reported illnesses in SA, were cross-sectional – with only a few short-term association studies. Short-term effects are effects experienced after being exposed to air pollution for a few hours or days, which may result in irritation to the nose, throat, skin, and eyes; illnesses such as bronchitis, pneumonia, or myocardial infarctions, and death. In contrast, long-term effects are the result of cumulative long-term or lifetime exposure resulting in chronic ailments, diseases, and ultimately decreased life expectancy due to these effects (e.g. lung cancer, chronic obstructive lung diseases, or atherosclerosis and heart diseases).(12) This thesis focused on the acute effects of air pollution in Cape Town, South Africa. In 2012, cardiovascular diseases and lower respiratory infections made up 38% and 24%, respectively of the deaths attributed to $PM_{2.5}$ in SA.(7) A study in Cape Town found strong short-term associations between daily mean concentrations of three of the criteria pollutants (PM_{10}, SO_2, and NO_2) and deaths caused by cerebrovascular disease (CBD), respiratory (RD) and cardiovascular diseases (CVD). An interquartile range (IQR) increase for NO_2 (12 µg/m^3) and PM10 (12 µg/m^3) significantly increased CBD by 4% and 8% respectively, while 8 µg/m^3 and 12 µg/m^3 IQR increase in SO_2 and NO_2 significantly increased CVD by 3% respectively. (13)

Another multi-city study in SA that included Cape Town, Durban, and Johannesburg examined the associations between PM_{10}, NO_2, SO_2 and deaths due to RD and CVD. The authors reported for Cape Town, a 3.5% increased risk for CVD deaths was associated with an IQR rise of 17µg/m^3 in PM_{10}. This was the only significant association observed in the study for all the pollutants, health outcomes and cities.(14) SA has been included in two large multi-city studies on mortality where the authors reported that for a 10µg/m^3 change in ozone, PM_{10} and $PM_{2.5}$

there was an increased risk of 0.27% (95% CI: 0.13 – 0.42), 0.41% (95% CI: 0.14 – 0.68%) and 0.8%(95% CI: 0.16 – 1.44%), respectively.(15, 16) Other studies investigated temperature as a modifier of the effects of air pollution on health. A study in Secunda, one of SA's air pollution hotspots, reported an increased risk of 8.2% (95% CI: 1.3 – 15.6%) and 13.5% (95% CI: 0.4 – 28.3%) in daily RD hospital admissions for a 10µg/m^3 increase in $PM_{2.5}$ and SO_2, respectively during warms days (18.9 ºC).(17)

This thesis aimed to improve on the limited body of evidence on the short-term effects of air pollution on cardio-respiratory health in SA – with a particular focus on exposure due to multiple pollutants. It will also propose a new tool for communicating air quality.

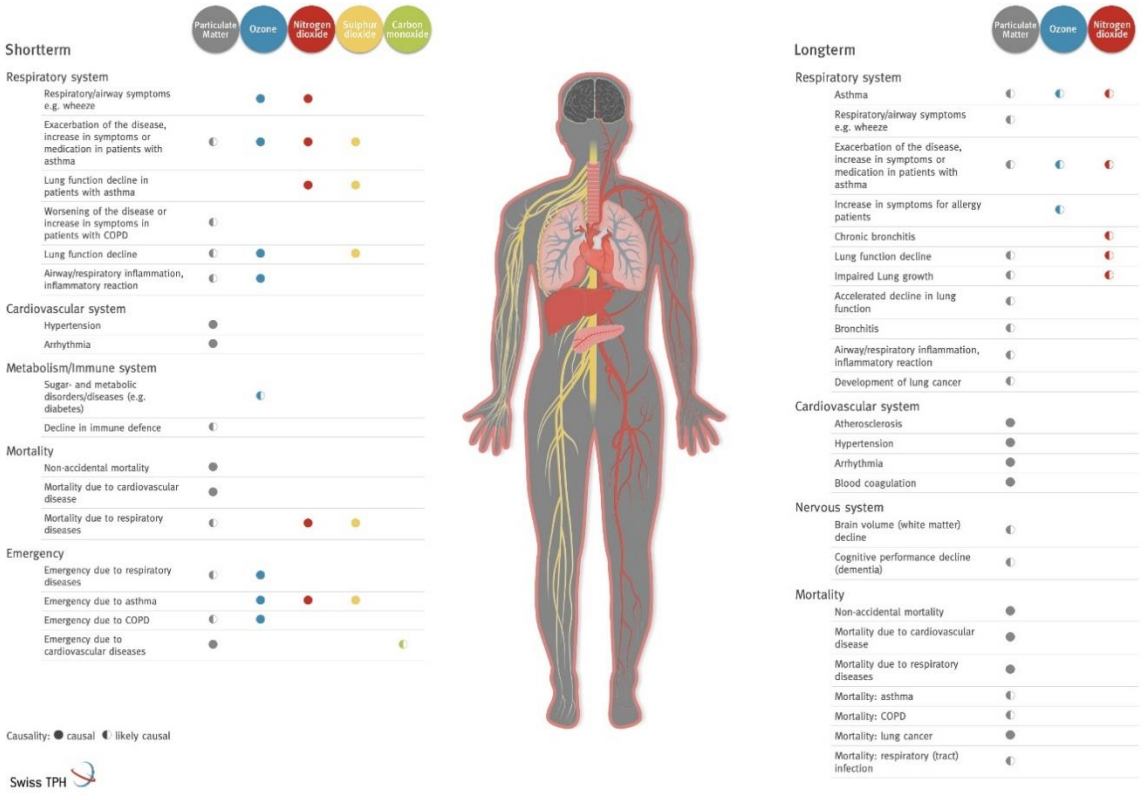

Figure 1: short and long-term health effects of ambient particulate matter (PM) and gaseous pollutants(1)

1.2 Combined effects of multiple pollutants

The effect estimates from most epidemiological studies on air pollution and health are based on ambient exposure to a single pollutant. However, people are exposed to a complex mixture of particles and gases in their environment – therefore, single pollutant analysis does not adequately capture the adverse effects of simultaneous exposure to multiple pollutants. In addition, most air quality policies and tools are geared towards single-pollutant strategies and

assessments. For example, criteria pollutants are identified where the scientific literature provides robust evidence of the effect of a pollutant on multiple health endpoints.(18) Consequently, numerical standards are set with an appropriate safety margin, and emission-control strategies are implemented to achieve these standards.(18) The multi-pollutant approach could support the full categorization of the complexity of the pollutant exposures and their health effects; identification of the most harmful sources of pollution (e.g. industry, agriculture, or transport); targeted regulation; effective air quality management (e.g. targeted reduction of PM sources, which would reduce the ozone concentrations).(18) However, this approach poses challenges such as the need for sound methodology and statistical techniques to estimate the independent effects of multiple pollutants, especially when they are highly correlated or when their interactions are tested. Time-series studies are primarily used to investigate short-term associations between air pollution and the acute onset of health problems. A time-series approach is used to relate daily variations in ambient air pollution levels to daily variations in the mortality or morbidity rates for diseases or conditions.(19) Time-series analysis of data requires careful consideration of seasonal trends and adjustment for other temporally co-varying factors such as temperature and other climate-related variables and gaseous co-pollutants.(20)

Given that air pollution is a complex mixture, it is understandable that there are a variety of possible options for dealing with the issues of multi-pollutant exposure and joint effects; such as dimension reduction, regression shrinkage, and penalization methods. However, the simplest approach would be to include all criteria air pollutants together with their interaction terms in a single regression model when examining the association with a particular health outcome. However, many ambient air pollutants are highly correlated with each other over time (i.e., from day to day), and adding them together in a regression model will result in an unstable model. As the number of air pollutants being included in a regression model increases, the number of possible second-order interactions becomes too large to include in any single model and these are rarely considered. Testing only a specific subset of these interaction terms requires considerable a priori knowledge of complex interactions. As model complexity increases, so does the challenge of interpretation. In addition, parameter estimates become increasingly unstable as the number of interaction terms increases. Other reasons for not using single-pollutant statistical methods to investigate the multi-pollutant exposures and their joint health effects include measurement error and potential non-linear relationships between levels

of air pollutant exposure and specific health outcomes.(21) Thus, there is a need to consider other options to deal with the multi-pollutant exposure and joint effect issues.

1.3 Further risk factors of cardio-respiratory health

Acute cardio-respiratory health can be triggered by other environmental exposures and may confound the association between air pollution and cardio-respiratory health. This is particularly the case for temperature and relative humidity, whereby the risk of morbidity or mortality can increase or reduce due to acute heat and cold exposure.

1.3.1 Temperature

Non-optimal temperature was listed as an environmental risk factor for the first time in the 2019 GBD study. It was estimated that 1.69 million deaths globally were attributable to non-optimal temperature (6 ºC – 28 ºC) and this burden was largely driven by cardiorespiratory and metabolic diseases.(22) The authors reported a protective effect of cold temperatures resulting in a negative cold-attributable burden in SA of -2.79 deaths per 100 000 (95% CI -3.49 – -2.13) and non-optimal temperature was attributed to 15.86 deaths per 100 000 (95% CI 14.11 – 17.67).(22) A national temperature-mortality association study in SA, which included 8.5 million recorded death between 1997 and 2013. Low and high temperatures (1st and 99th percentile of the temperature distribution) were attributed to 3% and 0.4% of the proportion of deaths nationwide, in addition, the risks were higher for CVD, RD, and in the youngest and oldest groups.(23) Wichmann investigated the association between daily apparent temperature (Tapp) and all-cause-non-accidental mortality in three major South African cities namely Cape Town, Durban, and Johannesburg. The strongest association was observed in Cape Town with a 3.3% increase in mortality per IQR increase in Tapp (13 ºC) above the city-specific threshold (18.6 ºC). The risk was particularly higher among the age group >65+ with women (9.6%) being significantly more vulnerable than men in comparison to the younger age groups.(24) A recent study on temperature variability and hospital admissions of CVD and RD in Cape Town, reported a total effect estimate of 2.68% (95% CI: 1.27 – 4.11%) at lag 0-3 and 2.79 (95% CI: 1.44 – 4.17) at lag 0-1 for CVD and RD hospitalizations, respectively.(25) Relative humidity is often included as a confounding factor in environmental epidemiological studies because it is a function of the changes in air temperature and water vapour and therefore may not be directly related to health outcomes. It is also usually included in the calculation of apparent temperature.(26)

1.4 Air Quality Index vs Air Quality Health Index

Many studies, mostly conducted in Europe and North America have demonstrated the influence of air pollution on various health outcomes for emergencies, hospital admissions and, more seriously, deaths. In addition, these studies have shown that there is no level at which the effect of air pollution is non-existent, i.e., threshold of no effect. Liu et al., showed a consistent increase in the concentration-response curve between mortality and both PM measurements with no indication of a threshold.(16) The 2021 WHO report states that for all the criteria pollutants there is no evidence of a concentration below which the risk of adverse health effects is zero.(3) However, this is rarely taken into account in air quality communication tools such air quality index (AQI). The primary purpose of an AQI is to provide the public with information that allows them the opportunity to monitor the state of air quality in their area without having to understand the complexities of individual pollutants and the construction of the index. As a result, the public has a simple guide to take necessary action to protect themselves from the adverse health effects of air pollution. Some of these actions include limiting strenuous outdoor activities when air pollution levels are high and choosing the most appropriate time of day and following medical advice on the treatment of pre-existing conditions such as asthma. It also raises awareness of the effects of exposure to air pollution and encourages changes in individual behaviour and public policy. This can ultimately lead to a reduction in air pollution emissions from anthropogenic sources, and consequent improvements in public health.(27)

The (AQI) is formulated based on ambient concentrations of criteria pollutants, such as SO_2, PM_{10}, NO_2, CO and O_3, and $PM_{2.5}$ where each pollutant is compared with its air quality limit value, and the pollutant with the highest value relative to its limit value is reported as the AQI, thus providing a single integrated measure of "air quality".(28) In this method, one pollutant determines the index and pollutants with lower values are not considered in relation to their limit value. Thus, the cumulative effect is not captured. (29)

AQIs have been used as a single-exposure approach to reflect the amount of air pollution present at a given time and its health significance.(30) Data from fixed-site monitors are used to assess population exposure.(31) Most of the AQIs differ in the calculation method (e.g. number of air pollutants determining the final index value) and in the number, range, area of origin, and, – if they are health impact-related – the corresponding health effects associated with different index classes. The AQI values are often scaled to different ranges (e.g., 0 – 50, 0 – 100, and 0 – 500), and presented in aggregated categories represented with colours and

descriptions. The index is considered to be a simple and understandable way of measuring air quality in terms of its effects on human health.(32)

The main criticism of the AQI is that the current state of the index does not accurately reflect our understanding of the adverse health effects of ambient air pollution, particularly the occurrence of effects at low levels of exposure. It cannot reflect additive, interactive, or non-linear effects. In 2001, a review of Ontario's AQI reported that 92% of mortalities and hospitalizations attributed to short-term effects of air pollution occurred at times when the AQI was in the "very good" or "good range".(33) This shows that the concentration range used to classify air quality as "good" or "very good" does not always correspond to the level of pollutants causing adverse health effects. It also highlights the endemic nature of the effects of air pollution, which are not accurately reflected in the standard-based AQI and the contradiction between the levels of air pollution and its classification of "good" or "green".

The Air Quality Health Index (AQHI) is based on a multi-pollutant modeling approach, as opposed to the single pollutant approach of the AQI. It considers the combined effects associated with simultaneous exposure to multiple pollutants. The AQHI considers the overall health effect as the sum of the mortality effects associated with each pollutant independently.(31) Table 1 shows the AQHIs developed in other studies(29-31, 34, 35) where they assumed additive effects of the pollutants. The concentrations of individual pollutants are weighted by their effect estimates to quantify the percentage risk of a particular health outcome, which could be death or hospital admissions. The percentage increase for each pollutant is added together to give the overall risk attributed to the pollutant mixture. This overall risk is presented on an arbitrary scale, with low values representing "low risk" and vice versa. This approach results in an epidemiology-based index that is more directly linked to a specific health endpoint.(36) An important distinction is that the AQHI has been shown to detect the risk of excess deaths even at low levels of air pollution. For example, in Canada, when the AQHI was reported to be "moderate risk" (AQHI: 3 - 6), the range of excess daily mortality risk was 2.6% - 6.8%. These deaths were likely to occur in vulnerable groups such as infants, the elderly or people with respiratory or cardiovascular diseases.(37) It is clear that reports based on daily values and standards for daily concentrations can be misleading especially when the results are green or "healthy". The consequence of this is that the "clean" categories include

concentrations well above the health-based long-term air quality standards set to protect the public's health. Using the traditional reporting method can therefore misinform the public, as relatively high daily concentrations can be considered "healthy" on most days of the year, with an annual average that is well above the air quality guideline set for annual averages.

A crucial aspect of this thesis was to develop an AQHI that comprehensively accounts short-term effects of multi-pollutants and incorporates the WHO 2021 AQG long-term values to classify the "green" or "low risk" level.

1.5 Environmental health equity

The uneven distribution of air pollution and its associated health effects across the population contributes to health inequalities, as socially disadvantaged groups bear a disproportionate burden of exposure to high and harmful levels of air pollution. These inequalities also exist in terms of who produces the pollution and who suffers the consequences - high-income countries are associated with high carbon footprints, but the effects are worse in poorer countries.(38) Environmental inequalities also revolve around economic gain, as in the case of Swiss commodity trading companies that deliberately took advantage of lax standards in Africa and sold dirty diesel with excessively high sulphur content (3000 ppm), resulting in poor air quality as reported by the public eye.(39) The revelation caused an outcry in West Africa and led to a new binding standard with a sixty-fold reduction in the permitted sulphur content (50 ppm) for diesel imports.(39)

Other material indicators such as low socio-economic status (SES), education level, poor housing, and living area may influence an individual's sensitivity and resilience in adapting to or avoiding future risks associated with exposure to air pollution. In SA, poor land use planning in the past has resulted in heavy industrial developments being located close to densely populated residential areas. Studies in SA have shown adverse health effects in children attending schools in the vicinity of coal mines and mine dumps due to exposure to high levels of PM_{10}, NO_2, SO_2, O_3 and indoor respirable dust compared to those further away.(40-42) Another study found a positive association between $PM_{2.5}$ and self-reported cardiovascular morbidity (chest pain) in adults living in four informal settlements in the Western Cape Province of SA.(43)

Cape Town is the fourth most unequal city in the world because of its extreme inequality; Figure 2 shows an aerial view of a typical part of the city. The crowded informal settlement (Imizamo Yethu) is a black community with people squatting in shacks separated by greenery from the

affluent neighborhood with a wealthy, mainly white community. Hout Bay is a microcosm of SA where race is a social determinant of health and a key indicator of vulnerability to disease. A World Bank report identified race as a key factor in SA's inequality, where 80% of the country's wealth is owned by 10% of the population; ethnicity contributes 41% to income inequality and 30% to education inequality.(44) This inequality is compounded by the legacy of colonialism and apartheid, which are embedded in the racial and spatial segregation. As a result, communities like Imizamo Yethu lack adequate infrastructure such as energy supply, water and sanitation, transport system, and education. This leads to a heavy reliance on solid fuels for the generation of energy for heating and cooking thus resulting in consistently high levels of pollution. In some cases, the use of solid fuels, open burning of waste and adverse weather conditions has led to the rapid spread of wildfires. It is therefore important to consider individual susceptibility, social and economic characteristics, and their capacity to respond to environmental exposures, in addition to their varying levels of exposure, when examining their associated health outcomes.

1.6 Current air quality policy in South Africa

In SA, Section 24 of the constitution and the National Environmental Air Quality Act (AQA, 2004) charges the government with the role of ensuring the resident's right to a healthy environment that is protected from pollution and ecological degradation - that is people are entitled to breathing air that is not harmful to their health and wellbeing.(45) To fulfill this mandate, SA has been monitoring and evaluating its air quality, in addition the country implemented an AQI in 2018. SA's monitoring network consists of 121 government-managed ambient air quality monitoring stations, with seven of the nine provinces in the country having an air quality management plan (AQMP).(46) Although there are 278 municipalities in SA and the 2004 Air Quality Act requires one station per municipality to ensure widespread spatial coverage for effective compliance monitoring, more than half of the municipalities have yet to implement this Act, leaving certain areas unmonitored.(46) Nevertheless, SA has one of the most comprehensive air quality monitoring networks in SSA.

South Africa has strong air quality policies, but it lacks adequate implementations, which contributes to the inaction towards achieving clean air. As alluded to in the background of this thesis, the reliance on coal for electricity generation accounts for at least 42% of South Africa's emissions. In 2021, at the United Nations Climate Change Conference (UNFCC COP26) South Africa announced its Just Energy Transition (JET);(47) an ambitious long-term plan to

decarbonize its energy and transition the country to cleaner and renewable energy sources in partnership with other international groups and countries.

Figure 2: Hout Bay, Cape Town, South Africa(48)

Table 1: Developed AQHI by study area, pollutants, index and scaling

Study area	Pollutants	Index	Banding scale and health risks
Guangzhou, China(49)	SO_2, NO_2, $PM_{2.5}$ and O_3	$AQHI_t = \frac{10 * daily\ total\ ER_t}{max\ (daily\ total\ ER_1, daily\ total\ ER_2, \ldots\ daily\ total\ ER_n)}$	0 – 3: low 3 – 4: moderate 4 – 6: unhealthy for vulnerable population 6 – 9: high 9+: serious
Canada – multi-city(30)	NO_2, O_3 and $PM_{2.5}$	$AQHI = \left({}^{10}/_{c}\right) \sum_{i=1\ldots p} 100\ (e^{B_i x_i} - 1)$	0 – 3: low risk 4 – 6: moderate risk 7 – 10: high risk 10+: very high risk
Hong Kong, China(34)	NO_2, O_3, PM_{10} and SO_2	$\%ER = \sum_{i=1\ldots p} 100\ (e^{B_i x_{ij}} - 1) * 100\%$	1 – 3: low 4 – 6: moderate health risk 7: high 8 – 10: very high 10+: serious
EPA Adjusted Health Based Index (AHBI)(50)	$PM_{2.5}$, O_3, NO_2 and SO_2	$AHBI = \left(\frac{10}{M}\right) \sum_{t=i\ldots p} \ln[100(e^{B_i X_{it}} - 1)]$	No scale
Shanghai, China(51)	$PM_{2.5}/NO_2$ PM_{10}/NO_2	$PM_{2.5} = \frac{10}{15} * 100 * [exp(0.000172 * PM_{2.5}) - 1 + exp(0.000664 * NO_2 - 1)]$ $PM_{10} = \frac{10}{17} * 100 * [exp(0.000154 * PM_{10}) - 1 + exp(0.000664 * NO_2 - 1)]$	0 – 3: low risk 4 – 6: moderate risk 7 – 10: high risk 10+: very high risk

Stockholm, Sweden(29)	NOx, O_3, PM_{10} and birch pollen	$AQHI = \sum_{i=1\ldots p} 100\ (e^{B_i X_i} - 1)$	No scale
Cote d'Azur, France(35)	$PM_{2.5}$, PM_{10}, O_3, NO_2 and SO_2	$ARI = \sum_i (RR_i - 1) = \sum_i index_i = \sum_i a_i * C_i$	Risk of mortality/morbidity using WHO studies 1 – 3: low risk of increased 0.7 to 2.9% 4 – 6: moderate risk of increased 3.0 to 5.1% 7 – 9: high risk of increased 5.2 to 7.5% 10: very high risk of increase > 7.5%
Cape Town, South Africa(31)	$PM_{2.5}$, PM_{10}, O_3, NO_2, CO and SO_2	$ARI = \sum_i PSI_i = \sum_i a_i * C_i$	Risk of mortality 1 – 3: low risk of increased 1.5 to 6.0% 4 – 6: moderate risk of increased 6.1 to 10.6% 7 – 9: high risk of increased 10.7 to 15.3% 10: very high risk of increase > 15.3%

1.7 Study objectives

The initial aim of this thesis was to develop an Air Quality Health Index (AQHI) for the City of Cape Town; however, the 2021 WHO Air Quality Guideline (AQG) and the associated effect estimates from the systematic reviews provided an opportunity to move from a single-city based index to a global index, which was then applied to the Cape Town. According to the original plan, it was necessary first to investigate the associations between multiple air pollutants and health in Cape Town.

1.7.1 Goals

Develop an air quality health index based on the WHO AQG values

1.7.2 Hypothesis

The combined effects of ambient air pollutants exceed those captured by the parallel assessment of single pollutant effects on public health. Thus, single pollutant risk assessments may underestimate the burden of acute effects of ambient air pollution.

1.7.3 Research question

What is the association between daily multiple pollutants and health in Cape Town?

1.7.4 Specific objectives

I. To investigate the association between daily multiple pollutants (PM_{10}, NO_2, and SO_2) and daily hospital admissions?

II. To investigate the association between daily multiple pollutants (SO_2, NO_2, SO_2 and O_3) and daily mortality?

III. Develop an AQHI and apply to the City of Cape Town using data from 2006 - 2015

1.7.5 Thesis structure

The acute effects of multiple air pollutants are presented in Chapters 2 and 3, while Chapter 4 shows the construction and application of the global AQHI. Chapter 5 presents the general discussion, conclusions, and outlook.

Acute health effects of multiple air pollutants

CHAPTER 2:

Short-Term Joint Effects of SO_2, NO_2 and SO_2 on Cardio-Respiratory Disease Hospital Admissions in Cape Town, South Africa

Article

Short-Term Joint Effects of PM_{10}, NO_2 and SO_2 on Cardio-Respiratory Disease Hospital Admissions in Cape Town, South Africa

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Abstract: Background/Aim: In sub-Sahara Africa, few studies have investigated the short-term association between hospital admissions and ambient air pollution. Therefore, this study explored the association between multiple air pollutants and hospital admissions in Cape Town, South Africa. Methods: Generalized additive quasi-Poisson models were used within a distributed lag linear modelling framework to estimate the cumulative effects of PM_{10}, NO_2, and SO_2 up to a lag of 21 days. We further conducted multi-pollutant models and stratified our analysis by age group, sex, and season. Results: The overall relative risk (95% confidence interval (CI)) for PM_{10}, NO_2, and SO_2 at lag0–1 for hospital admissions due to respiratory disease (RD) were 1.9% (0.5–3.2%), 2.3% (0.6–4%), and 1.1% (−0.2–2.4%), respectively. For cardiovascular disease (CVD), these values were 2.1% (0.6–3.5%), 1% (−0.8–2.8%), and −0.3% (−1.6–1.1%), respectively, per inter-quartile range increase of 12 ug/m^3 for PM_{10}, 7.3 ug/m^3 for NO_2, and 3.6 ug/m3 for SO_2. The overall cumulative risks for RD per IQR increase in PM_{10} and NO_2 for children were 2% (0.2–3.9%) and 3.1% (0.7–5.6%), respectively. Conclusion: We found robust associations of daily respiratory disease hospital admissions with daily PM_{10} and NO_2 concentrations. Associations were strongest among children and warm season for RD.

Keywords: ambient air pollution; cardiovascular disease; respiratory disease; multi pollutant; short-term; DLNM; Cape Town; South Africa; time-series analysis

1. Introduction

Over four million deaths are attributed to outdoor air pollution yearly, as reported by the World Health Organization (WHO); the majority of these deaths are largely cardiovascular and respiratory diseases (52). Air pollution is the biggest threat to public health, of which the highest exposure is in low- and middle-income countries (53). In these countries, the air quality levels are not compliant with the new WHO guideline values nor the previous ones (3, 52).

Air pollution is composed of a complex mixture of gases and particulate matter. The most common pollutants are nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ground-level ozone (O_3), carbon monoxide (CO), and particulate matter (PM). PM are subdivided on the basis of their sizes: particles with 2.5 microns in diameter or less are $PM_{2.5}$, while particles up to 10 microns in diameter are PM_{10}. The mixtures and concentrations of these pollutants differ by countries.

Several studies have demonstrated the short-term associations of ambient air pollutants with cardio-respiratory diseases and death. An Italian study reported a 10 $\mu g/m^3$ increase in ambient NO_2 was associated with 1.19% (0.23–2.15%) and 1.20% (0.17–2.23%) increases in respiratory disease (RD) and in chronic obstructive pulmonary disease (COPD) hospital admissions, respectively. In addition, a 10 $\mu g/m^3$ increase in the daily mean of PM_{10} was associated with a 0.59% (0.10–1.08%) and 0.67% (−0.02–1.35%) rise in RD and COPD hospital admissions, respectively (54). A Belgian study found an association between CVD hospital admissions and NO_2 with an overall risk of 3.5% (2.4–4.7%) per 10 $\mu g/m^3$ (55). In addition, Liu et.al., conducted a study which involved 652 cities and found an 0.4% increased risk in all-cause mortality in South Africa per 10 $\mu g/m^3$ of PM_{10} (16).

There is an insufficient number of studies on ambient air pollution (AAP) from sub-Sahara Africa (SSA), and the majority of air pollution studies are on indoor air pollution due to the burning of fuel for household use. In 2018, a systematic review reported only 12 studies from SSA that derived concentration-response functions (CRF) for any health outcome using ambient air pollution (AAP) measurements (56).

Therefore, the wealth of knowledge on the subject and the current evidence stems from Europe and North America. It is rather uncertain whether these results can be extrapolated to sub-Saharan African (SSA) countries. Air pollution levels are not only higher in the latter but also from different sources. In addition, effects of air pollution could be more strongly influenced by population-level vulnerability and individual-level susceptibility in SSA than in high income countries (HICs). These vulnerabilities include but are not limited to differences in socioeconomic risk factors, environmental conditions, or the co-occurrence of the double burden of chronic and infectious diseases such as tuberculosis (TB) and HIV/AIDS (56).

For instance, South Africa has a large double burden of diseases from both communicable diseases—HIV/AIDS and TB—and non-communicable diseases (NCDs) such as cardiovascular and chronic lung diseases (including asthma) (57). The high infection rate could make people more vulnerable to inflammatory effects of ambient air pollution that sustain NCDs. Furthermore, in addition to these diseases being a risk for the development or worsening of cardiorespiratory diseases, South Africans are exposed to levels of air pollution that exceed the 2021 WHO guideline values and concentrations observed in Europe or North American countries (8).

In 2012, Wichmann et al. reported a 3% increase in daily CVD deaths per 12 $\mu g/m^3$ and 8 $\mu g/m^3$ contrasts in NO_2 and SO_2 daily means, respectively. These estimates are substantially larger than what was published in systematic reviews from other countries. A review from China found an increase of 0.75% and 1.12% for a corresponding rise of 10 $\mu g/m^3$ in NO_2 and SO_2 for CVD deaths, respectively (58).

There have been a few studies to date in SA and SSA at large that have explored the short-term association between monitored air pollutants and any health outcomes (13, 14, 16, 59), but none has quantified the joint health effects of multiple pollutants on hospital admissions for any health outcome.

Therefore, the objective of this study was to address this gap in knowledge by investigating the short-term associations between daily averages of three routinely monitored air pollutants (PM_{10}, NO_2, SO_2) and daily hospital admissions due to cardiorespiratory disease in the City of Cape Town using a time-series analysis. In addition, we evaluated the difference in associations by sex, age, season, cumulative lag effects, and multi-pollutant models. This study is in line with the sustainable development goals (SDGs), particularly goals 3 and 13; furthermore, findings from this study can contribute to policymaking and the re-evaluation of South Africa's air quality guidelines.

2. Methods

2.1. Study Area

Data from Cape Town (CT), South Africa, was used to conduct this study. CT is the second most populous city in SA, with an estimated population of 3.7 million residents, 69.6% being in the working age group (15–64 years). The population density is 1530 people per km^2 in a total area of 2461 km^2 with over 1 million households. It has a subtropical Mediterranean climate, where the winter (May–August) cold front comes from the Atlantic Ocean with heavy precipitation and strong northwesterly winds. The summer months are warm (September–April) and dry, with frequent strong winds from the southeast (Indian Ocean) and the north (semi-arid Karoo interior).

2.2. Hospital Admission Data

Daily counts of respiratory and cardiovascular diseases hospital admissions were obtained by age and sex from seven private hospitals from 1 January 2011 to 30 October 2016. The health outcomes were coded using the International Classification of Disease, 10th version (ICD−10) (J00-J99) and (I00-I99). Private hospital data were used at the time of the study because the City of Cape Town public hospital data were not electronically available.

2.3. Air Pollution Data

Daily hourly averages of PM_{10}, NO_2, and SO_2 were obtained from the City of Cape Town air quality monitoring stations for the same study period. Ambient air quality has been monitored in the City of Cape Town since the 1960s with 14 stations in their network. $PM_{2.5}$ was not included in the analyses as the South African standard only came into effect in 2012; thus, time series are shorter and less complete (60). We used PM_{10}, NO_2, and SO_2 data from January 2011 to October 2016; during this period, $PM_{2.5}$ data were unavailable for some years and missing for others. These pollutants were measured, but not at all the stations; out of the 14 monitoring stations, 8 measured PM_{10} and 7 measured NO_2 and SO_2. A map with the locations of the monitoring stations and a description of annual measurements are provided in the Supplementary Material.

South Africa requires continuous monitoring of criteria air pollutants, as stated in the National Environmental Management Act: Air

Quality Act in 2004 (61). For each station, the daily means were derived if a minimum of 18 hours (75%) of hourly data were available. To obtain a city-level daily mean, the daily average across all stations for days with measurements were calculated. We then took a step further by imputing measurements for stations with missing values to be additionally used in calculating the city-level daily average. This required the presence of at least one measurement at any of the remaining stations on the respective day. The respective algorithm is explained in detail in the online Supplementary Material. A different approach was applied in the prediction of missing PM_{10} data in a different study using monitoring stations from Cape Town. It was reported that models for each site performed better in capturing the variability of PM_{10} concentration (62).

2.4. Meteorological Data

Daily meteorological variables, which included temperature and relative humidity, were obtained from the South Africa Weather Service (SAWS), while wind direction, wind speed, and solar radiation were obtained from the European Centre for Medium-Range Weather Forecasts (ECMWF) re-analysis dataset (63).

2.5. Statistical Analysis

Descriptive daily statistics of hospital admissions, air pollutants, and meteorological variables were calculated for the entire study period, with data presented for the total population and after stratification by sex (male and female), age (years 0−14, 15–64, and ≥ 65), and seasons—warm (Jan–Apr and Sep–Dec) and cold (May–Aug). The temporal correlation between the air pollutants and meteorological variables was assessed using Spearman's rank correlation coefficient.

The associations between daily mean concentrations of the air pollutants and daily counts of respiratory and cardiovascular hospital admissions were assessed in separate analyses using generalized additive quasi-Poisson models. This approach has been used in several time-series studies (64); it uses several parameters to explain the contributions of different time lags of pollutant exposures to the total effect of the respective pollutant from within the respective time window on the daily number of events. Therefore, it provides a comprehensive picture of the time-dependency of the exposure–response relationship over different specified lags (65). The core model included natural cubic spline functions of calendar time with a fixed number of yearly knots, 12 for respiratory diseases (RD) and 4 for cardiovascular diseases (CVD), to control for time trends and seasonal patterns in hospital admissions. In addition, indicator variables for public holidays as defined by the government and for the different days of the week were added. Furthermore, we created variables cost and sin t with periods of one year and added them to the models along with interaction terms with the day of the week indicator variables, in order to capture potential seasonal variations in the day-of-the week effects. These variables were defined as shown below:

$$cos\ t = \cos\left(\frac{time \times 2 \times \pi}{365.25}\right) \quad (1)$$

$$sin\ t = \sin\left(\frac{time \times 2 \times \pi}{365.25}\right) \quad (2)$$

We controlled for effects of temperature and relative humidity with natural spline functions of their averages over lags 0 to 3. The primary pollutant variables were the two-day means over lags 0 and 1. RD and CVD had to be modelled slightly differently, as RD required more degrees of freedom per year than CVD. Autoregressive terms were added if we were unable to adequately remove partial autocorrelation at short lags.

$$\begin{aligned}\log\left(E(CVD_{total})\right) = {} & gam(CVD_{total} \sim pollutant_{lag_{0-1}} + ns(time, df \\ & = 4 \times 6) + s(temp_{lag_{0-3}}) + s(rh_{lag_{0-3}}) \\ & + as.factor(dow) \times cost + as.factor(dow) \times sint \\ & + as.factor(pubday), method = "REML", family \\ & = "quasipoisson", data = data, na.action = na.exclude)\end{aligned} \quad (3)$$

$$\begin{aligned}\log\left(E(RD_{total})\right) = {} & gam(RD_{total} \sim pollutant_{lag_{0-1}} + s(time, df \\ & = 12 \times 6) + s(temp_{lag_{0-3}}) + s(rh_{lag_{0-3}}) + as.factor(dow) \times cost \\ & + as.factor(dow) \times sint + as.factor(pubday), method \\ & = "REML", family = "quasipoisson", data = data, na.action \\ & = na.exclude)\end{aligned} \quad (4)$$

Residuals of lag 1 were added after the core model was derived, in order to remove existing lag1-autocorrelation of residuals. Single pollutant models were derived for PM_{10}, NO_2, and SO_2 separately, followed by two- and three-pollutant models. To facilitate comparison of associations across pollutants, we presented the results as relative risks (RR) and 95% confidence intervals (CI) for an interquartile range increase in the respective pollutant variable. Results for a 10 μg/m^3 increment are tabulated in the Supplementary Materials.

In addition to the overall analysis, the models were stratified by sex (male vs. female), age groups (< 15, 15–64, and > 65), and seasons (warm vs. cold months). Statistical significance was defined as two-tailed p-value < 0.05. Chi^2 tests were used to compare effect estimates across different subgroups.

Finally, within a distributed lag non-linear model (DLNM) framework, we used a cross basis function for the lag model of each pollutant variable, which included a linear exposure–response function and a natural cubic spline for the lag weights. A total of 21 lags were considered and knots were placed at lags 2, 5, and 9. For temperature and relative humidity, we considered lags 0 to 3 and used argvar and arglag with natural spline and 5 degrees of freedom for the exposure–response relation. The respective equations in R are given below. The statistical analysis was performed using R software, version 4.0.3 (R Foundation for Statistical Computing), using the mgcv and dlnm packages for fitting the models.

$$\begin{aligned}poll_{cs} = crossbasis\,(poll_{conc}, lag = 21, argvar = list(fun = "lin"), arglag \\ = list(fun = ns, knots = c(2,5,9)\end{aligned} \quad (5)$$

$$\begin{aligned}met_{cs} = crossbasis(\,met, lag = 3, argvar = list\,(fun = "ns", df = 5), \\ arglag = list(fun = "ns")\,)\end{aligned} \quad (6)$$

where $poll_{cons}$ = daily pollutant concentration, met = daily average of meteorological variable, lin = linear, ns = natural cubic spline, met = daily temperature and relative humidity.

3. Results

During the study period 1st Jan 2011–31st Oct 2016, 54,818 cardiovascular (25.7 cases per day) and 58,317 (27.4 cases per day)

respiratory disease hospital admissions were recorded, as described in Table 1.

The daily average of CVD admissions was similar in both warm and cold seasons; however, there were more admissions in the cold season than the warm season for RD, 33 compared to 24 per day. There were only 498 CVD admissions observed among ages 0–14 during the study period; this group was excluded from further analysis for CVD models.

The overall daily mean concentrations of PM_{10}, NO_2, and SO_2 were 24.4 μg/m^3, 15 μg/m^3, and 9.4 μg/m^3, respectively; average concentrations were similar for both warm and cold seasons, except for NO_2. The highest PM_{10} level was 80.2 μg/m^3 (Table 1), and PM_{10} exceeded the daily WHO 2021 guideline values of 45 μg/m^3 on 123 days, NO_2 exceeded the value of 25 μg/m^3 on 237 days, and SO_2 exceeded the guideline of 40 μg/m^3 on 9 days.

Daily temperature and relative humidity were 17.3 ºC and 68.6%, respectively. Table 2 shows the Spearman correlation coefficients for daily air pollutants and meteorological variables. Correlations among pollutants were relatively low. For instance, PM_{10} and NO_2 had a weak correlation of only 0.30. In the cold months, the latter correlation increased to 0.57, whereas in the warmer months, correlations between pollutants were lower, for instance, 0.19 for PM_{10} and NO_2.

Table 1. Summary statistics of daily number of cardiovascular and respiratory disease hospital admissions, daily mean concentrations of ambient air pollutants, and meteorological conditions in Cape Town, South Africa, from 1 January 2011 to 31 October 2016.

						Percentiles			By Season - Mean (SD)	
Variable	**Mean**	**SD**	**Min**	**Max**	**IQR**	**25th**	**50th**	**75th**	**Warm**	**Cold**
Cardiovascular disease									n = 35,487	n = 19,331
All ages and sex n = 54,818	25.7	13	2	66	23	13	27	36	25.5 (13.2)	26.2 (12.6)
0–14 years n = 498	0.2	0.5	0	3	0	0	0	0	0.2 (0.5)	0.2 (0.5)
15–64 years n = 27,225	12.8	7	0	33	12	6	13	18	12.8 (7.1)	12.7 (6.9)
>65 years n = 27,095	12.7	6.9	0	43	11	7	12	18	12.4 (7)	13.3 (6.8)
Female n = 22,914	10.8	5.9	0	35	10	5	11	15	10.6 (6)	11.1 (5.9)
Male n = 31,904	15	8.1	1	40	13	8	15	21	14.9 (8.2)	15.1 (7.8)
Respiratory disease									n = 33,840	n = 24,477
All ages and sex n = 58,317	27.4	13.1	1	75	21	16	27	37	24.3 (12)	33.2 (13)
0–14 years n = 28,518	13.4	7.4	0	37	11	7	13	18	11.8 (7)	16.3 (7.3)
15–64 years n = 19,418	9.1	5.4	0	32	8	5	9	13	8.2 (5.1)	10.9 (5.5)
>65 years n = 10,381	4.9	2.9	0	17	4	3	4	7	4.3 (2.6)	6 (3.1)
Female n = 29,741	14	7.2	0	44	11	8	13	19	12.2 (6.6)	17.2 (7.3)

Male n = 28,576	13.4	6.9	0	40	10	8	13	18	12.1 (6.5)	16 (6.9)
Air pollutants										
PM_{10} ($\mu g/m^3$)	24.4	9.5	6.9	80.2	12	17.3	22.7	29.3	24.1 (8.7)	25 (10.7)
NO_2 ($\mu g/m^3$)	15	5.5	3.9	42	7.3	10.9	14.1	18.2	13.5 (4.8)	17.8 (5.8)
SO_2 ($\mu g/m^3$)	9.4	2.8	2.6	23.2	3.6	7.3	9	10.9	9.3 (2.9)	9.6 (2.8)
Meteorological data										
Temperature (º C)	17.3	4.3	7.5	29.3	7	13.8	17	20.8	19.4 (3.6)	13.5 (2.3)
Relative humidity (%)	68.6	10.5	30.7	100	15	61	69	76	65.6 (9.4)	74.2 (10.1)

Abbreviations : SD—standard deviation ; Min—minimum ; Max—maximum ; IQR—interquartile range. Warm period: January to April and September to December; cold period: May to August.

Table 2. Spearman's rank correlation between city-level daily mean PM10, NO_2, SO_2, and meteorological parameters during the period of 1st Jan 2011 to 31 Oct 2016 in Cape Town, South Africa.

	PM_{10}	**NO_2**	**SO_2**	**Temperature**	**Humidity**
PM_{10}	1				
NO_2	0.30	1			
SO_2	0.20	0.27	1		
Temperature	0.23	−0.38	0.01	1	
Humidity	−0.29	0.02	−0.11	−0.39	1

Table 3 shows the risk ratios and 95% confidence intervals of hospital admissions for respiratory and cardiovascular disease per interquartile range (IQR) of the 2-day moving average (lag 0–1) mean concentrations of the pollutants. PM_{10} showed a positive and statistically significant association with admissions for respiratory diseases, with an overall effect estimate of 1.9% (95%CI 0.5–3.2%) per IQR increase of 12 $\mu g/m^3$. The strongest effect estimates were observed in age 0–14 years (2%, 95% CI 0.2–3.9%) and males (2%, 95% CI 0.2–3.7%) for the same unit. NO_2 also showed a positive association, with an estimated increase by of 2.3% (0.6–4%) in RD admissions per IQR rise of 7.3 $\mu g/m^3$. The corresponding estimate was 3.1% (95% CI 0.7–5.6%) among children below the age of 15. The other groups also showed positive associations that did not reach statistical significance. However, we also observed a positive association with RD-admissions for SO_2, with an estimate of 1.1% (−0.2–2.4%) per IQR increment of 3.6 $\mu g/m^3$. The respective estimates were similar in all subgroups.

Cardiovascular disease (CVD) admissions increased with increasing PM_{10} and NO_2 levels, but only PM_{10} risk estimates were statistically significant. In the unstratified analysis, an interquartile range increase in PM_{10} increased CVD hospitalizations significantly by 2.1% (0.6–3.5%). Statistically significant positive associations were observed in all groups. The overall percentage change in risk for CVD hospitalization associated with an interquartile increase of NO_2 was 1% (−0.8–2.8%), while the respective estimate for SO_2 was −0.3% (−1.6–1.1%). We observed stronger associations with RD than CVD hospital admissions for all three pollutants.

Table 3. Overall relative risk estimated from quasi-Poisson regression models of respiratory and cardiovascular disease hospitalizations, adjusting for time trends and seasonal variation, day of the week, public holiday, and meteorological factors including temperature and relative humidity.

Estimates are presented per interquartile range (shown in Table 1) increase in the 2-day moving average (lag 0–1) of PM_{10}, NO_2, and SO_2 concentrations for respiratory and cardiovascular disease hospital admissions for different age groups and sexes.

Respiratory Disease Hospitalization by Pollutants									
	Per 12 μg/m³ PM_{10}			Per 7.3 μg/m³ NO_2			Per 3.6 μg/m³ SO_2		
Groups	RR	95% Confidence Interval		RR	95% Confidence Interval		RR	95% Confidence Interval	
		Lower	Upper		Lower	Upper		Lower	Upper
All	1.019	1.005	1.032	1.023	1.006	1.04	1.011	0.998	1.024
Age 0–14	1.02	1.002	1.039	1.031	1.007	1.056	1.015	0.997	1.033
Age 15–64	1.009	0.988	1.03	1.003	0.976	1.03	1.011	0.99	1.032
Age ≥ 65	1.019	0.994	1.046	1.005	0.972	1.039	0.989	0.963	1.015
Female	1.014	0.997	1.032	1.013	0.991	1.036	1.006	0.989	1.023
Male	1.02	1.002	1.037	1.019	0.997	1.042	1.015	0.998	1.032
Cardiovascular Disease Hospitalizations by Pollutants									
	Per 12 μg/m³ PM_{10}			Per 7.3 μg/m³ NO_2			Per 3.6 μg/m³ SO_2		
Groups	RR	95% Confidence Interval		RR	95% Confidence Interval		RR	95% Confidence Interval	
		Lower	Upper		Lower	Upper		Lower	Upper
All	1.021	1.006	1.035	1.01	0.992	1.028	0.997	0.984	1.011
Age 15–64	1.021	1.002	1.039	1.006	0.983	1.03	0.998	0.98	1.015
Age ≥ 65	1.022	1.004	1.041	1.017	0.994	1.041	0.995	0.978	1.012
Female	1.02	1.001	1.04	1.007	0.983	1.033	1.009	0.99	1.028
Male	1.021	1.003	1.038	1.015	0.993	1.037	0.987	0.971	1.003

Results of single- and multi-pollutant models are presented in Figure 1. NO_2-related effect estimates for respiratory diseases were largest (per IQR) across all models for this health outcome; the results were statistically significant for the single pollutant model and the two-pollutant model with SO_2. In addition, a stronger association was observed among children (3.1%). In the multi-pollutant models, the overall percentage change for NO_2 was 1.6% and 2.1% when adjusted for PM_{10} and SO_2, respectively; results are found in the Supplementary Materials. The estimate for NO_2 decreased after the inclusion of PM_{10} and was lowest in the three-pollutant model with 1.5%. Similarly, the PM_{10} estimate was reduced from 1.9% to a non-significant value of 0.9% after adjusting for NO_2, while SO_2 effect estimates were statistically insignificant for all ages, groups, and models. In CVD, associations per IQR were strongest for PM_{10}, and the respective RR estimates were not sensitive to adjustment with NO_2 and SO_2. The group-specific risk of PM_{10} on CVD hospitalization increased from 2.2% and 2.1% in a single pollutant model for age ≥ 65 years and males to 2.6% when adjusted for SO_2, respectively; this is reported in the Supplementary Materials. Associations for NO_2 and SO_2 with CVD hospitalizations were not statistically significant.

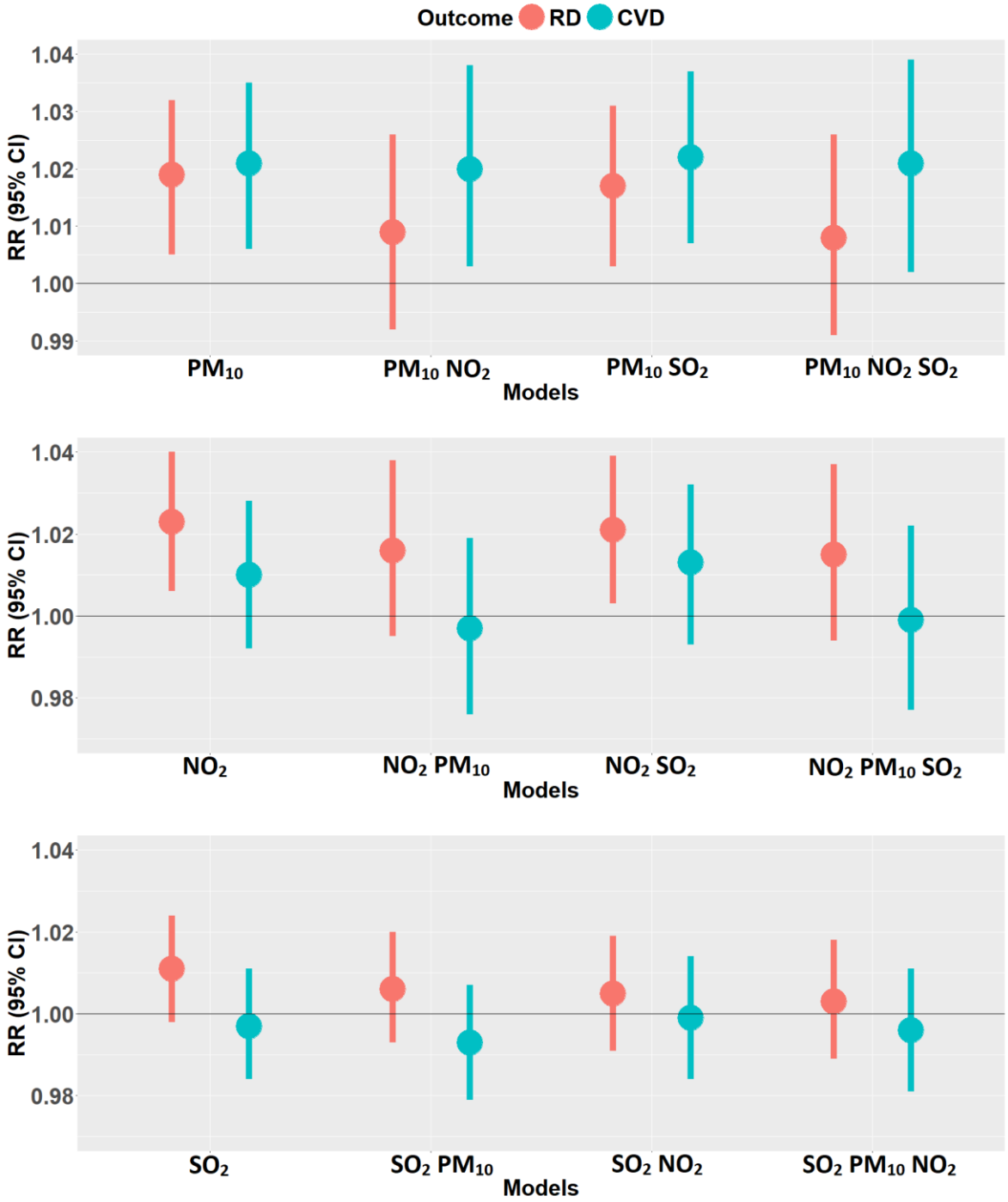

Figure 1. Estimated overall (lag 0–1) relative risks (with 95% confidence intervals) for respiratory (RD) and cardiovascular disease (CVD) admissions, per one interquartile range increase in the two-day moving averages of PM_{10} (top panel), NO_2 (middle panel), and SO_2 (bottom panel) for single and multipollutant models. Sex- and age-specific estimates are reported in the Supplementary Materials.

Season-specific associations for respiratory diseases in single pollutant models of PM_{10}, NO_2, and SO_2 are presented in Figure 2. PM_{10} and NO_2 showed stronger associations in the warmer months (Sep–Apr) compared to the colder months (May–Aug) for CVD. However, the differences between seasonal estimates were not statistically significant.

In the warmer months, respiratory disease (RD) admissions were positively associated with only PM_{10}, with estimates of 2.2% (95% CI 0.5–

3.9%) per IQR rise in lag0–1 of PM_{10}. For an IQR rise in the two-day moving average of NO_2, there was a risk of 2.3% (−0.4–4.9%), and a similar null finding in the two-day moving average of SO_2, an IQR increase corresponding with a relative risk of 1.3% (−0.4–3.1%).

Daily CVD hospital admissions were positively associated with PM_{10} and NO_2 in the warmer months. An IQR increase in the two-day moving average of PM_{10} corresponded with an increased risk of 3.4% (1.5–5.3%), which was the strongest association observed for all three pollutants. NO_2 showed an increased risk of 2.7% (95% CI 0.2–5.4%) for an IQR increase in the two-day moving average, while SO_2 had a negative association with a risk ratio of −0.8% (95% CI −2.4–0.9%). In the colder months, there were no statistically significant associations for all the pollutants.

In the colder months, only NO_2 showed any statistically significant association. The relative risk estimates for RD hospital admissions associated with an IQR increase in the two-day moving average of NO_2 was 2.3% (95% CI 0.1–4.6%), while the corresponding estimates for PM_{10} and SO_2 were 1.3% (95% CI −0.4–3.3%) and 0.8% (95% CI −1.2–2.9%), respectively.

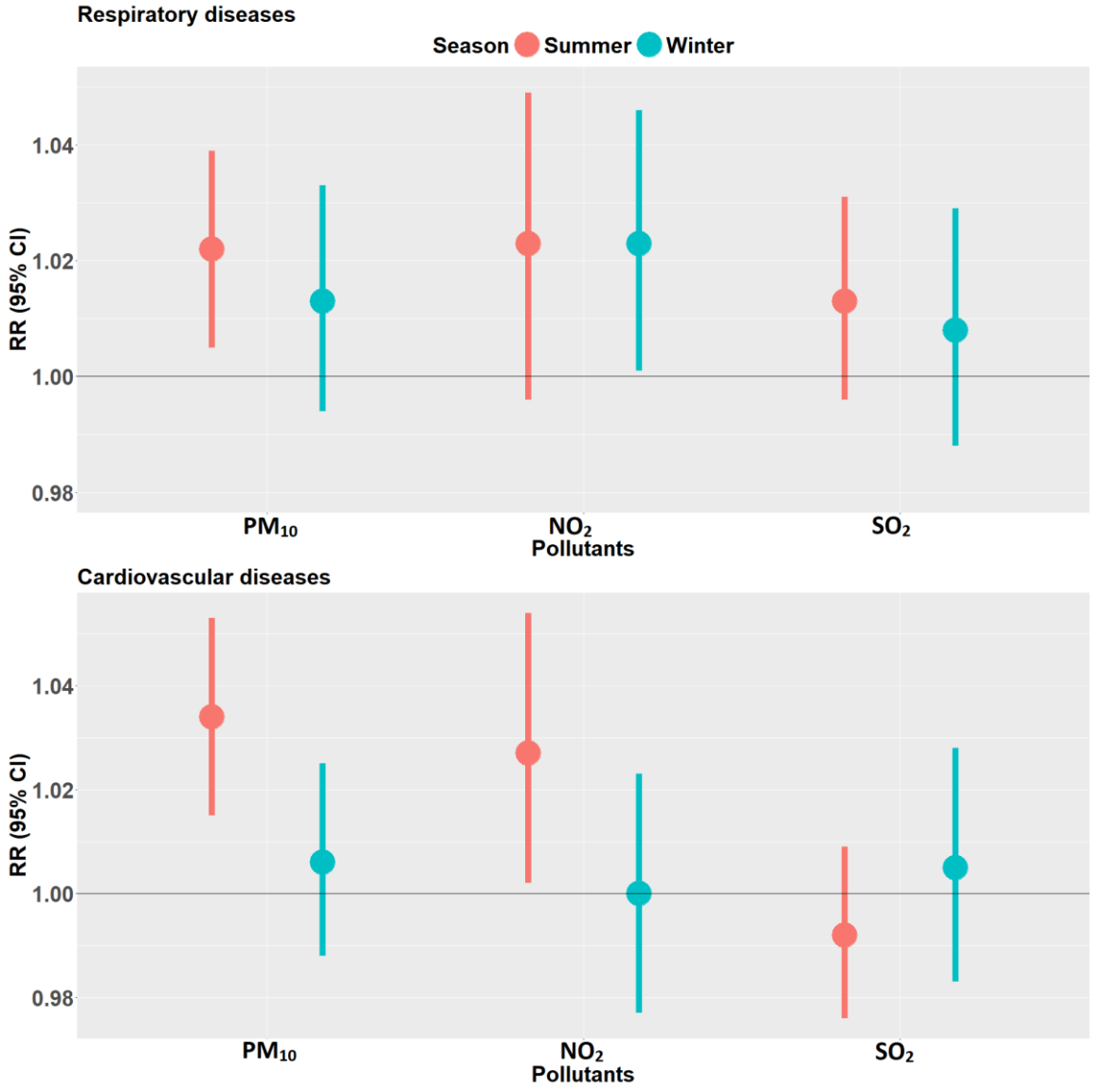

Figure 2. Season-specific relative risks of RD and CVD hospitalizations per interquartile range increase in the two-day moving average (lag 0–1) of the respective pollutant. Summer season (Jan–Apr and Sep–Dec) and winter season (May–Aug), for respiratory (upper panel) and cardiovascular (lower panel) diseases, with bars representing 95% confidence intervals.

3.1. Lag Models

Figure 3 presents the estimated lag structure of the effects of a 10 μg/m^3 increase in PM_{10}, NO_2, and SO_2 concentration on respiratory disease admissions for the whole group. Age-specific lag structures for PM_{10} are illustrated for ages 0–14 and ages ≥ 15 years; we noted from Table 3 that ages 0−14 appeared to be driving the estimates for PM_{10}, and this was confirmed by the graphs. This age group showed both acute (lag 0–1) and delayed (lag 6–7) associations in comparison to the age group 15 years and older. Conversely, for NO_2, we observed no acute effect at lag 0–1 for the whole group, even though the two-day moving average was significant, whereas SO_2 showed significant negative effect from lags 8 to 18. We tested for differences in estimates between age groups and sex using chi-squared tests but found no statistically significant differences.

When we analyzed the effect of a 10 μg/m^3 increase in PM_{10} on cardiovascular disease admissions, as presented in Figure 4, we saw a similar pattern to RD; however, in this case, the effect was observed in all groups, as indicated in Table 3. There were acute effects from lags 0–1 and delayed effects from lags 5–9. For NO_2, lag 0 was the only statistically significant contributor to CVD hospitalizations as the confidence interval for lag1 reached below 1, while we did not see any significant contributions from SO_2 across all lags. In addition, when the data were stratified by age and sex, we observed no association for each respective pollutant on CVD admissions.

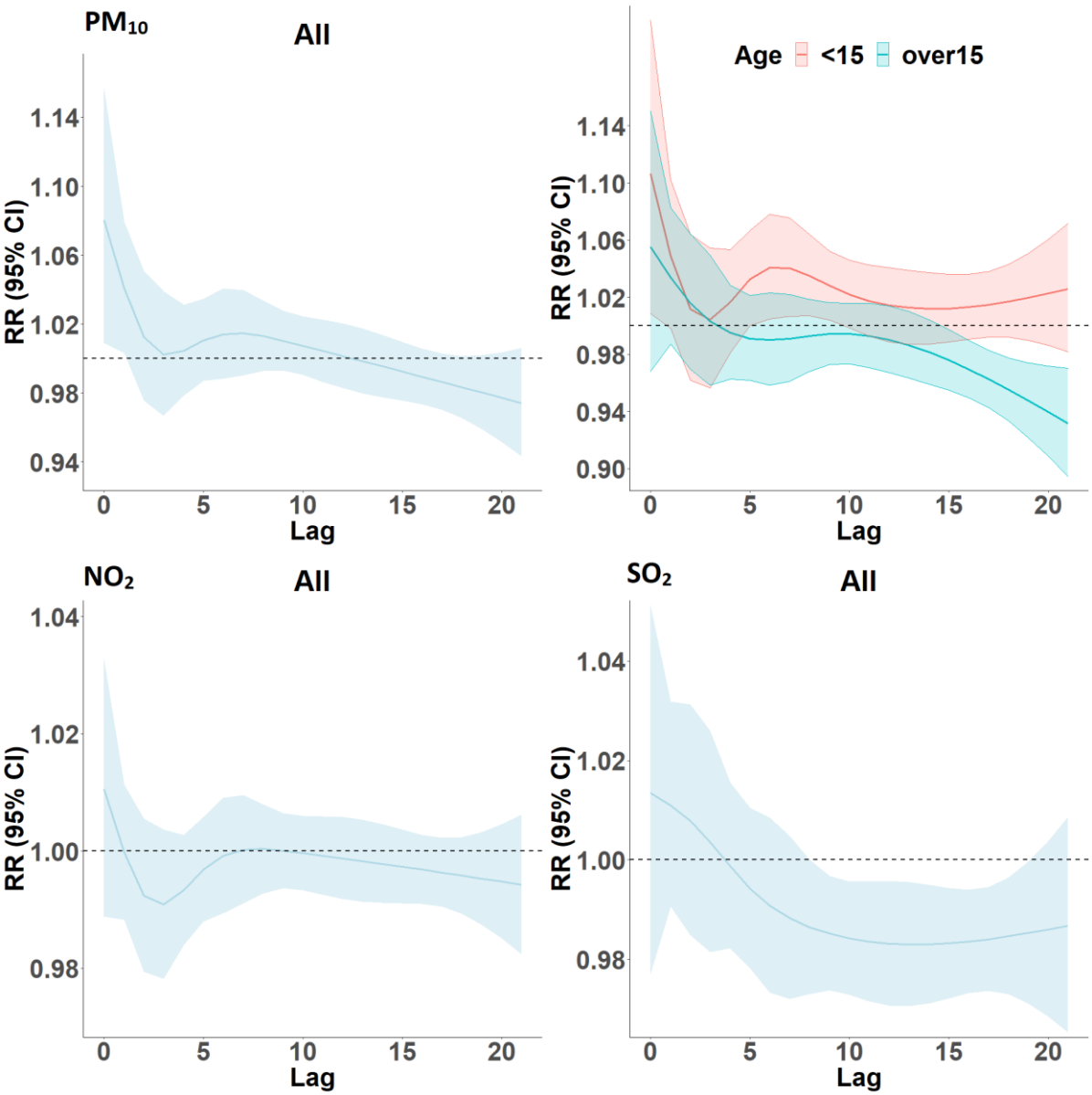

Figure 3. Estimated lagged effects (over 21 days) of PM_{10}, NO_2, and SO_2 on respiratory disease hospital admissions, overall, and by age group for PM_{10} in Cape Town, South Africa, 2011–2016. Effect estimates are per 10 ug/m3 increment of the respective pollutant.

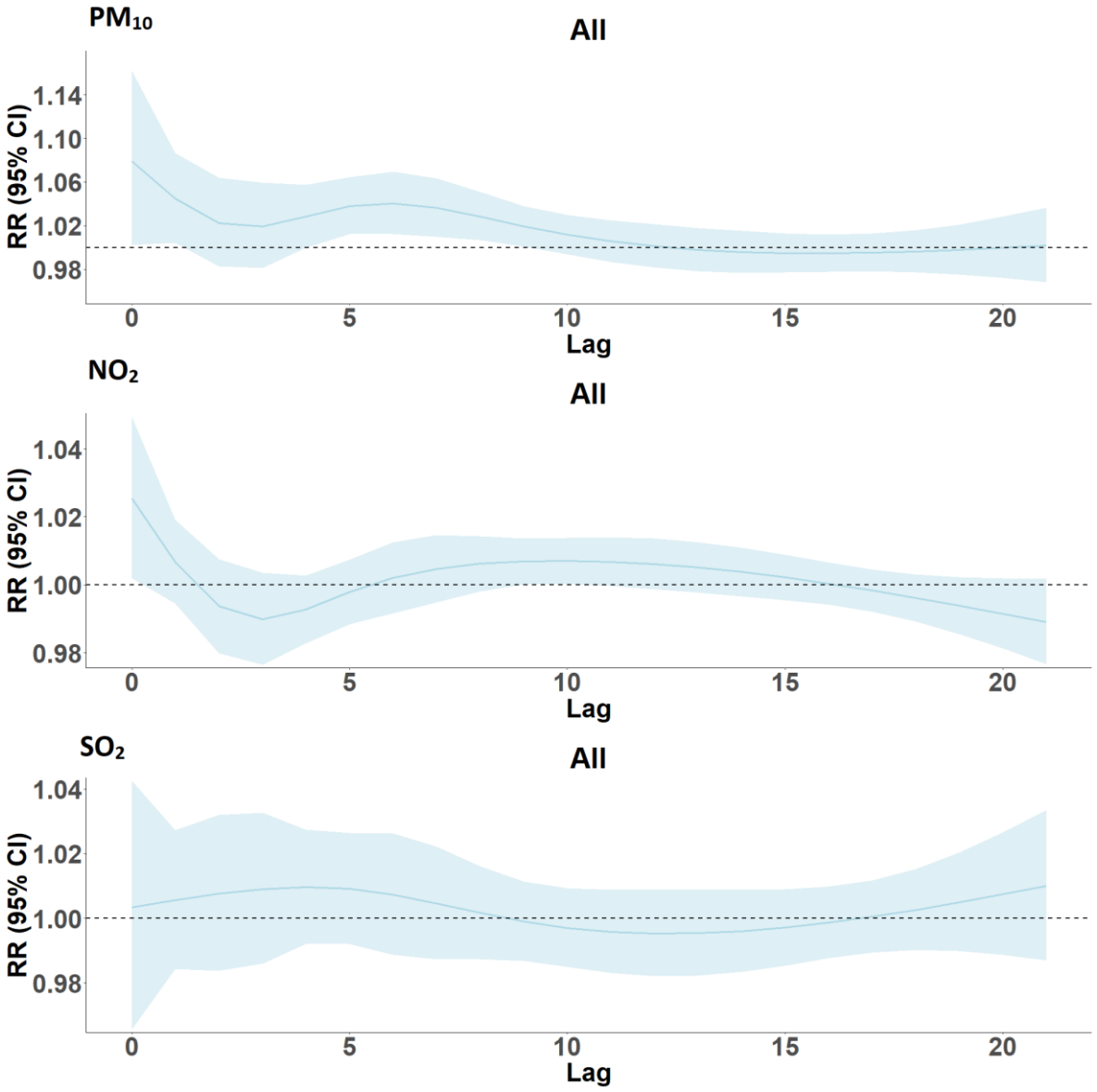

Figure 4. Lag structure (0–21) of the effects of a 10 μg/m^3 increase in PM_{10}, NO_2, and SO_2 concentrations on cardiovascular disease hospital admissions in Cape Town, South Africa, 2011–2016.

4. Discussion

This is the first study in sub-Sahara Africa to investigate the association between multiple air pollutants and hospital admission due to cardiovascular (CVD) and respiratory diseases (RD). Associations for RD hospital admissions were consistently observed with PM_{10} and NO_2 in both single- and SO_2-adjusted models; however, for CVD, only PM_{10} showed positive associations. In contrast to various other studies, the temporal correlations between the three pollutants were rather low; thus, our study had the opportunity to investigate the independent associations of each pollutant. We did not find statistically significant associations between SO_2 and hospital admissions of RD and CVD.

Our findings for PM_{10} are in line with the current knowledge about the ability of fine particles to penetrate into the respiratory tract and the lungs and affect the heart. Numerous studies have demonstrated that exposure to air pollution is followed by an oxidative stress reaction initiated by inflammatory response to PM entering the lung (66, 67). The

oxidative reaction from the lung is further amplified through a different enzymatic pathway finally leading to a systemic vascular oxidative stress reaction (68). Systemic inflammatory responses have been demonstrated in both animal and controlled human studies (69). The particle dose and composition determines the extent of the pulmonary inflammation; controlled human exposure studies have demonstrated increased markers for pulmonary inflammation for exposure to a variety of particle types (70).

However, in comparison to other studies, for a 10 $\mu g/m^3$ increase in PM_{10}, our estimates of 1.8% for RD and 1.9% for CVD were higher than the pooled estimates reported globally and from low- and middle-income countries (LMIC) for cardiorespiratory morbidities. Newell et al. conducted a meta-analysis and systematic review of association between PM_{10} per 10 $\mu g/m^3$ increase across a 0–1 day lag and cardiorespiratory outcomes in 39 studies and reported a RR(CI) of 0.39% (–0·04–0.8%) in daily RD hospitalization (71). In Switzerland, a 10 $\mu g/m^3$ increment in PM_{10} was associated with increased risks for RD and CVD daily admissions by 0.22% (95% CI: − 0.43 to 0.87%) and by 0.43% (95% CI: 0.12–0.73%), respectively (72). However, similar findings with stronger associations were observed for RD and CVD mortality in a study based on Cape Town data (13).

The larger association with PM_{10} observed in our study might be explained by a number of reasons. The maximum concentrations of 80.2 ug/m^3, 42ug/m^3, and 23.2ug/m^3 for PM_{10}, NO_2, and SO_2, respectively, were quite comparable to what has been reported in other European studies (73), given the advantageous coastal location of Cape Town.

Firstly, the difference in sources, composition, and toxicity of the pollutant with respect to the study area might play a role. In SA, residents are exposed to air emissions from landfill sites, tires and open refuse burning, airports, agricultural activities, windblown dust, and transboundary air pollution (74). Furthermore, the City of Cape Town is prone to structural and vegetation fires. Yearly, the city deals with an average of 8600 vegetation fires and more than 100 fires from informal settlements as a result of accidents with paraffin stoves (75). Consequently, these sources of exposure will have an influence on the chemical composition of PM_{10} with possibly different constituents including more crustal materials. Research has shown that during high pollution days in Cape Town, most of the air parcels have travelled from major dust source regions such as the Kalahari and Namib deserts before arriving over the city. In addition to favorable atmospheric conditions for the dispersion of air pollution, peaks in PM_{10} concentrations are associated with transport of PM_{10} plume driven by northerly flow induced by coastal and continental high pressure systems (76). Another study from Cape Town investigated the sources and chemical composition of $PM_{2.5}$ and soot levels, finding significant correlations with PM_{10} levels measured 3 km from one of the monitoring stations used in this study. Cl^-, NO_3^-, SO_4^{2-}, Al, Ca, Fe, Mg, Na, and Zn were detected in the samples collected for 121 days, of which the largest fraction of the $PM_{2.5}$ samples were due to anionic and metallic species. If those levels are assumed to be representative for the city, one may observe higher risk estimates (77). Secondly, these stronger effects may also represent difference in vulnerability and high prevalence of pre-existing diseases such as hypertension and atherosclerosis, which increases their susceptibility to stronger acute effects (78).

4.1. Overall Association of Hospital Admissions and NO_2

We found statistically significant associations between NO_2 and RD hospitalizations but not with CVD. For both health outcomes, the observed point estimates were higher in our study than reported by others. For instance, a systematic review from 2015 using estimates from 18 WHO regions reported 0.57% (95% CI 0.33–0.82%) and 0.66% (95% CI 0.32–1.01%) increases in RD and CVD hospital admissions, respectively (79), while our respective estimates were 3.4% and 1.7% (per 10 $\mu g/m^3$).

A meta-analytic study investigating the association between NO_2 and hospital admissions from Italy's most polluted region showed risks of 1.20% (90% CI 0.53–1.81%) and 1.14% (90% CI 0.51–1.83%) for RD and CVD admissions, respectively (80). Sunyer et al. reported a 0.7% (95% CI: 0.1–1.3%) increase in CVD daily admissions per 10 $\mu g/m^3$ of NO_2 from seven European areas. However, another systematic review (71) from 22 studies reported increased risks ranging from 1.08% to 1.94% and 1.04% to 1.17% for RD and CVD hospitalization, respectively (81).

The major source of NO_2 is vehicle emissions, especially in urban areas where they may be responsible for 60–70% of nitrogen oxides in the atmosphere (74). This is the case for areas with high traffic density such as central business districts. If the mix of traffic-related pollutants in South Africa is different from those observed in Europe, this might, at least in part, explain the higher effect estimates for NO_2 observed in our study. The current emission legislation in SA is equivalent to Euro II (Euro 2) only. Although the importation of used vehicles is banned, the overall car fleet is still not at the level found in Europe. Moreover, the fuel quality is much worse than in Europe, which may substantially affect the quality and toxicity of the emissions beyond NO_2. In 2018, the maximum sulfur limits in gasoline were 501–3500 parts per million (ppm), while road diesel had limits of 351–500 ppm, as compared to the much lower European limits of 5–10 ppm (82). Indeed, as shown in Figure 2, adjustment for ambient PM_{10} substantially reduced the associations with NO_2 to 1.6% for RD. This may also point in the direction of NO_2 being a marker for rather complex combustion-related constituents, which in turn are partly captured by particles.

4.2. Overall Association of Hospital Admissions and SO_2

Our study showed that daily concentrations of SO_2 were not significantly associated with RD nor CVD hospitalizations; these results are similar to findings from previous studies. A study conducted in England and Wales reported no association with CVD admissions with a risk of −0.3% (95% CI −1.0–0.3%) per 10th−90th centile increment in SO_2 (10.4 $\mu g/m^3$) from lag 0–4 days (83). The median concentration 3.1 $\mu g/m^3$ (2–6) in this study was smaller in comparison to our study (see Table 1).

In addition, a systematic review of low- and middle-income countries (LMIC) found an association between SO_2 exposure and cardiorespiratory morbidity. At lag 0–1 with 10 $\mu g/m^3$ rise in SO_2, the risk for RD was increased by 0.40% (95% CI 0.19–0.61%), while CVD, as in our data, was not associated with 10 $\mu g/m^3$ increase in SO_2 (0.07% 95% CI −0.40, 0.55%) (84). In our multipollutant models, SO_2 showed consistent positive but non-significant associations with RD hospitalizations and no associations with CVD hospitalizations, whereas effect estimates for NO_2 and PM_{10} on RD and CVD hospitalizations slightly increased when they were adjusted for SO_2.

SO_2 comes from burning of coal and oil, and SA generates more than 90% of its energy from coal burning. As a gaseous compound, the emission of SO_2 can lead to the formation of secondary particles while also acting as surrogate for other substances. According to the United States Environmental Protection Agency (US EPA), more than 12% of SO_2 emitted in urban areas are converted in the atmosphere to sulphate particulate matter (85). Furthermore, there is the issue of transboundary pollution from other parts of the country and neighboring countries. Concurrently, there are other sources of pollution such as open waste burning and emission from traffic that is worsened by the high sulfur content in fuel for on-road vehicles and industry. This results in a complex mixture of pollutants, making it difficult to disentangle their associations with health outcomes.

4.3. Effect Modification by Age Group, Sex, and Season

In our study, we found the highest estimates for PM_{10} and NO_2 on RD hospitalizations in children. This finding is in line with other studies on cardiorespiratory diseases showing greater sensitivity of the youngest to air pollution (86-91). However, the elderly also showed slightly higher estimates.

Individual response to air pollution exposure can be determined by several factors, which include pre-existing diseases, socio-economic status, age, and lifestyle. However, children are particularly vulnerable to the adverse effects of air pollution, and as reported by the WHO (90), more than 90% of children are exposed to toxic air, particularly in low- and middle-income countries. Air pollution can also alter the development and function of a child's lungs as they are still growing (92). In addition, children spend more time outdoors and engage in physical activity, which increases their breath rate and allows for environmental pollutants to be deposited in their respiratory tract in larger amounts (93). Furthermore, children are predominantly oral breathers, which means more polluted particles enter their lower airways as a result of their nasal filter being by-passed (94).

One possible cause of increased sensitivity to air pollution of the elderly is the higher prevalence of co-morbidities that reduce biological functions or resistance to infection and inflammatory ailments (95). The human body experiences physiological degeneration with increased age. The normal function of the body organs is affected by aging, which results in cardiovascular, urinary, and respiratory health conditions (96). Consequently, the ability of older people to adapt to increased concentrations of air pollution and changing weather conditions is reduced (97). Moreover, in comparison to young people, older people have lower immunity and antioxidant defense and more progressed atherosclerosis, which puts them at a higher risk for acute effects of air pollution (98).

Gender-specific estimates did not differ significantly; therefore, this may just reflect random variation. This is in line with a meta-analysis where 13 studies out of 14 on associations between short-term exposure to air pollution and cardiorespiratory disease hospital admission did not find statistically significant effect modification by sex (99).

We found stronger associations of air pollution with cardiovascular hospitalizations in warmer months than in colder months. In RD and CVD, the overall effect estimates for a 10 $\mu g/m^3$ increase in PM_{10}, NO_2, and SO_2 were considerably larger in the warmer than in the colder

months. Similar findings were observed in an earlier study that investigated temperature as a modifier of the effects of air pollution on CVD hospitalizations in Cape Town. The study reported stronger associations in warmer months compared to colder months (59). The higher and significant effect estimates observed in warmer months might be explained by the time spent outdoors for leisure and physical activities. Increased duration of exposure and increased respiratory rate due to outdoor activities both contribute to higher doses of inhaled air pollution. In addition, wildfires are more frequent in summer than winter, particularly from burning of waste at landfill sites. This will have an influence on the characteristics of the pollutants and possibly the level of toxicity of the mixture of pollutants. During warmer months, oxidant pollutants such as ozone and other secondary pollutants are also higher, which may amplify the effects of pollution. Furthermore, temperature and humidity drive the dispersion of air pollution differently in both seasons. For instance, humidity is higher in winter than in summer, which reduces the distribution of air pollution in winter.

4.4. Strength and Limitations

This study has some limitations; firstly, misclassification of air pollution exposure could be a potential source of bias in our study as it is likely that, in an urban city such as Cape Town, there will be substantial spatial heterogeneity of these concentrations. Although all monitoring stations in the city were used to calculate daily average ambient pollutant concentrations, these will differ to some extent from the population-averaged daily exposure levels, which would ideally be used in time series analyses of hospital admission. However, population-averaged exposure estimates would have required models of daily pollutant levels of high spatial resolution, which were not available. On the other hand, it has been reported that the temporal variation at fixed monitoring sites is well correlated with the temporal variation of personal exposure to particulate matter, which should reduce random misclassification (100, 101). However, high correlation between individual exposure and fixed site levels does not imply that there will be little bias in the estimate.

Secondly, we did not include ozone in the analysis because there was insufficient data. Ozone may not only affect health but could potentially confound or modify the associations seen with other pollutants, especially during the warmer months when ozone levels are high.

Thirdly, NO_2 and SO_2 had a considerable amount of data missing due to issues such as power failure, faulty equipment, and relocation of air quality monitors. However, we do not expect the pattern of missingness to be systematically associated with important factors such as toxicity and source of pollution. Therefore, this is unlikely to be a major source of bias for our estimates.

Lastly, the health outcome data were obtained from private hospitals, being part of the private health sector, which covers only 16% of the population (102). People who can afford to pay out of pocket and those with health insurance have access to these hospitals, which are most likely people with middle and higher socio-economic status (SES). Therefore, generalizing of our effect estimates to the entire population of Cape Town and South Africa will need some caution. In addition, at the time of the study, public hospital data were not readily available electronically; however, the South African government has developed

strategies to establish data electronic data sharing agreement between government entities and third-party users (103).

We would expect SES to modify the effect estimates of air pollution on cardiorespiratory health in Cape Town. People with lower SES are more likely to live in poorer and disadvantaged neighborhoods with less delivery of public services such as housing, electricity, and education, as well as less access to healthcare, healthy diet, water, and good roads. This could lead to increased susceptibility to the effects of air pollution combined with higher levels of exposure as there is a higher likelihood of them living closer to the roadways with increased traffic density and to more polluted areas. People with disadvantaged SES are also likely to live in houses with poor ventilation or increased indoor air pollution due to burning of wood and coal to generate heat. In addition, in the past, South Africa had a poor land use planning that resulted in heavy industrial developments in proximity to highly populated residential areas; residents of these areas are mostly people with lower and middle SES, and they may be exposed to higher levels of air pollution than those at monitoring stations. Furthermore, people with higher SES may live in areas with lower air pollution exposure and more green space. Moreover, they may have reduced susceptibility to air pollution effects in comparison with people with lower SES. In addition, the duration, frequency, and intensity of these exposures can contribute to variations in the magnitude of associations between different socio-economic groups.

A systematic review on stroke found that there was a stronger association with pooled estimates from low- and middle-income countries (LMIC) for NO_2 and PM_{10} in comparison with high-income countries (HIC). They found higher median pollutant concentrations for both PM_{10} and NO_2 in LMICs compared to HICs (104). An Italian study reported a linear correlation between high levels of NO_2 and PM_{10} concentrations and the lack of possession of a home, low level of education, and population density (105). Numerous studies have investigated the influence of SES on adverse health effects of air pollution, and there have been conflicting reports of effect modification (106, 107). This makes it difficult to draw a definitive conclusion on whether the short-term effects of air pollution on health are modified by SES. Therefore, it is important that future studies use public hospital data to understand the influence of exposure to ambient air pollution on cardiorespiratory health for different sub-groups in a South African context.

5. Conclusions

In conclusion, PM_{10} and NO_2 were found to be associated with RD, particularly in children, and with CVD. Associations were stronger in the warmer months. Our estimates are higher than what has been reported in North American and European studies, despite similar concentration levels. This may be due to the different sources and characteristics of the pollutants in SA. Given that we found stronger associations at relatively low levels and in light of the updated WHO air quality guideline values, it is crucial that interventions to reduce air pollution are implemented in South Africa, as this could potentially reduce the risk of morbidity, particularly for children and the elderly. Therefore, further investigation is needed, whilst health-based air quality standards should be adopted and enforced to protect public health.

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Supplementary Materials: This document describes the air pollution data by station for each year and outlines the imputation analysis. In addition, it tabulates the estimates for age groups, sex, and season per interquartile range and 10 μg/m^3.

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Ethical approval: The study was approved by the Faculty of Health Sciences Research Ethics Committee at the University of Pretoria with ethics number 671/2019. In addition, it was conducted in accordance with the ethical guidelines of the 1964 Declaration of Helsinki and its amendments and comparable ethical standards. Informed consent was not required for this study.

Informed Consent Statement: Not applicable.

Data Availability Statement: Exposure data are available for download on the South African Air Quality Information System (SAAQIS) https://saaqis.environment.gov.za/; (accessed on 22 April 2019) however, restrictions apply to the health outcome data.

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Paper 1 Appendix

Short-Term Joint Effects of PM10, NO2 and SO2 on Cardio-Respiratory Disease Hospital Admissions in Cape Town, South Africa

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Supplentary material - Imputation analysis of ambient air pollutant data and time-series results

Hourly air pollution data for PM10, NO2 and SO2 were collected from 12 stations – seven stations for PM10, 12 for NO2 and SO2, respectively. These concentration were then aggregated to daily level provided at least 75% of the data for that day was available.

The figures below shows the annual proportion of daily means data available for each pollutant from the air quality monitoring stations.

Figure 3: The proportion of PM10 daily means data collected from seven stations from 1st Jan 2011 – 31 October 2016 in Cape Town.

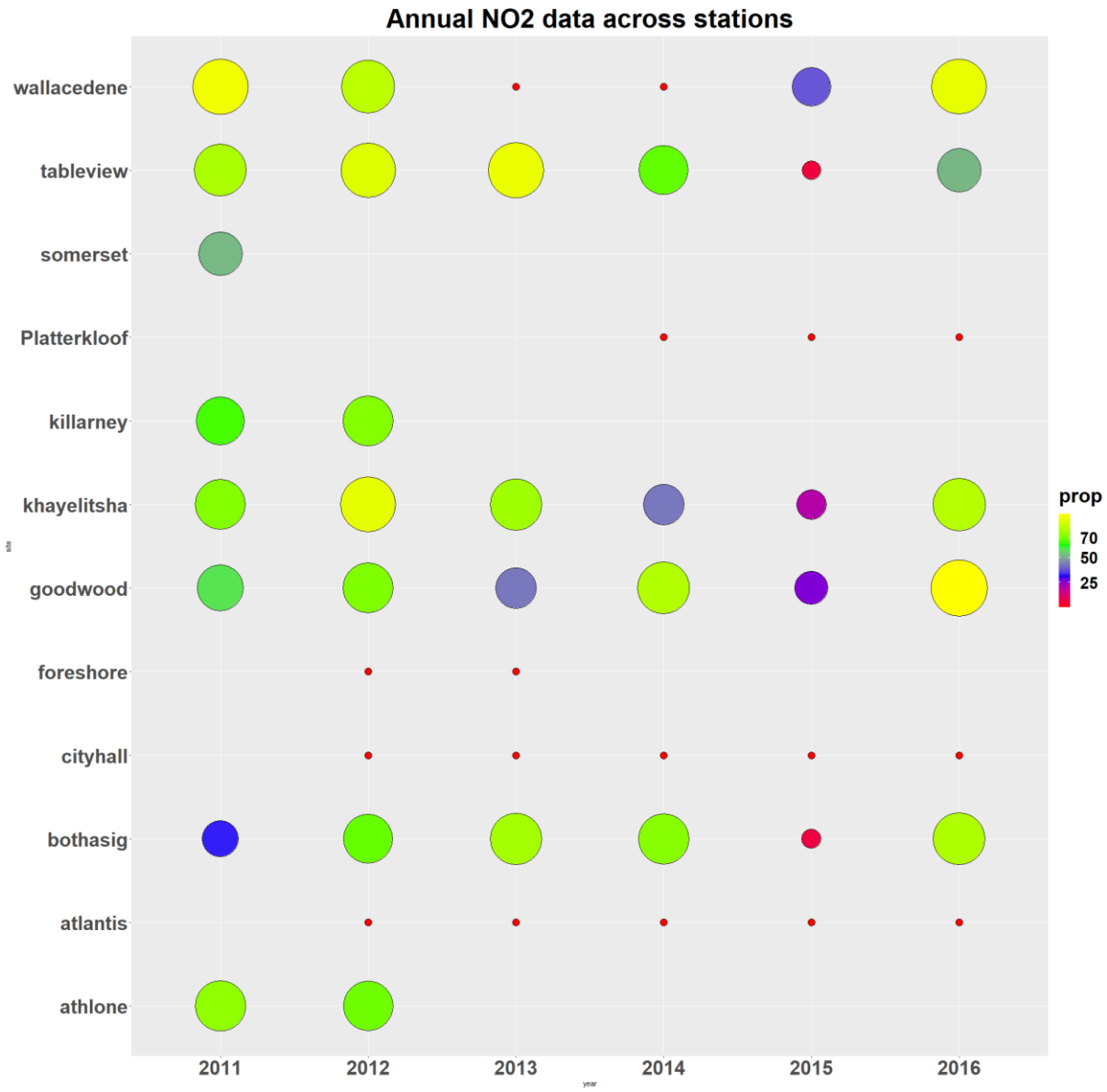

Figure 4: The proportion of NO2 daily means data collected from 12 stations from 1st Jan 2011 – 31 October 2016 in Cape Town.

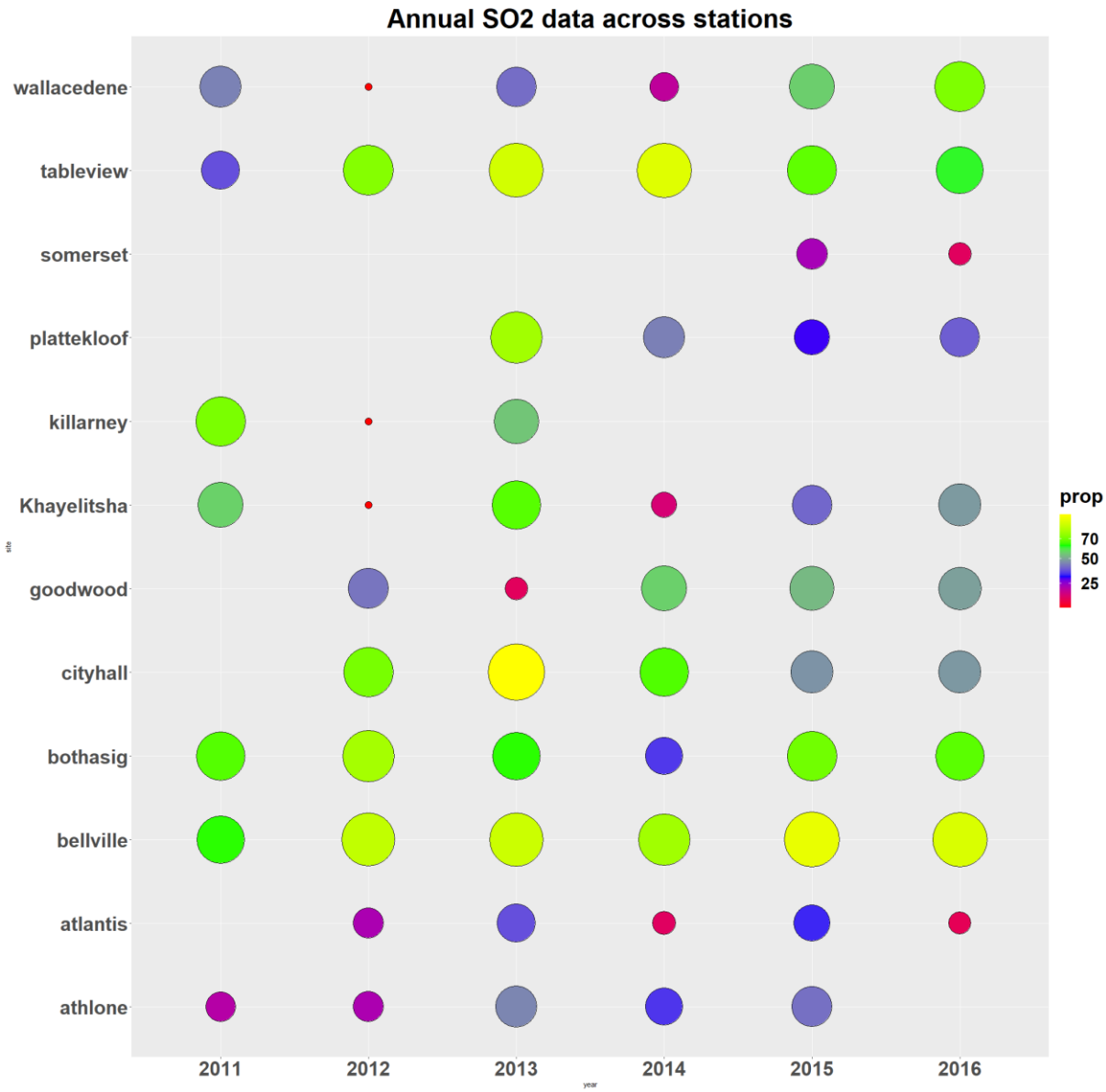

Figure 5: The proportion of SO2 daily means data collected from 12 stations from 1st Jan 2011 – 31 October 2016 in Cape Town.

The geographical locations of some of the stations and their classifications are shown in the map below.

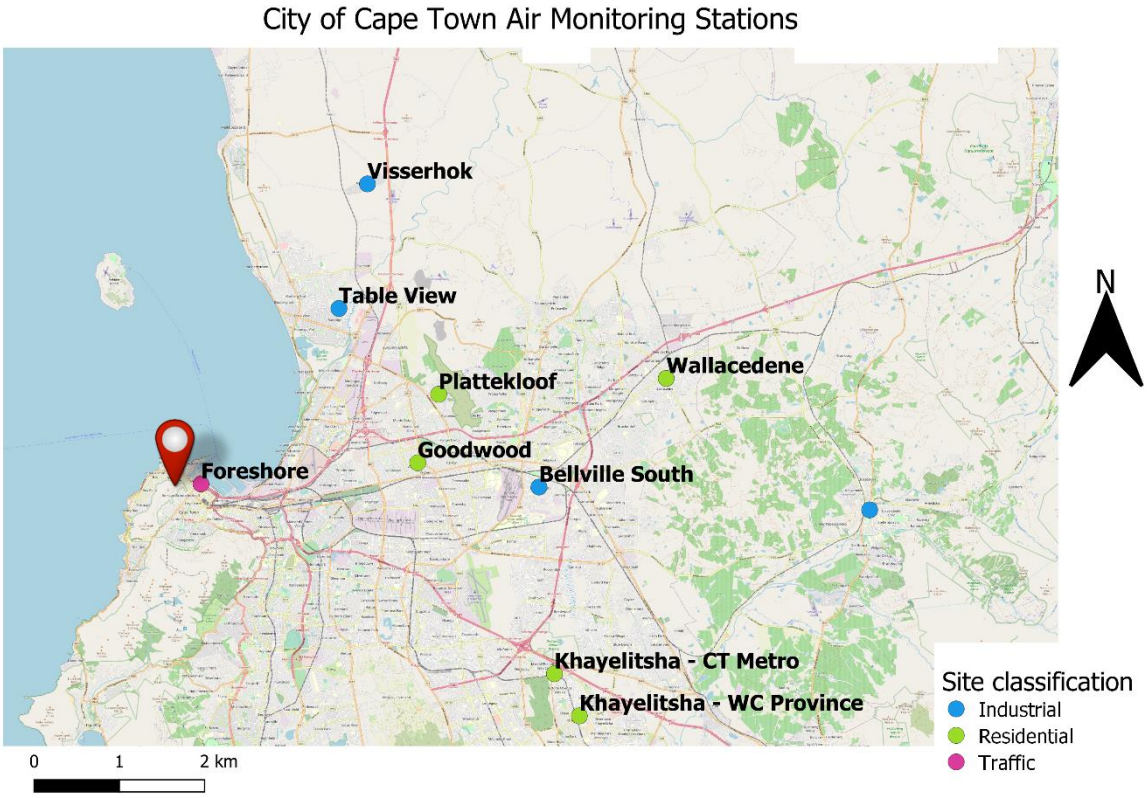

Figure 1: Air quality monitoring station in the City of Cape Town and their classifications. Stations shown on this map are those in close proximity to the City of Cape Town but all 12 stations were used in the analysis.

Correlation among stations

Spearman correlation was used to test the correlation among the stations for each pollutant's daily means during the the study period. We found high degree of correlation among PM10 stations, moderate correlation for NO2 and low degree of correlation among SO2 stations. This is illustrated in the correlation matrix below.

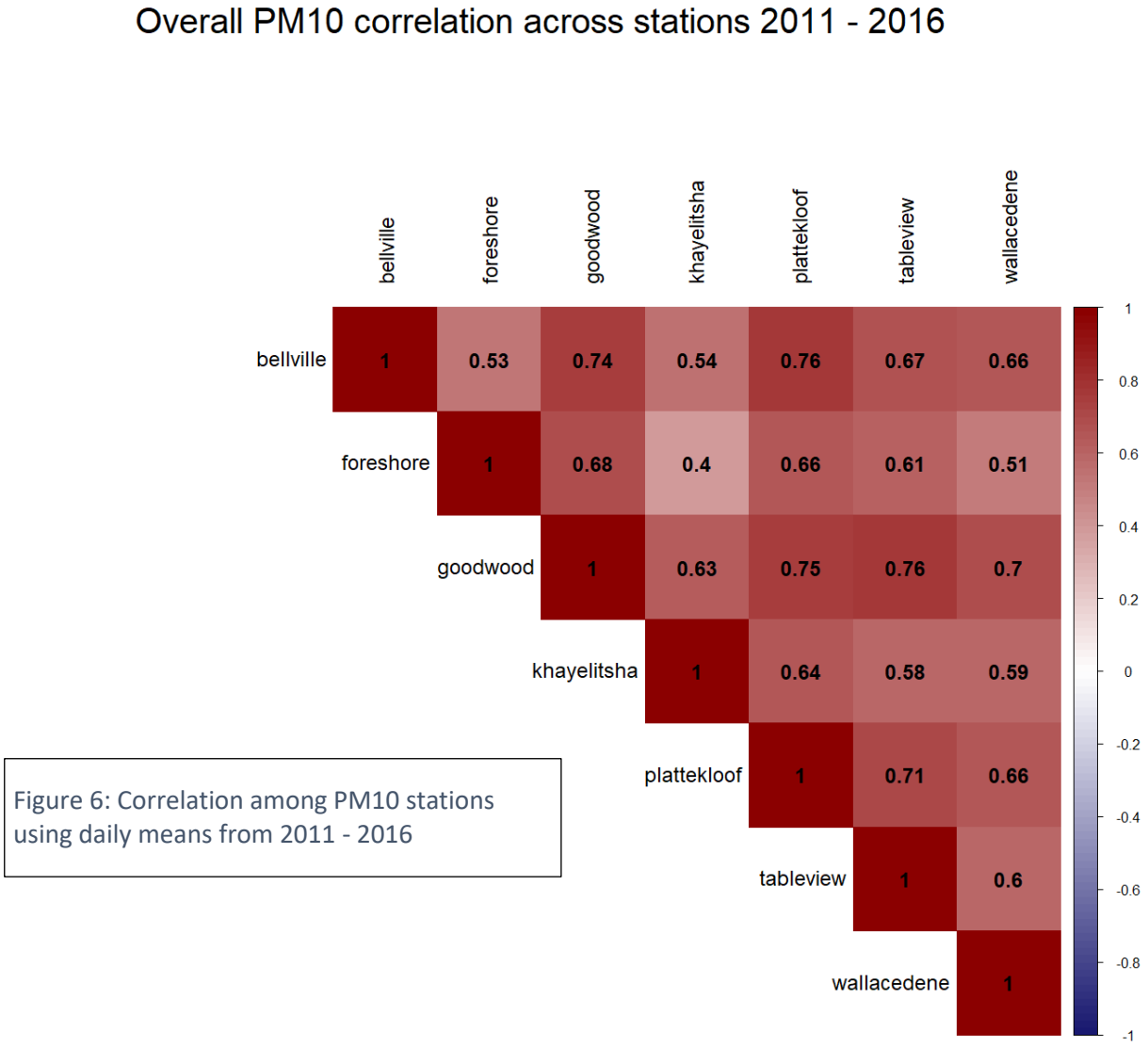

Figure 6: Correlation among PM10 stations using daily means from 2011 - 2016

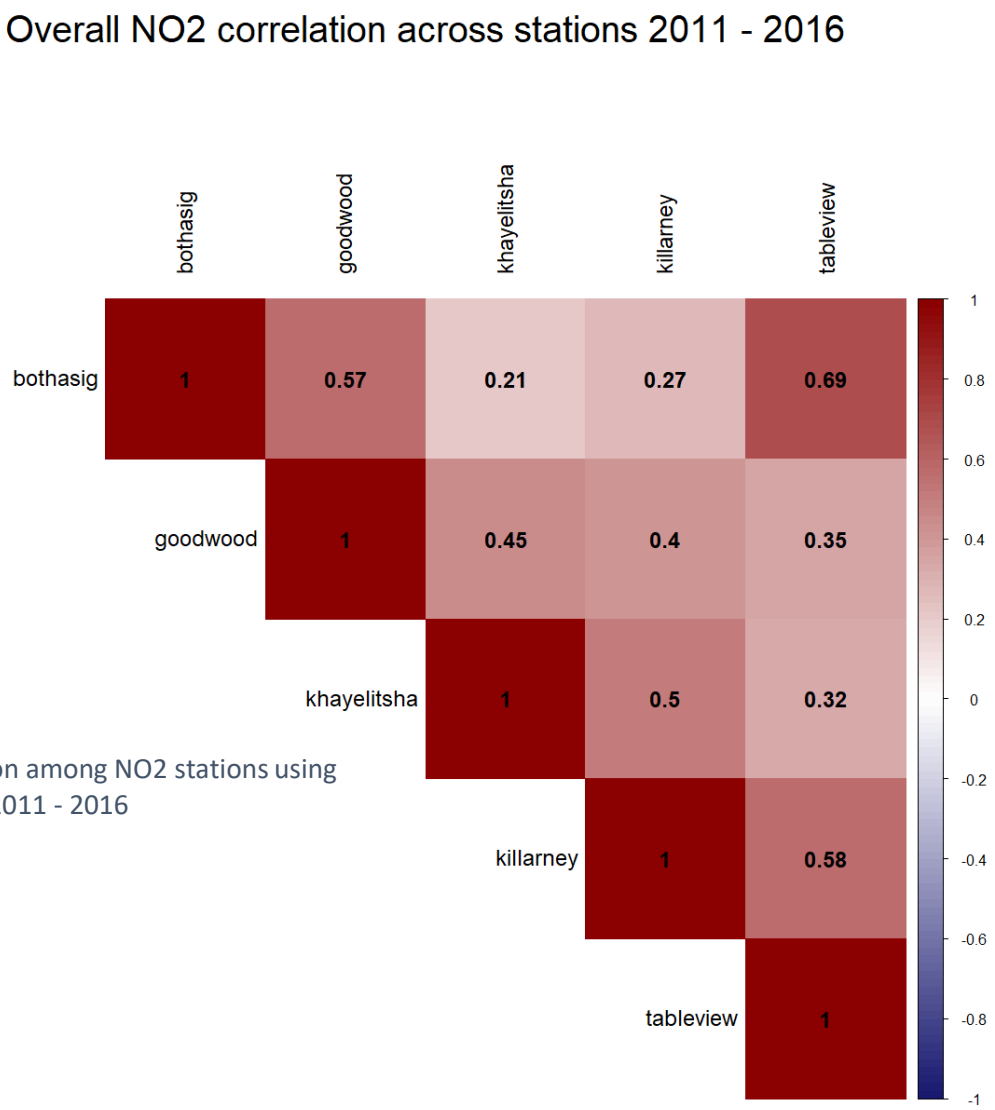

Figure 7: Correlation among NO2 stations using daily means from 2011 - 2016

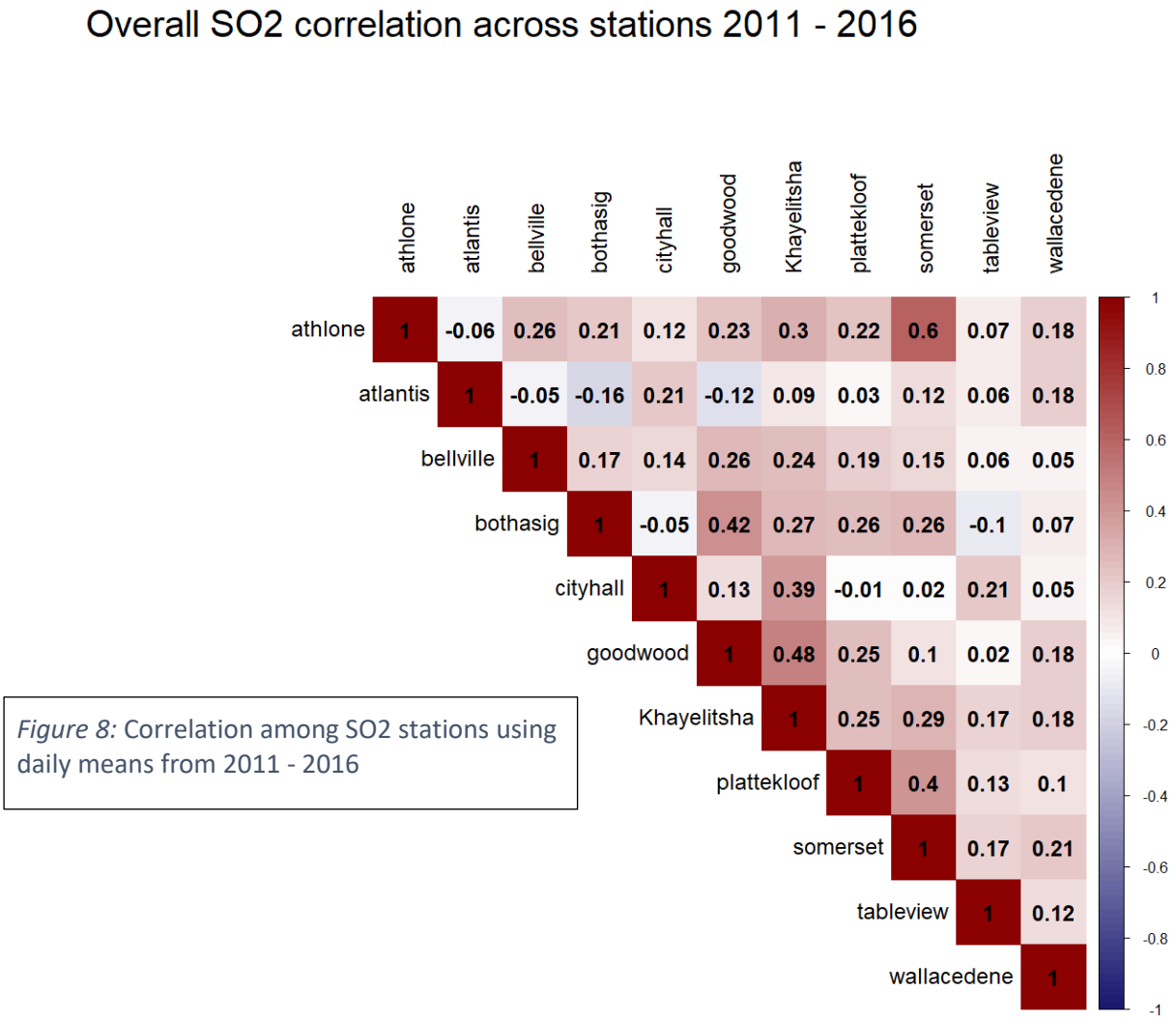

Figure 8: Correlation among SO2 stations using daily means from 2011 - 2016

Imputation of daily air pollutant data

The data obtained included missing days for all stations and pollutants; this is illustrated in Figure 3 Figure 4 and Figure 5. Thus, the intuitive solution for each pollutant was to take the average measurement on each day for all the stations with available data to obtain a city-level mean for the time-series analysis. However, this will introduce data gaps in the daily mean levels of the time series data. Therefore, we went a step further by imputing for stations with missing daily means we imputed an estimated mean based on the data of other stations. In case no station had a valid daily mean value, the concentration was defined as "missing". For instance, if day 5 has a daily city-level mean (that is mean across all stations) but 2 out of 7 stations had no measurement, we imputed daily means for those 2 stations. Furthermore, if day 10 has no measurement from all stations which means no city-level mean, this was left as missing and no imputation was done.

First, we describe the notation as - Let $\mathcal{M} = \{1, \dots, M\}$ denote the set of monitoring stations and let $C_i(t)$ denote the mean concentration of the pollutant of interest at station $i\ on\ day\ t$. Moreover, let $m_i(t)$ take the value 1 if a mean value is not available from station $i\ on\ day\ t$ and the value 0 otherwise.

Therefore,

$$S(t) = \sum_{i \in \mathcal{M}: m_i(t) = 0} C_{i\,(t)} \qquad (1)$$

The algorithm

In order to derive the daily city-level imputation factors, $S(t)$ is estimated using a non-linear regression model.

$$\begin{aligned} \mathrm{E}[S(t)] = \exp(&\beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \cos(t/365.25 \times 2\pi) \\ &+ \beta_4 \sin(t/365.25 \times 2\pi) + \sum_{i \in \mathcal{M}} \gamma_i m_i(t) \\ &+ f(meteo\ variables) \\ &+ g\big(meteo\ variables, m_i(t), \dots, m_M(t)\big)\big) \end{aligned} \qquad (2)$$

The meteo variables used were temperature, relative humidity, wind speed and wind direction.

Where f is a linear function of meteo-variables with unknown parameters and g is a linear function of the product terms between meteo variables and missing indicators variables $m_i(t)$, each with an unknown parameter.

Furthermore, let

$$\begin{aligned} I(t) = \exp(&\beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \cos(t/365.25 \times 2\pi) \\ &+ \beta_4 \sin(t/365.25 \times 2\pi) + \hat{f}(meteo\ variables)) \end{aligned} \qquad (3)$$

We then further defined

	$S^{imp}(t) = S(t)/\hat{S}(t) \times I(t)$	(4)

Where $\hat{S}(t)$ is the estimate of $S(t)$ from the regression model. Finally, let

	$C(t) = \frac{S^{imp}(t)}{M}$	(5)

If there are no missing values on a day t across all M stations, then all $m_i(t)$ are 0, implying that $I(t) = \hat{S}(t)$ and thus $S^{imp}(t) = S(t)$. In this case, $C(t) = \frac{S(t)}{M}$ equal the mean of daily concentration values across all M stations. Therefore, on days with complete data, the algorithm makes no imputation.

Time-series analysis results.

Table A1: Temporal spearman rank correlation coefficients among daily mean concentrations of ambient air pollutants and meteorological variables during the year and by seasons

	PM_{10}	NO_2	SO_2	Temperature	Humidity
	Overall year				
PM_{10}	1				
NO_2	0.302	1			
SO_2	0.195	0.274	1		
Temperature	0.227	-0.378	0.006	1	
Humidity	-0.293	0.019	-0.108	-0.392	1
Warm season	September – April				
PM10	1				
NO2	0.19	1			
SO2	0.174	0.184	1		
Temperature	0.391	-0.214	0.065	1	
Humidity	-0.303	-0.038	-0.126	-0.234	1
Cold season	May – August				
PM_{10}	1				
NO_2	0.572	1			
SO_2	0.321	0.402	1		
Temperature	0.026	-0.087	0.067	1	
Humidity	-0.271	-0.337	-0.231	-0.006	1

Table A2: Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of PM10 concentrations and hospital admissions due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2011 - 31 October.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (12ug/m3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM10	1.019	1.005	1.032	1.021	1.006	1.035
Age 0 - 14		1.02	1.002	1.039			
Age 15 - 64		1.009	0.988	1.03	1.021	1.002	1.039
Age >65		1.019	0.994	1.046	1.022	1.004	1.041
Female		1.014	0.997	1.032	1.02	1.001	1.04
Male		1.02	1.002	1.037	1.021	1.003	1.038
All ages and sex	$PM10_{NO2}$	1.009	0.992	1.026	1.02	1.003	1.038
Age 0 - 14		1.008	0.984	1.031			
Age 15 - 64		1.005	0.978	1.033	1.022	1	1.045
Age >65		1.02	0.986	1.055	1.022	0.999	1.044
Female		1.006	0.985	1.029	1.022	0.997	1.046
Male		1.012	0.989	1.034	1.02	0.999	1.042
All ages and sex	$PM10_{SO2}$	1.017	1.003	1.031	1.022	1.007	1.037
Age 0 - 14		1.016	0.997	1.035			
Age 15 - 64		1.011	0.989	1.033	1.021	1.002	1.041
Age >65		1.023	0.995	1.051	1.026	1.007	1.045
Female		1.016	0.998	1.034	1.02	0.999	1.041
Male		1.016	0.998	1.035	1.026	1.008	1.044
All ages and sex	$PM10_{NO2\ SO2}$	1.008	0.991	1.026	1.021	1.002	1.039
Age 0 - 14		1.004	0.98	1.028			

Age 15 - 64		1.003	0.975	1.031	1.02	0.997	1.044
Age >65		1.024	0.989	1.06	1.025	1.002	1.048
Female		1.006	0.984	1.029	1.02	0.996	1.046
Male		1.01	0.987	1.033	1.024	1.002	1.046

Interquartile range: PM10: 12 ug/m3, NO2 7.3 µg/m3, SO2 = 3.6 µg/m3. Relative risk estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday meteorological factors including temperature and relative humidity. $PM10_{N02}$, $PM10_{SO2}$ and $PM10_{NO2\ SO2}$ refers to the estimate of PM10 in multiple pollutant models. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size.

Table A3: Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of NO2 concentrations and hospital admissions due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2011 - 31 October.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (7.3 ug/m3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	NO2	1.023	1.006	1.04	1.01	0.992	1.028
Age 0 - 14		1.031	1.007	1.056			
Age 15 - 64		1.003	0.976	1.03	1.006	0.983	1.03
Age >65		1.005	0.972	1.039	1.017	0.994	1.041
Female		1.013	0.991	1.036	1.007	0.983	1.033
Male		1.019	0.997	1.042	1.015	0.993	1.037
All ages and sex	$NO2_{PM10}$	1.016	0.995	1.038	0.997	0.976	1.019
Age 0 - 14		1.027	0.998	1.058			
Age 15 - 64		1.012	0.979	1.047	0.992	0.965	1.02
Age >65		0.995	0.953	1.038	1.003	0.977	1.031
Female		1.018	0.99	1.047	0.994	0.965	1.024
Male		1.012	0.985	1.041	1.002	0.976	1.028

All ages and sex	$NO2_{SO2}$	1.021	1.003	1.039	1.013	0.993	1.032
Age 0 - 14		1.032	1.007	1.058			
Age 15 - 64		1.01	0.981	1.039	1.009	0.985	1.033
Age >65		1.015	0.979	1.053	1.02	0.997	1.045
Female		1.021	0.998	1.045	1.006	0.981	1.033
Male		1.018	0.995	1.042	1.019	0.997	1.043
All ages and sex	$NO2_{PM10\ SO2}$	1.015	0.994	1.037	0.999	0.977	1.022
Age 0 - 14		1.029	0.999	1.061			
Age 15 - 64		1.009	0.975	1.044	0.996	0.969	1.024
Age >65		0.999	0.956	1.043	1.005	0.978	1.033
Female		1.017	0.989	1.046	0.994	0.965	1.024
Male		1.011	0.983	1.04	1.005	0.979	1.032

Interquartile range: PM10: 12 ug/m3, NO2 7.3 µg/m3, SO2 = 3.6 µg/m3. Relative risk estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday meteorological factors including temperature and relative humidity. $NO2_{PM10}$, $NO2_{SO2}$ and $NO2_{PM10\ SO2}$ refers to the estimate of NO2 in multiple pollutant models. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size.

Table A4: Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of SO2 concentrations and hospital admissions due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2011 - 31 October.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (3.2ug/m3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	SO2	1.011	0.998	1.024	0.997	0.984	1.011
Age 0 - 14		1.015	0.997	1.033			
Age 15 - 64		1.011	0.99	1.032	0.998	0.98	1.015
Age >65		0.989	0.963	1.015	0.995	0.978	1.012
Female		1.006	0.989	1.023	1.009	0.99	1.028
Male		1.015	0.998	1.032	0.987	0.971	1.003

All ages and sex	$SO2_{PM10}$	1.006	0.993	1.02	0.993	0.979	1.007
Age 0 - 14		1.011	0.991	1.03			
Age 15 - 64		1.011	0.989	1.033	0.992	0.974	1.011
Age >65		0.986	0.959	1.014	0.989	0.972	1.007
Female		1.005	0.987	1.023	1.004	0.985	1.024
Male		1.008	0.99	1.027	0.981	0.965	0.998
All ages and sex	$SO2_{NO2}$	1.005	0.991	1.019	0.999	0.984	1.014
Age 0 - 14		1.005	0.985	1.025			
Age 15 - 64		1.016	0.992	1.039	1.001	0.982	1.02
Age >65		0.981	0.953	1.011	0.992	0.974	1.011
Female		1.003	0.984	1.022	1.008	0.987	1.028
Male		1.007	0.988	1.026	0.987	0.969	1.004
All ages and sex	$SO2_{PM10\ NO2}$	1.003	0.989	1.018	0.996	0.981	1.011
Age 0 - 14		1.004	0.984	1.025			
Age 15 - 64		1.015	0.991	1.039	0.998	0.979	1.017
Age >65		0.978	0.949	1.008	0.989	0.97	1.008
Female		1.001	0.982	1.021	1.004	0.984	1.025
Male		1.006	0.986	1.025	0.983	0.965	1.001

Interquartile range: PM10: 12 ug/m3, NO2 7.3 µg/m3, SO2 = 3.6 µg/m3. Relative risk estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday meteorological factors including temperature and relative humidity. $SO2_{PM10}$, $SO2_{NO2}$ and $SO2_{PM10\ NO2}$ refers to the estimate of SO2 in multiple pollutant models. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size.

Table A5: Warm season – Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of PM10 concentrations and hospital admissions due to cardiovascular and respiratory diseases in all ages, Cape Town, South Africa, 1 January 2011 - 31 October.

		Respiratory disease	Cardiovascular disease

	Pollutant IQR (ug/m3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM10	1.022	1.005	1.039	1.034	1.015	1.053
	NO2	1.013	0.994	1.033	1.006	0.988	1.025
	SO2	1.023	0.996	1.049	1.027	1.002	1.054

Interquartile range: PM10: 9.7 ug/m3, NO2 5.4 µg/m3, SO2 = 3.0 µg/m3. Relative risk estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday meteorological factors including temperature and relative humidity. $PM10_{N02}$, $PM10_{SO2}$ and $PM10_{NO2\ SO2}$ refers to the estimate of PM10 in multiple pollutant models. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size. The warm season were the months of September – April.

Table A6: Cold season – Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of PM10 concentrations and hospital admissions due to cardiovascular and respiratory diseases in all ages, Cape Town, South Africa, 1 January 2011 - 31 October.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (ug/m3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM10	1.013	0.994	1.033	1.006	0.988	1.025
	NO2	1.023	0.996	1.049	1.027	1.002	1.054
	SO2	1.023	1.001	1.046	1	0.977	1.023

Table A7: Single and multiple pollutant model adjusted relative risk (RR) for 10 ug/m3 increase in the two-day moving average of PM10 concentrations and hospital admissions due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2011 - 31 October.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10ug/m3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM10	1.018	1.005	1.03	1.019	1.006	1.033
Age 0 - 14		1.02	1.002	1.037			
Age 15 - 64		1.009	0.989	1.029	1.019	1.001	1.037
Age >65		1.018	0.994	1.044	1.021	1.004	1.039
Female		1.014	0.997	1.031	1.019	1.001	1.039
Male		1.019	1.002	1.035	1.02	1.003	1.036
All ages and sex	$PM10_{NO2}$	1.009	0.993	1.025	1.019	1.002	1.036
Age 0 - 14		1.007	0.985	1.03			
Age 15 - 64		1.005	0.979	1.031	1.021	1	1.043
Age >65		1.019	0.986	1.052	1.021	0.999	1.042
Female		1.006	0.985	1.027	1.021	0.998	1.044
Male		1.011	0.99	1.033	1.019	0.999	1.04
All ages and sex	$PM10_{SO2}$	1.016	1.003	1.029	1.023	1.009	1.038
Age 0 - 14		1.018	0.999	1.036			
Age 15 - 64		1.01	0.989	1.032	1.02	1.002	1.039
Age >65		1.022	0.995	1.049	1.025	1.007	1.043
Female		1.015	0.998	1.033	1.019	0.999	1.039
Male		1.016	0.998	1.033	1.025	1.008	1.042
All ages and sex	$PM10_{NO2\ SO2}$	1.008	0.992	1.025	1.022	1.005	1.039
Age 0 - 14		1.006	0.983	1.029			
Age 15 - 64		1.003	0.976	1.029	1.021	0.999	1.043
Age >65		1.023	0.99	1.057	1.024	1.002	1.046
Female		1.006	0.985	1.028	1.019	0.996	1.044
Male		1.01	0.988	1.032	1.023	1.002	1.044

Average: PM10: 24.4 ug/m3, NO2 15 µg/m3, SO2 = 9.4 µg/m3. Relative risk estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday meteorological factors including temperature and relative humidity. $PM10_{N02}$, $PM10_{SO2}$ and $PM10_{NO2\ SO2}$ refers to the estimate of PM10 in multiple pollutant models. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size.

Table A8: Single and multiple pollutant model adjusted relative risk (RR) for 10 ug/m3 increase in the two-day moving average of NO2 concentrations and hospital admissions due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2011 - 31 October.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (6.8ug/m3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	NO2	1.034	1.008	1.059	1.013	0.987	1.04
Age 0 - 14		1.048	1.013	1.084			
Age 15 - 64		1.004	0.965	1.044	1.009	0.975	1.044
Age >65		1.008	0.959	1.058	1.025	0.991	1.06
Female		1.021	0.989	1.055	1.011	0.975	1.049
Male		1.029	0.996	1.062	1.022	0.989	1.055
All ages and sex	$NO2_{PM10}$	1.024	0.993	1.056	0.996	0.964	1.028
Age 0 - 14		1.04	0.997	1.086			
Age 15 - 64		1.018	0.969	1.07	0.988	0.949	1.029
Age >65		0.992	0.931	1.057	1.005	0.966	1.046
Female		1.027	0.986	1.069	0.991	0.949	1.035
Male		1.018	0.978	1.061	1.003	0.965	1.041
All ages and sex	$NO2_{SO2}$	1.031	1.004	1.058	1.022	0.994	1.051
Age 0 - 14		1.045	1.008	1.084			
Age 15 - 64		1.015	0.973	1.058	1.01	0.976	1.047
Age >65		1.023	0.97	1.079	1.03	0.995	1.066
Female		1.032	0.997	1.067	1.009	0.972	1.048
Male		1.027	0.992	1.063	1.029	0.995	1.063

All ages and sex	$NO2_{PM10\ SO2}$	1.022	0.991	1.054	1.001	0.969	1.034
Age 0 - 14		1.039	0.995	1.085			
Age 15 - 64		1.013	0.963	1.065	0.992	0.952	1.033
Age >65		0.998	0.936	1.064	1.007	0.968	1.049
Female		1.026	0.984	1.069	0.991	0.949	1.036
Male		1.016	0.975	1.059	1.008	0.97	1.047

Average: PM10: 24.4 ug/m3, NO2 15 µg/m3, SO2 = 9.4 µg/m3. Relative risk estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday meteorological factors including temperature and relative humidity. $NO2_{PM10}$, $NO2_{SO2}$ and $NO2_{PM10\ SO2}$ refers to the estimate of NO2 in multiple pollutant models. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size.

Table A9: Single and multiple pollutant model adjusted relative risk (RR) for 10 ug/m3 increase in the two-day moving average of SO2 concentrations and hospital admissions due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2011 - 31 October.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (3.2ug/m3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	SO2	1.035	0.993	1.078	0.988	0.947	1.031
Age 0 - 14		1.044	0.988	1.104			
Age 15 - 64		1.035	0.97	1.103	0.993	0.94	1.049
Age >65		0.966	0.891	1.048	0.984	0.932	1.039
Female		1.012	0.96	1.067	1.028	0.97	1.091
Male		1.035	0.978	1.094	0.96	0.912	1.011
All ages and sex	$SO2_{PM10}$	1.02	0.977	1.064	0.973	0.931	1.017
Age 0 - 14		1.03	0.971	1.093			
Age 15 - 64		1.034	0.965	1.107	0.976	0.923	1.033
Age >65		0.958	0.878	1.046	0.967	0.914	1.023
Female		1.015	0.96	1.073	1.014	0.954	1.077
Male		1.025	0.969	1.085	0.943	0.894	0.994

All ages and sex	$SO2_{NO2}$	1.015	0.971	1.062	0.985	0.94	1.032
Age 0 - 14		1.016	0.954	1.081			
Age 15 - 64		1.05	0.977	1.128	0.997	0.941	1.058
Age >65		0.943	0.86	1.034	0.976	0.92	1.035
Female		1.01	0.952	1.071	1.024	0.961	1.091
Male		1.021	0.962	1.084	0.959	0.907	1.014
All ages and sex	$SO2_{PM10\ NO2}$	1.01	0.965	1.057	0.975	0.931	1.022
Age 0 - 14		1.012	0.95	1.078			
Age 15 - 64		1.046	0.973	1.126	0.986	0.929	1.046
Age >65		0.934	0.85	1.025	0.966	0.91	1.025
Female		1.004	0.946	1.065	1.014	0.951	1.081
Male		1.018	0.958	1.081	0.949	0.896	1.004

Average: PM10: 24.4 ug/m3, NO2 15 µg/m3, SO2 = 9.4 µg/m3. Relative risk estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday meteorological factors including temperature and relative humidity. $SO2_{PM10}$, $SO2_{NO2}$ and $SO2_{PM10\ NO2}$ refers to the estimate of SO2 in multiple pollutant models. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size. For cardiovascular disease age 0-14 was excluded from the modelling due to small sample size.

CHAPTER 3:

Short-Term Effects of PM_{10}, NO_2, SO_2 and O_3 on Cardio-Respiratory Mortality in Cape Town, South Africa, 2006–2015

Article

Short-Term Effects of PM_{10}, NO_2, SO_2 and O_3 on Cardio-Respiratory Mortality in Cape Town, South Africa, 2006–2015

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Abstract: Background: The health effect of air pollution is rarely quantified in Africa, and this is evident in global systematic reviews and multi-city studies which only includes South Africa. Methods: A time-series analysis was conducted on daily mortality (cardiovascular (CVD) and respiratory diseases (RD)) and air pollution from 2006–2015 for the city of Cape Town. We fitted single- and multi-pollutant models to test the independent effects of particulate matter (PM_{10}), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and ozone (O_3) from co-pollutants. Results: daily average concentrations per interquartile range (IQR) increase of 16.4 μg/m^3 PM_{10}, 10.7 μg/m^3 NO_2, 6 μg/m^3 SO_2 and 15.6 μg/m^3 O_3 lag 0–1 were positively associated with CVD, with an increased risk of 2.4% (95% CI: 0.9–3.9%), 2.2 (95% CI: 0.4–4.1%), 1.4% (95% CI: 0–2.8%) and 2.5% (95% CI: 0.2–4.8%), respectively. For RD, only NO_2 showed a significant positive association with a 4.5% (95% CI: 1.4–7.6%) increase per IQR. In multi-pollutant models, associations of NO_2 with RD remained unchanged when adjusted for PM_{10} and SO_2 but was weakened for O_3. In CVD, O_3 estimates were insensitive to other pollutants showing an increased risk. Interestingly, CVD and RD lag structures of PM_{10}, showed significant acute effect with evidence of mortality displacement. Conclusion: The findings suggest that air pollution is associated with mortality, and exposure to PM_{10} advances the death of frail population.

Keywords: multi-pollutant; air pollution; mortality; harvesting; South Africa

1. Introduction

Since the first half of the twentieth century, the association between ambient air pollution and adverse health outcomes has been documented extensively with historical events such as the smog incidents in Meuse Valley, Belgium (1930), Donora, Pennsylvania (1948), and London (1952). Exposure to high levels of air pollution resulted in increased hospitalization and deaths for cardiovascular and respiratory diseases, particularly in the elderly and those with comorbidities (108). In a recent assessment, ambient air pollution ranked seventh among modifiable disease risk factors, above other factors such as high cholesterol, household air pollution and alcohol use (109); in contrast to the other risk factors, air pollution is not easily modifiable at individual levels.

Air pollution consists of a complex heterogeneous mixture of gases and particles, some of which are routinely monitored and referred to as criteria pollutants; these include gaseous pollutants such as nitrogen dioxide (NO_2), sulphur dioxide (SO_2), ozone (O_3) and particles namely-PM_{10} (diameter < 10 μm) and $PM_{2.5}$ (diameter < 2.5 μm). There is no evidence of no-effect-thresholds for these pollutants. In fact, health outcomes have been observed even at levels lower than stringent air quality guidelines promoted by the World Health Organization (WHO) Air Quality Guidelines (AQG) in 2005 (110). Accordingly, WHO updated its air quality guidelines (AQG) in 2021 based on accumulated evidence from six systematic reviews that considered more than 500 articles on air pollution and health (3). The new guideline values are lower than in the 2005 edition, for instance, 24-h and annual average values for PM10 were reduced to 45 μg/m^3 from 50 μg/m^3, and to 15 μg/m^3 from 20 μg/m^3, respectively. The guideline value for the NO2 annual average had the most substantial reduction from 40 to 10 μg/m^3. In addition, new guideline values for NO_2 and ozone were introduced: 25 μg/m^3 for NO_2 24-h mean and 60 μg/m^3, for O_3 peak season value—which is the 8-h mean from the highest six-month running-average concentration.

Some of the systematic reviews that contributed to the development of the new AQG reported that a 10 μg/m^3 rise in the daily mean concentration of PM_{10} was associated with 0.6% (95% CI 0.44–0.77%) and 0.9% (95% CI 0.63–1.2%) increases in daily cardiovascular and respiratory disease mortality, respectively. In addition, 10 μg/m^3 increases in NO_2 and O_3 were associated with an elevated risk of 0.72% (95% CI 0.59–0.85%) and 0.43% (95% CI 0.34–0.52%) in daily all-cause mortality, respectively (111). Another meta-analysis found a positive association between SO_2 and all-cause mortality with an estimated additional risk of 0.59% (95% CI: 0.46–0.71%), for a 10 μg/m^3 increment in 24-h concentration (112).

A total of 263 studies were included in the two reviews, but only one study was from Africa (13). People in African countries disproportionately experience the burden of outdoor air pollution, however respective health effects are rarely quantified for those countries, with South Africa accounting for the majority of the studies from the region. Thus, the current evidence is largely dominated by single and multi-city studies from North America and Europe (113-117).

Two Multi-Country Multi-City (MCC) Collaborative Research Network studies on air pollution (PM_{10} and O_3) and mortality have been conducted which included South Africa cities; in both studies it was the only African country (15, 16). Air quality monitoring in other regions of the African continent is not well established, resulting in a lack of data for such studies. In the City of Cape Town, epidemiological time-series studies have shown short-term associations between air pollution and cardio-respiratory disease mortality (13, 14), however none of them assessed the independent effects of multiple pollutants. As people are exposed to multiple pollutants in the atmosphere—it is crucial to estimate the independent short-term effects of individual pollutants in multi-pollutant models by including the different pollutants simultaneously. The multipollutant approach is also relevant for the distinction of different sources of air pollution. For instance, PM_{10} is a marker of traffic emissions in addition to other combustion and non-combustion sources. In many cities, NO_2 is a marker of traffic pollution, while SO_2 may point to power plant emissions and other fossil fuel combustion sources. In addition, SO_2 is converted to SO_4^{2-} in the presence of nitrogen oxides when sunlight is at its brightest and contributes to PM (77); O_3, as a secondary pollutant, is a marker of anthropogenic and natural sources (118). Therefore, using single pollutants as a proxy for complex mixtures of pollutants does not properly account for the health effects caused by the simultaneous exposure to multiple pollutants whose concentrations do not vary proportionally over time (18).

The present study aims to bridge this gap by estimating the associations of daily concentrations of PM_{10}, NO_2, SO_2, O_3 with daily mortality due to respiratory and cardiovascular diseases, using both single and multi-pollutant models. In addition, we investigate whether associations differ by age groups, sex, and seasons, and provide detailed effect estimates across a lag period of three weeks.

2. Method

2.1. Study Area

The City of Cape Town is South Africa's legislative capital and the capital city for the Western Cape Province. It has a population of 4.6 million people and approximately 1.9 million households in 2020 (119). A majority of the population are the economically active group within the ages of 15–64 years, which comprise 69.5% of the population.

2.2. Outcome and Exposure Data

The study is based on three datasets: cardio-respiratory mortality, air pollution and meteorological data from the City of Cape Town, covering the period 1 January 2006 to 31 December 2015. Mortality data was obtained from Statistics South Africa (StatsSA) after signing a Data User Agreement. The data included daily counts of cardiovascular and respiratory deaths aggregated by age groups (excluding <15 which was not provided by StatsSA) and sex for the study period using the International Classification of Disease, 10th version (ICD–10) (J00-J99) and (I00-I99) to select respiratory and cardiovascular deaths, respectively.

Daily hourly measurements of air pollution data for PM_{10}, NO_2, SO_2, and O_3 were obtained for the study period from the City of Cape Town. These are routinely monitored pollutants within the air quality monitoring network of 14 stations. We obtained the daily mean for each station by using a minimum of 18 h measurements (75%) and thereafter calculated the city-level daily mean by taking the averages across stations. Missing values were imputed for stations without measurements provided other stations on the same day were non-missing; otherwise, days without measurements at all stations were left as missing. The details and the imputation algorithms are illustrated in an earlier study (120).

$PM_{2.5}$ data was not included because this standard only came into effect in 2012, and measurements have been very incomplete until recently. According to South Africa, air quality information system (SAAQIS), monthly reports including statistical description of $PM_{2.5}$ measurements only became available in December 2018, thereafter two stations were added in 2019 (Khayelitsha) and 2020 (Foreshore) (121).

Daily means of hourly temperature and relative humidity data were obtained from South Weather Service (SAWS) for the study period.

2.3. Statistical Analysis

We described the distributions of daily death counts, air pollutant levels and meteorological variables using means, standard deviations and percentiles (Table 1). Statistics are presented for the total population and stratified by age group (15–64 and >65), sex (male and female) and season (warm/dry (Nov–Mar) and cold/wet (Apr–Oct)). In addition, we examined the temporal correlation between the air pollutant and meteorological daily means using Spearman correlation coefficients (Table 2).

Table 1. Descriptive statistics for daily counts of cardiovascular and respiratory mortality, daily concentrations of PM_{10}, NO_2, SO_2 and O_3 and daily meteorological variables in Cape Town, South Africa during 1 January 2006 to 31 December 2015.

						Percentiles			By Season-Mean (SD)	
Variable	**Mean**	**SD**	**Min**	**Max**	**IQR**	**25th**	**50th**	**75th**	**Warm/Dry**	**Cold/Wet**
Cardiovascular disease									n = 33,427	n = 20,929
All ages and sex n = 54,356	14.88	4.49	2	33	6	12	15	18	13.80 (4.01)	17.01 (4.61)
15–64 years n = 20,145	5.52	2.50	0	18	3	4	5	7	5.25 (2.37)	6.05 (2.67)
>65 years n = 34,164	9.35	3.49	0	26	5	7	9	12	8.54 (3.12)	11 (3.61)
Female n = 28,133	7.70	3.01	0	20	4	6	7	10	7.14 (2.78)	8.81 (3.13)
Male n = 26,167	7.17	2.90	0	23	4	5	7	9	6.65 (2.68)	8.19 (3.04)
Respiratory disease									n = 11,625	n = 8751
All ages and sex n = 20,376	5.58	2.85	0	75	3	4	5	7	4.80 (2.36)	7.11 (3.09)
15–64 years n = 9735	2.67	1.78	0	32	3	1	2	4	2.31 (1.55)	3.36 (1.98)
>65 years n = 10,588	2.90	1.93	0	17	3	1	3	4	2.47 (1.67)	3.74 (2.14)
Female n = 11,270	2.48	1.74	0	44	2	1	2	3	2.12 (1.53)	3.19 (1.91)
Male n = 9063	3.09	1.94	0	40	2	2	3	4	2.67 (1.68)	3.90 (2.18)
Air pollutants										
PM_{10} (μg/m^3) n = 3647	30.35	13.6	6.56	98.63	16.35	20.44	27.32	36.8	29.5 (12.33)	31.53 (15.73)
NO_2 (μg/m^3) n = 3603	16.63	8.81	2.63	59.24	10.66	10.47	14.77	21.13	14.57 (7.61)	20.33 (9.58)
SO_2 (μg/m^3) n = 2769	10.54	5.46	2.31	49	6	6.88	9.20	12.87	9.81 (4.78)	12 (6.35)
O_3 (μg/m^3) n = 2672	33.06	12.28	2.38	89.08	15.60	24.87	33.06	40.46	32.35 (12)	34.55 (12.7)
Meteorological data										
Temperature (°C)	17.39	11.02	30.67	100	15.67	62	70.3	77	19.3 (3.49)	13.6 (2.33)
Relative humidity (%)	69.8	4.2	7.5	30	6.8	14	17.3	20.7	67 (10)	76 (10.8)

Abbreviations : SD—standard deviation ; Min—minimum; Max—maximum; IQR—interquartile range. Warm/dry period: November–March; Cold/wet period: April–October.

Table 2. Spearman's rank correlation between city-level daily mean PM_{10}, NO_2, SO_2, O_3 and meteorological parameters during the period of 1 January 2006 to 31 December 2015 in Cape Town, South Africa.

	PM_{10}	NO_2	SO_2	O_3	Temperature	Humidity
PM_{10}	1	0.38	0.27	0.12	0.17	−0.25
NO_2		1	0.40	0.06	−0.35	0.07
SO_2			1	−0.11	−0.12	−0.01
O_3				1	−0.13	0.01
Temperature					1	−0.41
Humidity						1

We investigated the association between daily counts of cardiovascular and respiratory disease (CVD and RD) deaths and air pollutant levels of PM_{10}, NO_2, SO_2 and O_3 using quasi-Poisson regression models. The core model was developed without the pollutant variables. Natural splines were used to model time trends and seasonal variations and penalized spline was used for the influences of temperature and relative humidity. An appropriate placement and selection of knots of the spline of calendar time is crucial to avoid overfitting, which may reduce the effects of air pollution, and underfitting, which could bias the results due to confounding by uncontrolled short-term influences. We started with natural splines by placing knots every 45 days over the study period of 3652 days (eight knots per year), which resulted in a sequence of 81 knots. We then iteratively removed the least significant knots until the sum of partial autocorrelations across lags 1 to 28 changed from negative to positive. This process produced 46 knots for CVD and 63 knots for RD. The respective knot sequences were then used in the pollutant models. In addition, we controlled for temperature and relative humidity using penalized splines of their moving average levels over four days (including the day of the event). Finally, "day of the week" and "public holiday" were included as categorical variables with 6 and 1 degrees of freedom, respectively. The basic pollutant model may be written as follows:

$$\log(E[Y_i]) = \alpha + \beta_1 \times poll + ns(time, knots = knotseq) + s(avgtemp03) + s(avgrh03) + \Sigma\, \beta_{2i} DOW_i + \beta_3 \times Pubday \quad (7)$$

where $E[Y_i]$ is the expected number of deaths on day *given the predictor variables*, $poll$ is the two-day moving average of the respective pollutant, $time$ is time in days, starting at 1 January 2006, $avgtemp03$ and $avgrh03$ are the averages of temperature and relative humidity across lags 0 to 3, DOW_i (i = 1,…,6) are indicator variables for the six days of the week other than Sunday, and $Pubday$ is an indicator variable for government recognized public holidays. The Greek letters stand for regression parameters, ns for "natural spline" and s for "penalized spline function". The moving averages of two-day and three-day for pollutant and meteorological covariates are typically used in studies investigating short-term effects.

Two-, three- and four-pollutant models were run for all respective combinations among the four pollutants. In addition to the overall analysis, the models included interaction terms to assess effect modification by sex (male vs. female), age groups (15–64 and >65) and seasons (warm/dry vs. cold/wet months).

To estimate the cumulative effects over 21 lags, we used a cross basis function for each pollutant within a distributed lag non-linear (DLNM) framework (65). A linear

exposure-response function with a natural cubic spline for the lag weights were specified in addition to placing knots at lags 2, 5, and 9. We again considered lags 0 to 3 for temperature and relative humidity and defined the crossbasis for the two variables involving natural splines for *argvar* and *arglag* with 5 and 3 degrees of freedom, respectively.

All statistical analyses were conducted using R statistical software version 4.0.3 using mgcv, splines and dlnm packages.

3. Results

There was a total of 54 356 CVD deaths and 20 376 RD deaths between 1 January 2006 and 31 December 2015, as reported in Table 1. The mean number of deaths per day was 15 for CVD and 6 for RD; mean daily levels of air pollutants were 30.4 μg/m^3, 16.6 μg/m^3, 10.5 μg/m^3, and 33.1 μg/m^3 for PM_{10}, NO_2, SO_2 and O_3, respectively. The 2021 WHO air quality guideline 24-h values were exceeded on 497 (13.6%) of the 3652-day study period for PM_{10} (>45 μg/m^3), 501 (13.7%) days for NO_2 (>25 μg/m^3), and 196 (5.4%) days for SO_2 (>40 μg/m^3). There was high variability in the pollutant levels during the study period. For instance, the minimum level for PM_{10} was 6.6 μg/m^3, while the maximum level was 98.6 μg/m^3. The daily average temperature and relative humidity were 17.4 °C and 69.8%, respectively. Table 2 shows weak but positive pairwise correlations for the daily mean concentrations of air pollutants, with the exception of SO_2 and O_3 ($r = -0.11$), whilst temperature and relative humidity were negatively correlated ($r = -0.41$). When stratified by season, the strength of the correlation between PM_{10} and NO_2 increased moderately ($r = 0.54$) during the cold/dry season compared to the weaker correlation ($r = 0.29$) observed in the warm/dry season. In addition, ozone was negatively correlated with other pollutants during the cold/dry season. Correlation results by season for the exposure variables are shown in the Supplementary Materials.

The estimated relative risks and 95% confidence intervals for deaths due to CVD and RD per interquartile range (IQR) increase of the 2-day moving average (lag 0–1) concentration of the four pollutants are presented in Table 3. The RR estimates for the corresponding 10 μg/m^3 increments are provided in the Supplementary Materials.

We observed positive and statistically significant associations between PM_{10} and CVD deaths. The overall risk of CVD death increased by 2.4% (95% 0.9–3.9%) per IQR increase of 16.4 μg/m^3 in PM_{10} exposure. In subgroup analyses, higher associations were observed for persons aged ≥65 years and females with risk increments of 3.3% (95% CI 1.4–5.2%) and 3.2% (1.2–5.3%), respectively. However, these results did not significantly differ from the ones in the complementary subgroup with *p*-values 0.26 and 0.72 for age and gender, respectively. NO_2 was also positively associated with CVD deaths, with an overall increased risk of 2.2% per IQR increase of 10.7 μg/m^3. This association was similar for females and elderly (age ≥ 65 years) except for age 15–64 and males where the relative increases in risk were 0.1% (95% CI −1.9% to 4.1%) and 1.9% (95% CI −0.7 to 4.5%), respectively. An IQR increase of 6 μg/m^3 in the two-day mean of SO_2 was associated with an increased risk of CVD-death by 1.4% (95% CI 0–2.8%); results in subgroups were not statistically significant with the exception of the risk increase by 2.2% (95% CI 0.3–4.1%) in males. Finally, for ozone the estimated overall increase in the risk of CV-death was 2.5% (95% CI 0.2–4.8%) per IQR increase of 15.6 μg/m^3. There were no statistically significant differences in the estimates across strata of age or gender. For example, the largest differences were seen for ozone, where the risk increment was higher in age ≥65 (2.9%;

95% CI 0–5.9%) versus age 15–64 (1.9%; 95% CI −1.8–5.7%), and males (3.5%; 95%CI 0.2–6.9%) versus females (1.8%; 95% CI −1.3–5%).

For RD mortality, we observed the strongest associations with NO_2. Overall, there was an estimated risk increase of 4.5% (95% CI 1.4–7.6%) for an IQR increase of 10.7 $\mu g/m^3$ in the 2-day mean of NO_2. In the age group ≥ 65 years, the respective estimate was 4.9% (95% CI 0.7–9.3%) and in females it was 4.9% (95% CI 0.4–9.6%). The association of daily RD-deaths with the two-day means of SO_2 was also positive overall, but did not reach statistical significance, while there was almost no association with PM_{10} and O_3.

Table 3. Relative risk estimated from Quasi-Poisson regression models of cardiovascular and respiratory disease deaths, adjusting for time trends and seasonal variation, day of the week, public holiday, and meteorological factors including temperature and relative humidity. Estimates are presented per IQR increase in the two-day moving average (lag 0–1) of PM_{10}, NO_2, SO_2 and O_3 for all age and sex groups.

Cardiovascular Disease Deaths by Pollutants											
Per IQR µg/m³	**Per 16 µg/m³ PM_{10}**			**Per 11 µg/m³ NO_2**			**Per 6 µg/m³ SO_2**			**Per 16 µg/m³ O_3**	
Groups	**RR**	**95% Confidence Interval**		**RR**	**95% Confidence Interval**		**RR**	**95% Confidence Interval**		**RR**	**95% Confidence Interval**	
		Lower	**Upper**		**Lower**	**Upper**		**Lower**	**Upper**		**Lower**	**Upper**
All	1.024	1.009	1.039	1.022	1.004	1.041	1.014	1	1.028	1.025	1.002	1.048
Age 15–64	1.011	0.986	1.036	1.01	0.981	1.041	1.01	0.988	1.032	1.019	0.982	1.057
Age ≥65	1.033	1.014	1.052	1.031	1.008	1.054	1.017	0.999	1.034	1.029	1	1.059
Female	1.032	1.012	1.053	1.026	1.001	1.051	1.007	0.989	1.026	1.018	0.987	1.05
Male	1.015	0.994	1.037	1.019	0.993	1.045	1.022	1.003	1.041	1.035	1.002	1.069
Respiratory disease deaths by Pollutants											
Per IQR µg/m³	**Per 16 µg/m³ PM_{10}**			**Per 11 µg/m³ NO_2**			**Per 6 µg/m³ SO_2**			**Per 16 µg/m³ O_3**	
Groups	**RR**	**95% Confidence Interval**		**RR**	**95% Confidence Interval**		**RR**	**95% Confidence Interval**		**RR**	**95% Confidence Interval**	
		Lower	**Upper**		**Lower**	**Upper**		**Lower**	**Upper**		**Lower**	**Upper**
All	1.003	0.978	1.029	1.045	1.014	1.076	1.013	0.99	1.036	1.006	0.965	1.049
Age 15–64	1.003	0.969	1.039	1.041	0.997	1.085	1.01	0.979	1.042	1.007	0.951	1.067
Age ≥65	1.003	0.969	1.038	1.049	1.007	1.093	1.016	0.985	1.047	1.004	0.948	1.063
Female	1.009	0.973	1.047	1.049	1.004	1.096	1.021	0.988	1.055	0.949	0.894	1.008
Male	1	0.967	1.033	1.042	1.002	1.083	1.005	0.976	1.035	1.054	0.998	1.113

The two-, three- and four-pollutant models presented in Figure 1 show an independent positive association between PM_{10} and CVD mortality. The percentage change associated with an IQR increment in PM_{10} increased from 2.4% to 2.8% after adjusting for O_3 and to 3% after adjusting for SO_2 and O_3, although it decreased to 1.9% when we controlled for NO_2. Adjustment for all three co-pollutants reduced the magnitude of the association to 2% and the statistical significance was no longer attained. The association between CVD mortality and NO_2 was substantially reduced after adjusting for PM_{10}, with a decrease in the risk increment from 2.2% to 1%, but the association remained rather stable in the multipollutant models not including PM_{10}. Estimates for SO_2 became weaker and non-significant in all multi-pollutant models and even turned negative after simultaneous adjustment for PM_{10} and O_3. Conversely, the association between O_3 and CVD mortality remained rather unaffected by the inclusion of other pollutants. In summary, associations of CVD-mortality with PM_{10} and NO_2 were weakened when both pollutants were included together, while associations with O_3 were not sensitive to the inclusion of other pollutants.

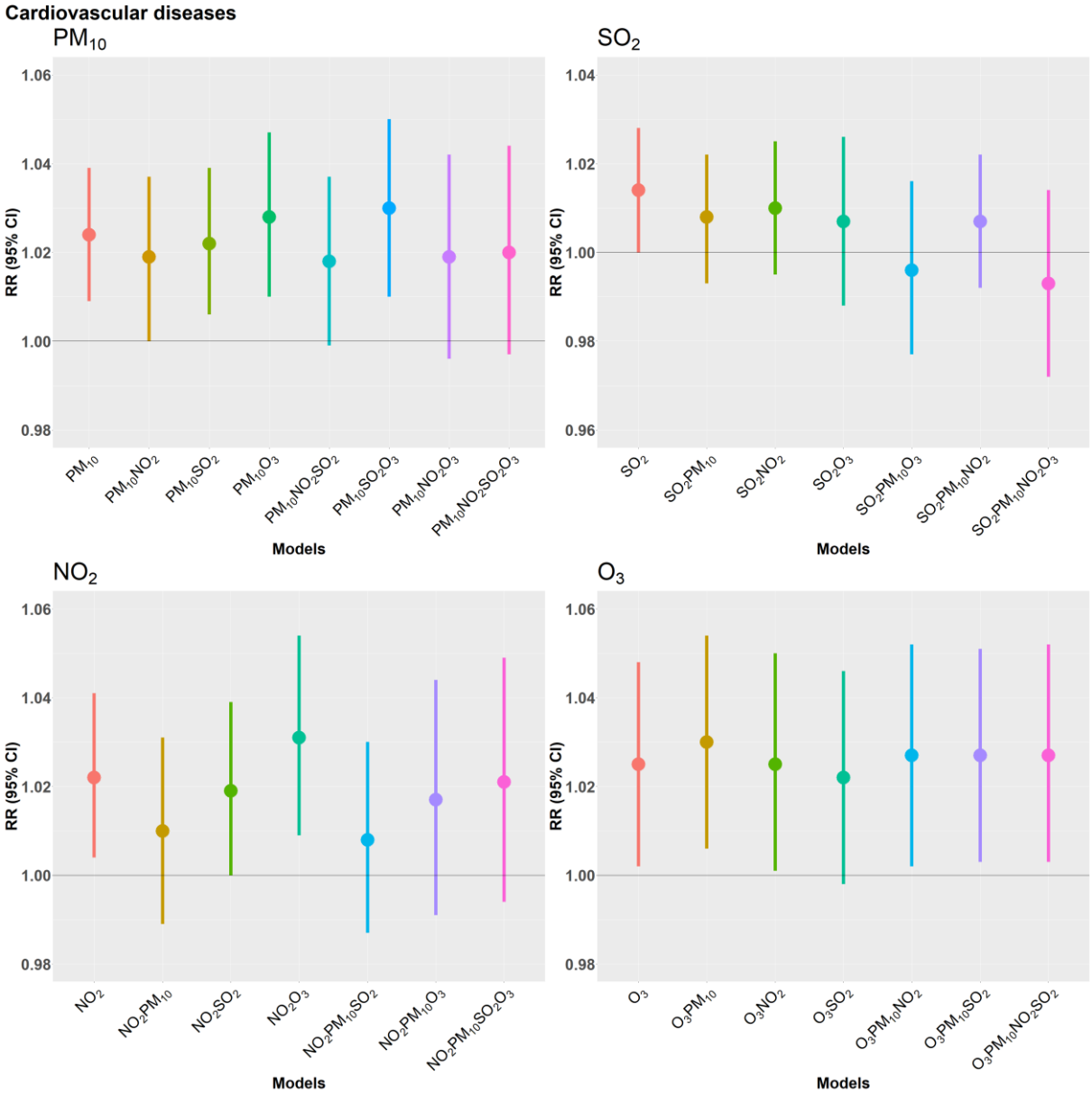

Figure 1. Overall relative risks estimated from Quasi-Poisson regression models of daily counts of cardiovascular disease deaths, adjusting for time trends and seasonal variation, day of the week, public holiday, temperature and relative humidity. Estimates are presented per IQR μg/m^3 increase in the two-day moving average (lag 0–1) of PM_{10}, NO_2, SO_2 and O_3 for the respective two-, three- and four-pollutant models.

Consistent with the single pollutant model, only NO_2 had a positive and significant association with RD mortality after adjusting for other pollutants, as seen in Figure 2. The estimated overall risk increment increased from 4.5% to 5.8% after adjusting for PM_{10}, while it was slightly reduced to 4.3% after adjusting for SO_2 and the estimates decreased and became statistically insignificant when adjusted for O_3. In the three-pollutant model with PM_{10} and SO_2, the estimate remained high at 5.5%. Adjusting for all three co-pollutants resulted in a slightly attenuated estimate of 4% which was no longer statistically significant. Conversely, the risk estimates for PM_{10} and O_3 in the multi-pollutant models confirm the corresponding null findings of the single pollutant models, with some random fluctuation of estimates across the various multi-pollutant models. Similar to the overall estimates of the three pollutants, their age and sex specific estimates were also not significant and are presented in the Supplementary Materials.

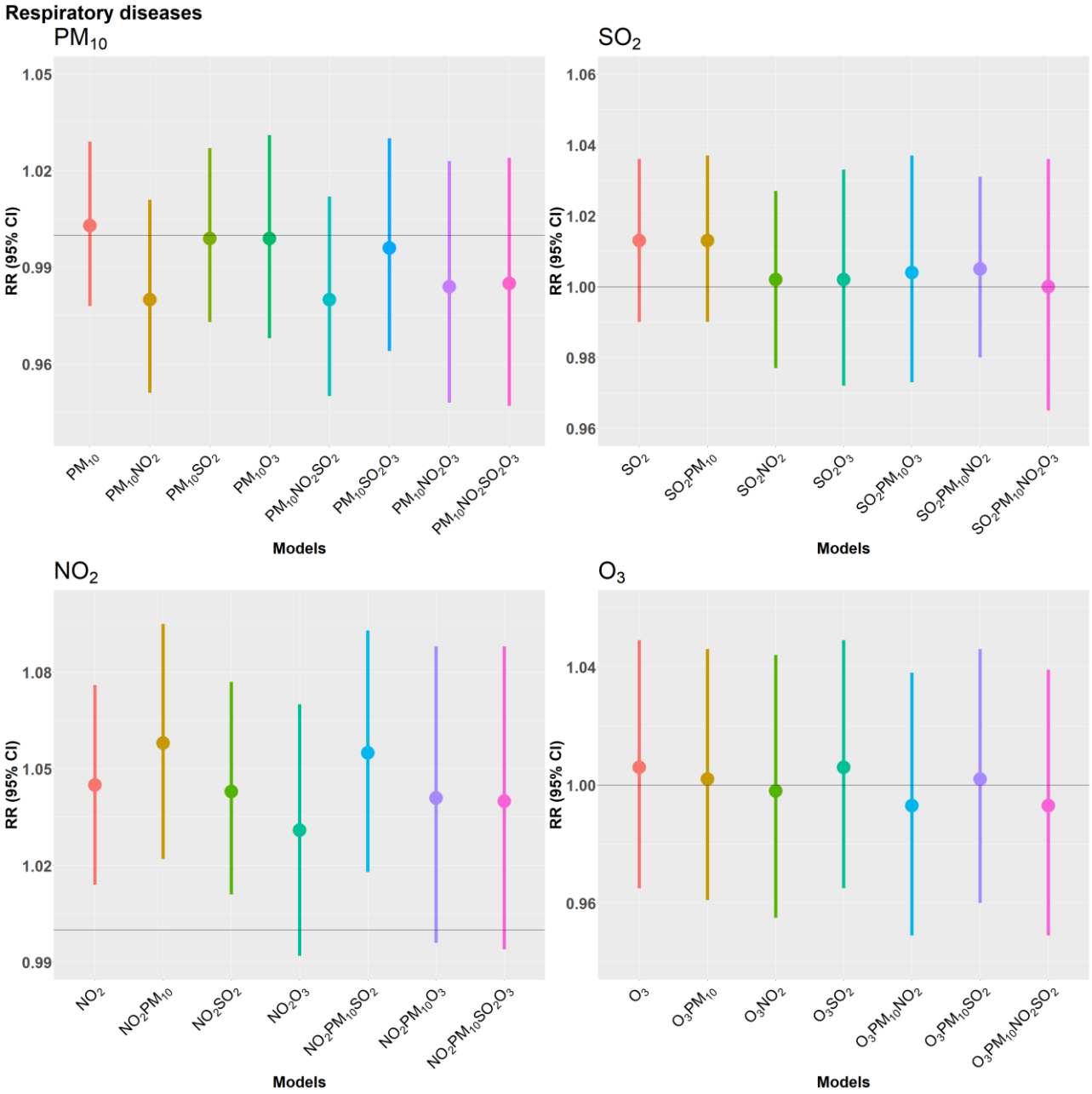

Figure 2. Overall relative risk estimated from Quasi-Poisson regression models of daily counts of respiratory disease deaths, adjusting for time trends and seasonal variation, day of the week, public holiday, temperature and relative humidity. Estimates are presented per IQR μg/m³ increase in the 2-day moving average (lag 0–1) of PM_{10}, NO_2, SO_2 and O_3 for the respective two-, three- and four-pollutant models.

Season specific results presented in Figure 3 reveal that associations of CVD mortality with PM_{10}, NO_2, SO_2, and O_3 are present in the cold and wet period only. This seasonal interaction reached statistical significance (p-value of 0.04) in case of SO_2. In contrast, results for RD remained rather similar across seasons with no material differences.

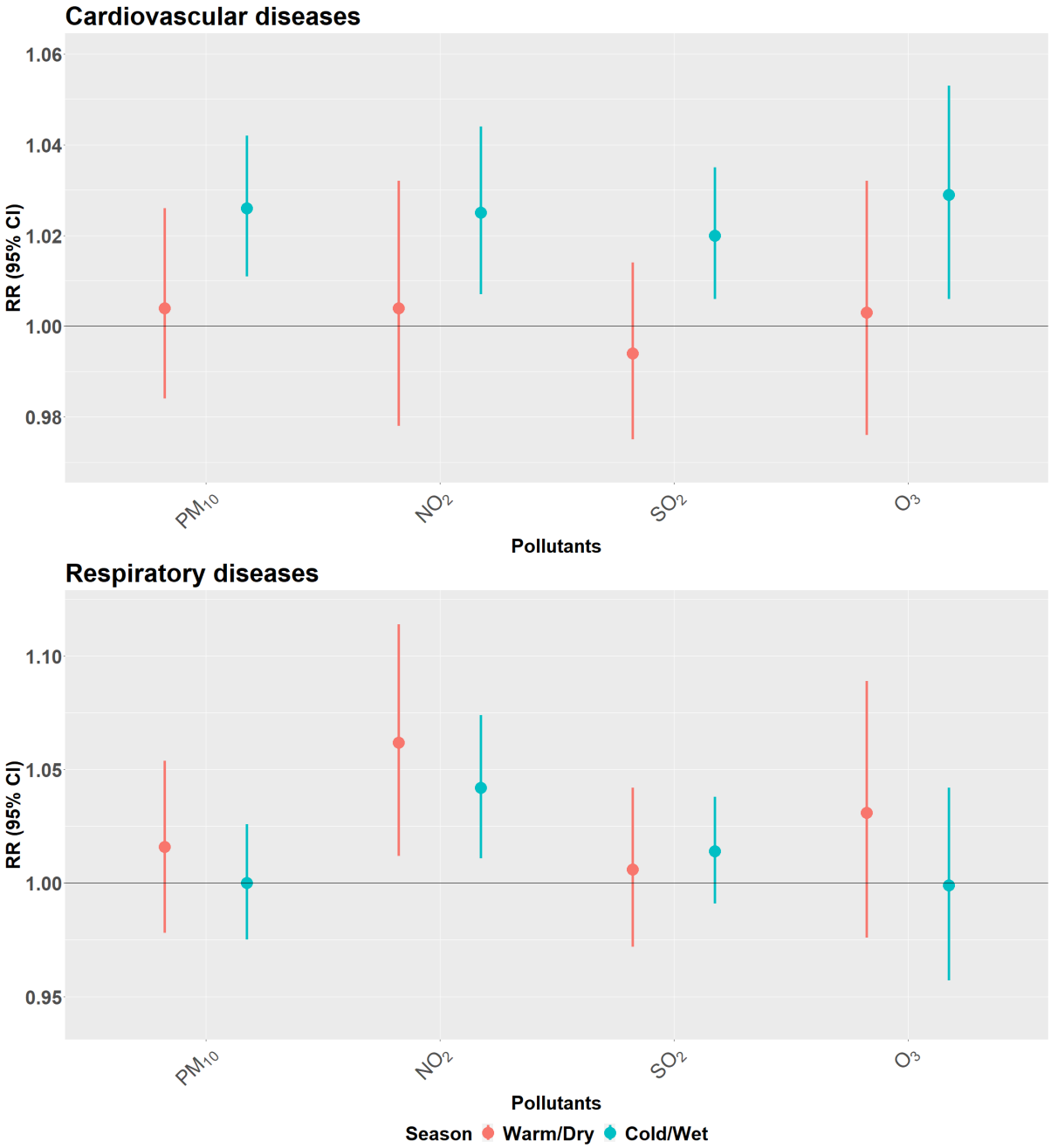

Figure 3. Overall season-specific estimates for daily counts of cardiovascular and respiratory deaths from Quasi-Poisson regression models adjusting for time trends and seasonal variation, day of the week, public holiday, temperature and relative humidity. Estimates are presented per IQR μg/m^3 increase in the two-day moving average (lag 0–1) of PM_{10}, NO_2, SO_2 and O_3.

Figure 4 illustrates the effects of a 10 μg/m^3 increase in the respective pollutants on CVD mortality across lags 0 to 21. These models reveal rather similar lag patterns for PM_{10}, NO_2 and SO_2, with positive estimates for the very first days but negative associations from approximately day three today 15, indicating the presence of harvesting. In case of PM_{10}, estimates are significantly negative across several lags. A similar observation is noted for RD mortality and PM_{10} (see Figure 5), with negative and significant estimates between lag 5–10. Here, lag 0–1 estimates for NO_2 reached statistical significance and slightly negative estimates were observed only for lags 10 to 14. However, the graph for O_3

is difficult to interpret given the troughs, whereas SO_2 is somewhat similar showing a non-significant immediate effect.

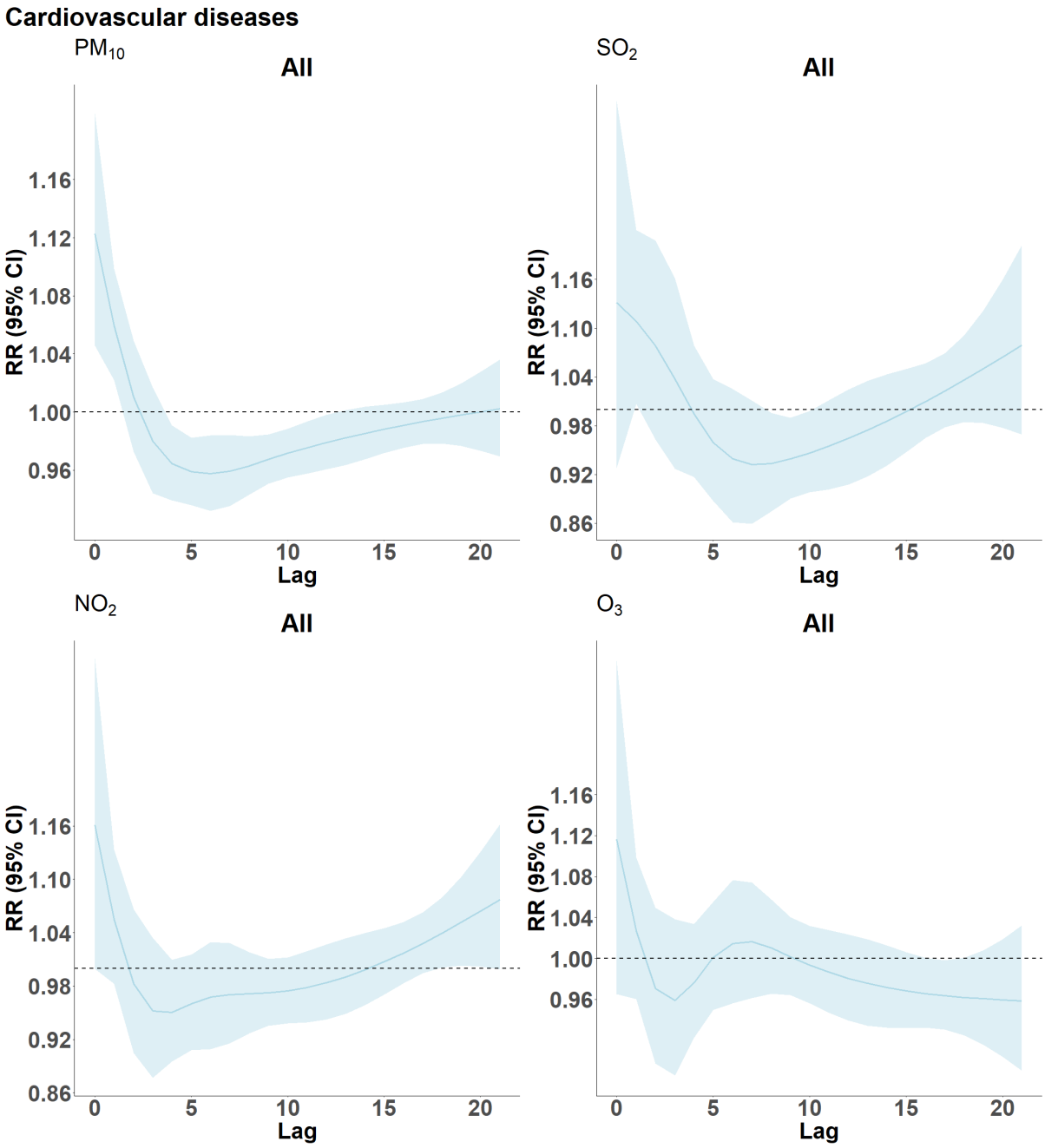

Figure 4. Lag structure (0–21) of the estimated effects of a 10 μg/m³ increase in PM_{10}, NO_2, SO_2 and O_3 concentrations on cardiovascular disease mortality in Cape Town, South Africa, 2006–2015. The blue curve gives the RR-estimates and the light blue band their 95%-confidence intervals.

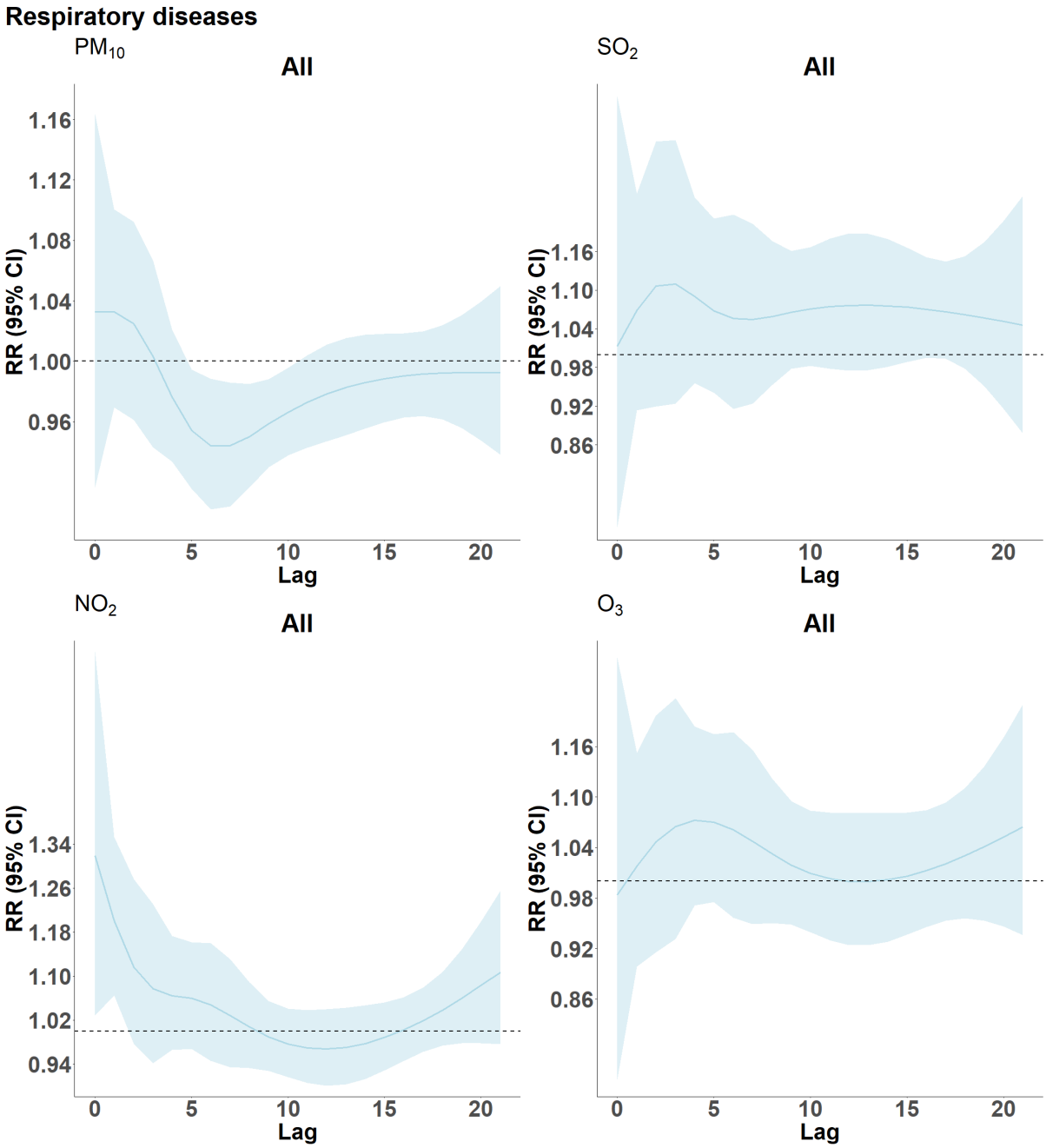

Figure 5. Lag structure (0–21) of the estimated effects of a 10 μg/m³ increase in PM10, NO2, SO2 and O3 concentrations on respiratory disease mortality in Cape Town, South Africa, 2006–2015. The blue curve gives the RR-estimates and the light blue band their 95%-confidence intervals.

4. Discussion

4.1. Brief Overview

In this study, we estimated short-term associations between ambient air pollutants (PM_{10}, NO_2, SO_2, and O_3) and deaths due to cardiovascular and respiratory diseases through separate single- and multiple-pollutant models, overall and by age group, sex and season, in Cape Town, South Africa. It is noteworthy that the air pollution level in the present study is similar to those reported in North America and Europe but stronger associations were detected. We found that PM_{10}, NO_2, SO_2, and O_3 were all associated with CVD death risk associations and were statistically significant during the wet and cold season but absent during the warm

and dry season. Associations with PM_{10} remained at least marginally significant across all multipollutant models, whereas those for NO_2 and O_3 were more sensitive to the adjustment for other pollutants. Results of SO_2 collapsed in all models involving more than two pollutants. Conversely, only NO_2 showed prominent and robust associations with RD mortality. For PM_{10}, NO_2 and SO_2, associations for age ≥ 65 years were slightly stronger than those for age 15 to 65 years. The role of gender in modifying estimates was conclusive only for O_3 on RD deaths, with significantly higher risk among men.

4.2. Cardiovascular Disease and Air Pollutants

Cardiovascular causes of death are usually due to a group of cardiovascular disorders affecting the heart and blood vessels, which may be the underlying cause of acute cardiovascular events leading to hospitalization and death. These acute events include cerebrovascular or pulmonary embolism or myocardial infarctions due to coronary heart diseases, to name a few (122). There are many risk factors triggering acute cardiovascular events, including exposure to air pollution. Nawrot et al. calculated population attributable fractions for air pollution and reported that a 10 $\mu g/m^3$ change in PM_{10} was associated with a 1.6% (0.9–2.4%) change in incidence of myocardial infarction (MI) (123). Additionally, interaction between physical exertion and ambient air pollution or temperature further increases the risk of MI (123). In the present study, a 10 $\mu g/m^3$ rise in daily mean PM_{10} concentrations was associated with a 1.2% to 1.8% increase in daily mortality. These estimates are at least two times higher than what has been reported for single-pollutant associations in systematic reviews and large multi-city studies (16, 71, 72, 111, 124). Although the estimate for PM_{10} decreased from 1.5% to 1.1% after adjustment for NO_2, it remains larger than expected from the literature. Similarly, NO_2 was also positively associated with CVD mortality. In comparison to multi-city studies, our estimates are at least five times higher than what the same authors reported for a 10 g/m^3 increase in NO_2 (125, 126), and two times higher than in another study (127). However, estimates produced from a systematic review restricted to results from low- and middle-income countries (LMIC) reported an increase of 1.7% per 10 $\mu g/m^3$ NO_2 (84) which is somewhat comparable to our findings. In addition, an Italian multi-city study reported an increased risk of 2.6% for cardiac mortality. This is compatible with our single pollutant estimate (2.1%), although their analysis used longer lags (0–5) and was restricted to ages over 35 (128). Interestingly, the significant positive association observed in our study is smaller as compared to earlier findings from the same study area which used data from 2001 to 2006. The authors reported a 3.4% increased risk per IQR rise of 12 $\mu g/m^3$ NO_2 compared to our 2.2% increased risk per 11 $\mu g/m^3$ (13). We observed a comparable association of 3.2% per 11 $\mu g/m^3$ only in models additionally containing O_3 and SO_2. Therefore, our results show evidence of a persisting increased CVD mortality risk due to NO_2 in the City of Cape Town over a period spanning 15 years.

Similarly, to other studies, Cape Town results for PM_{10} and NO_2 appear not to be fully independent, but partly capture overlapping characteristics of the two pollutants. In all CVD models which included both PM_{10} and NO_2, the respective estimates were attenuated—more strongly in case of NO_2—where confidence intervals included values consistent with the null hypotheses. As discussed in cases of similar previous findings, this attenuation might reflect the correlation of the two

markers of ambient air pollution sharing similar sources and perhaps health relevant seasonal patterns (16).

For SO_2, the significant positive association (risk increase = 2.3%, 95% CI: 0.1–4.7%) per 10 μg/m^3 was limited to the single pollutant model, with no evidence of independent associations, particularly after co-pollutant adjustments with PM_{10} and O_3. Our result is similar to the one of an earlier study (13) but is at least three times higher than pooled estimates from LMIC studies (84), two times higher than single and multiple-pollutant meta-analysis estimates for North America and Europe (129), and five times higher than a respective estimate for all-cause mortality (112).

We found both positive and independent associations between O_3 and CVD mortality with a risk increase of 1.6% for a 10 μg/m^3 increment in the two-day mean of O_3. The magnitude of this association is at least four times larger than what has been demonstrated in LMIC, North America, European and global systematic reviews [5,30,31,34]. Furthermore, when compared to a multi-city study including a South African province, our estimate is six times higher than what was reported per 10 μg/m^3 increase in O_3 (15). On the other hand, consistent with our results, an Italian multi-city study found an increased risk of 2.3% (95% CI: 1.1–3.5%) which remained unchanged when adjusted for PM_{10} (130). In contrast to an Asian multi-city study where the average concentrations of all four pollutants were at least twice the levels we observed in Cape Town, our CVD mortality estimates are at least twice what they reported per 10 μg/m^3 increase in each pollutant (131).

It is an interesting finding that all of our single-pollutant associations between the four pollutants and CVD mortality are consistently higher than what has been reported in the literature. A few things might be responsible for this unexpected observation. Firstly, South Africa is one of the most industrialized countries in the Southern hemisphere, with significant mining and metallurgical activities. It generates around 91% of its energy from coal burning (132). In addition, as an arid country, it has high natural dust levels, which adds to the particles from industrial and vehicular emissions. This, compounded with smoke from residential coal combustion in lower-income urban communities, was reported to contribute as much as 30% of the particulate pollution in the country (133). The pollutants' profiles and sources could modify the toxic properties—including the oxidative potential—of the air pollution mixture in Cape Town, which may not be fully captured by a purely mass-based characterisation of pollution. For example, the coarse fraction of PM_{10} was much more strongly associated with daily mortality during Sahara dust episodes as compared to other days in Europe. It was reported that a daily increase of 10 μg/m^3 in PM_{10} after adjusting for $PM_{2.5}$ on Saharan dust days increased mortality by 8.4% (95% CI 1.5–15.8%) compared with 1.3% (95% CI −0.8–3.4%) during non-Saharan dust days (*p*-value for interaction = 0.05) (134). In South Africa, 71% of dust plumes originate from the Free State province when agricultural areas are exposed to wind during drought from June to January, which overlaps with Cape Town's wet and dry seasons (135).

Given the lack of $PM_{2.5}$ data in our study, we cannot further evaluate whether our larger estimates are driven by the coarse fraction of PM_{10} or whether the fine $PM_{2.5}$ fraction is more toxic in Cape Town then elsewhere. Source apportionment of daily levels of $PM_{2.5}$ could further elucidate the reasons behind the stronger associations observed in our data. $PM_{2.5}$ samples were collected for 121 days in Cape Town, and when analysed Na, Cl^-,Mg, Ca, Zn, Al, Fe, SO_4^{2-}, and NO_3^- were detected in the samples

[16]. This indicates that the components found in the $PM_{2.5}$ samples are from multiple sources such as traffic, biomass fuel burning, soot, local road dust and natural sources such as sea sand, soil and mineral dust. Some of these components have been linked to adverse health effects such as SO_4^{2-}, and NO_3^- which were reported to be positively associated with all-cause mortality with an increased risk of 0.15% and 0.17% per 1 $\mu g/m^3$, respectively (136). However, those $PM_{2.5}$ speciation data are not sufficient to compare or qualify the toxicity of $PM_{2.5}$ in Cape Town as compared to elsewhere (77). $PM_{2.5}$ times-series analyses would be needed to better understand the role of the fine and course fractions of PM in Cape Town.

4.3. Respiratory Disease

Deaths from acute respiratory diseases (RD) are typically related to various acute exacerbations of lung diseases due to e.g., respiratory infections, including pneumonia, or asthma attacks. Acute deterioration of lung diseases can be caused by various ambient air pollutants. We found a statistically significant positive association with RD mortality only for NO_2 and a non-significant positive association with SO_2. This is in contrast with PM_{10} and O_3, where the associations were virtually absent. Positive associations of RD-mortality with NO_2 have been reported in other studies [5,31,42], although estimates were not quite as large as ours.

The null findings for PM_{10} and O_3 for RD mortality in our study are inconsistent with the existing literature. For instance, Orellano et al. found a 0.91% (95% CI: 0.6–1.2%) increased risk for a 10 $\mu g/m^3$ rise in PM_{10}, and Newell et al. reported a corresponding estimate of 0.38% (95% CI: 0·33–0·43). Our results are also consistent with other findings from Cape Town Wichmann et al. (13) and Thabethe et al. (14) reported non-significant positive associations of PM_{10} with daily RD mortality rates as well. The same studies also reported results similar to ours for SO2. Large multicity studies and systematic reviews demonstrated significant positive associations between SO_2 and RD-mortality (84, 112). Our null finding for O_3 and RD-mortality is consistent with the result from a systematic review involving studies from low- and middle-income countries having found statistically non-significant positive associations between RD-mortality and O_3, with a risk increase by 0.26% (95% CI: −0.09–0.61) for a 10 $\mu g/m^3$ increase in Ozone.

It might be that, in Cape Town, the exposure to features of air pollution relevant to respiratory diseases is better reflected by NO_2 than by the other pollutants due to specific sources and different population behavioural factors (137). The strong and independent association with NO_2 could indicate that it acts as a marker for specific mixtures of pollutants not well captured by PM_{10}, SO_2 or O_3, e.g., those particularly generated by vehicle exhausts including fine or ultrafine particles. In addition, the association between NO_2 and RD mortality may reflect, to a larger extent, the effects from sources other than traffic such as power plants (126).

4.4. Effect Modification by Sex

When we stratified the analysis by sex, we found a statistically significant difference (p-value = 0.01) in the association between O_3 and RD mortality only, with a higher risk in men. Shin et al. found a higher risk in females than males for O_3 using data covering 52% of the Canadian population (138). They also reported females to be at higher risk due to NO_2 exposure, which is consistent with our findings. Bell et al. conducted

a meta-analysis using nine ozone-RD mortality studies and concluded that the evidence of a higher association in females than males is limited or suggestive (139). Other studies have also reported inconsistencies for sex-specific health risk estimates associated with air pollutants (130). The minor sex-differences in our observed relative risks of CV-mortality with stronger associations among females for PM_{10} and NO_2 but stronger associations among males in the case of SO_2 and O_3 might be chance findings.

4.5. Effect Modification by Age

We did not find statistically significant effect modification by age. However, the association between all four pollutants and CVD mortality was consistently higher in age ≥65 years and the positive associations for age 15–64 years did not reach statistical significance. In contrast, RD mortality risk estimates were higher among the elderly only for NO_2 and SO_2. Older people showing stronger sensitivity to ambient pollution is well demonstrated in the literature [33,35,36,46,47]. This stronger association among the elderly is plausible given that, according to the 2019 Western Cape provincial burden of disease report, the most common causes of death among the elderly were CVD and other non-communicable disease (NCD) while people younger than 65 years die more from HIV/TB and intentional injuries (140). This is evident in our study as the number of deaths due to CVD for the elderly being1.7 times higher than in the 15–64 age group. In addition, the elderly are likely to have co-morbidities with reduced immune system and physiological changes, which may lead to decreased cardiac output, increased blood pressure, and the development of arteriosclerosis (96). Zeka et al. demonstrated that the risk of mortality for PM_{10} doubled by the presence of a secondary diagnosis such as pneumonia, stroke, diabetes, and heart failure (141). There is evidence of high polymorbidity in South Africa, as 47% of the deaths reported between 1997 and 2017 had more than one cause (142). Therefore, exposure to increased levels of air pollution may have advanced death events among frail individuals. This is suggested by the lag structure of PM_{10}-effects on CVD and RD mortality (Figure 4 and Figure S3 of Supplementary Material) showing harvesting with significant negative effects from lag 5–10. The pattern is even more pronounced among the elderly than when combining all age groups, suggesting that harvesting mostly occurred in the elderly.

4.6. Effect Modification by Season

The health effect estimates during the cold/wet season were higher than in the warm/dry season, but this difference was only statistically significant for SO_2. Our findings are not in agreement with evidence shown in multiple studies (139).

Results from other South African studies corroborate our findings of elevated pollution levels in the cold/wet season (143-145), as shown in Table 1. This is likely due to season-specific differences in anthropogenic activities and environmental and meteorological factors being associated with changes in sources, composition and toxicity of the pollutants

4.7. Harvesting of Frailty by Air Pollution

In contrast to many studies of the acute effects of ambient air pollution, our results for CVD and RD provide rather strong evidence for harvesting (146). The concept of harvesting assumes that air pollution

may advance death by just a few days among particularly frail people who are at a higher risk of dying at any given time. Under such a model, days with increased death rates due to air pollution would be followed by death rates falling below the expected averages as the pool of frail people had been reduced or "harvested" by the acute effects of air pollution. Several studies have investigated harvesting by air pollutants for different health outcomes (146-153). Of these, only one has reported significant results, Costa et al. found evidence of mortality displacement for non-accidental mortality associated with PM_{10} among the elderly across lags 0–30, while others have used lags up to 45 days with no evidence for acute effects being fully compensated by harvesting (146). Schwartz (152) and Zanobetti (149) described that subsequent to the harvesting period where negative effects are observed, there should be a rebound of risk estimates as a consequence of the replenishment of the risk pool. In our case, the period of three weeks may not have been long enough for this. Nonetheless, for CVD mortality we see prevailing short-term effects and considerable amount of mortality displacement in the curves for PM_{10}, NO_2 and SO_2 particularly with significant negative effects in PM_{10}. Additionally, there is indication of delayed acute effects with the rebound to positive estimates from lag 15 onward, for all the pollutants except O_3. This is more visible for PM_{10} when the lags are extended to 45 days (Figures S5 and S6 in Supplementary Materials).

On the other hand, for RD mortality, there is more evidence of delayed associations with NO_2 exposure for all ages (as shown in Figure 5) up until lag 8, while SO_2 and O_3 curves remain positive over the entire lag period (RR >1). Instead, PM_{10} associations for the first few days are statistically non-significant, while lags 5–10 indicate some harvesting with no signs of rebounds later on. Furthermore, it is important to note that the very short-term exposures to all four pollutants at lags 0 and 1 had the strongest association with CVD-mortality.

5. Strengths and Limitations

This study has several strengths. First, we examined the association of four important air pollutants with cardiovascular and respiratory mortality using a multipollutant approach. Secondly, this study benefitted from a relatively low correlation among the pollutants which enabled us to obtain relatively stable effect estimates in multipollutant models. Thirdly, the mortality data was collected from the national mortality database for the City of Cape Town, which allows for the generalization of the findings to the study area. Finally, our results contribute to the increasing body of evidence that support the independent health effects of ozone on cardiovascular mortality and of NO_2 on respiratory mortality.

We also acknowledge some limitations of this study. Exposure misclassification cannot be ruled out, as average daily concentration levels of the pollutants obtained from measurements at fixed monitoring sites may not be fully representative of the average exposure across the whole population of the city. While data on PM_{10} and NO_2 were quite complete, measurements of SO_2 were missing on 24% of the days, and O_3 measurements were missing for 29% of the study period. Therefore, multi-pollutant models including O_3 used fewer observations, for instance 62% of the data for four-pollutant models. However, when we restricted the single pollutant modelling of PM_{10}, NO_2 and SO_2 to days where ozone data were available, this shrunk the sample size by at least 1000 days. We observed that the effect estimates for PM_{10} (RR = 2.6%, 95% CI 0.7–4.4%)

and NO_2 (RR = 2.7%, 95% CI 0.5–5.0%) increased slightly, while those for SO_2 were reduced (RR = 0.6%, 95% CI −1.3–2.5%), resulting in a wider confidence interval due to the smaller sample size. This suggests that environmental conditions on days with missing O_3-data were slightly different from those on days with O_3-data. In addition, there was a lack of information on individual characteristics that would help us understand the stronger associations between air pollution and mortality when compared to other settings.

6. Conclusions

This study advances our understanding of the mortality risk associated with short-term exposure of multiple air pollutants (PM_{10}, NO_2, SO_2, and O_3) in Cape Town, South Africa. We found evidence of a positive association between the four pollutants and CVD-mortality, but only NO_2 was significantly associated with RD mortality. In addition, CVD-mortality among the elderly was advanced by a few days due to short-term PM_{10} exposure. Additional research is needed to confirm our findings, particularly in regard to better quality data and $PM_{2.5}$

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1. This document tabulates the correlations among environmental variables and provides estimates for the two-day means of the four pollutants by age group, sex and season, and for the lag structures of effects over 21 days by age group.

Author Contributions: Conceptualization T.C.A.-O. and J.W.; Methodology T.C.A.-O., N.K., C.S. and J.W.; Data collection, T.C.A.-O. and J.W.; Analysis T.C.A.-O. and C.S.; Writing T.C.A.-O.; all authors including O.O.A. and N.P.-H. contributed and reviewed the article prior to submission. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethical approval (reference 671/2019) was obtained from the Research Ethics Committee, Faculty of Health Sciences, University of Pretoria in 2019, there after an approval to conduct the study was requested from City Health, Cape Town with a project ID 8236. We also applied to the Ethics Committee Northwest and Central Switzerland (EKNZ), however, our research does not fall under the remit of the cantonal and federal law Human Research Act (HRA). Therefore, only the local ethics approval in South Africa was necessary and applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Exposure data are available for download on the South African Air Quality Information System (SAAQIS) website; however, restrictions apply to the health outcome data.

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Paper 2: Appendix

Short-Term Effects of PM_{10}, NO_2, SO_2 and O_3 on Cardio-Respiratory Mortality in Cape Town, South Africa, 2006 - 2015

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Time-series analysis results.

This document tabulates the correlations among environmental variables and provides estimates for the two-day means of the four pollutants by age group, sex and season, and for the lag structures of effects over 21 days by age group.

Table A1: Temporal spearman rank correlation coefficients among daily mean concentrations of ambient air pollutants and meteorological variables during the year and by seasons

	PM_{10}	NO_2	SO_2	O_3	Temperature	Humidity
PM_{10}	1	0.38	0.27	0.12	0.17	-0.25
NO_2		1	0.4	0.06	-0.35	0.07
SO_2			1	-0.11	-0.12	-0.01
O_3				1	-0.13	0.01
Temperature					1	-0.41
Humidity						1
Warm /dry season		November - March				
PM_{10}	1	0.29	0.28	0.23	0.33	-0.27
NO_2		1	0.32	0.09	-0.22	-0.03
SO_2			1	-0.07	0.01	-0.07
O_3				1	-0.14	-0.02
Temperature					1	-0.26
Humidity						1
Cold / wet season		April – October				
PM_{10}	1	0.54	0.27	-0.09	0.03	-0.3
NO_2		1	0.46	-0.15	-0.11	-0.15
SO_2			1	-0.25	-0.05	-0.11
O_3				1	0.01	-0.01
Temperature					1	-0.02
Humidity						1

The relative risk presented in the following table were estimated from Quasi-Poisson regression models of respiratory and cardiovascular disease deaths, adjusting for time trends and seasonal variation, day of the week, public holiday, and meteorological factors including temperature and relative humidity.

Table A2: Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of PM_{10} concentrations and mortality due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (16 $\mu g/m^3$)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM_{10}	1.003	0.978	1.029	1.024	1.009	1.039
Age 15 - 64		1.003	0.969	1.039	1.011	0.986	1.036
Age >65		1.003	0.969	1.038	1.033	1.014	1.052
Female		1.009	0.973	1.047	1.032	1.012	1.053
Male		1	0.967	1.033	1.015	0.994	1.037
All ages and sex	PM_{10} NO_2	0.98	0.951	1.011	1.019	1	1.037
Age 15 - 64		0.975	0.934	1.018	1.004	0.974	1.035
Age >65		0.985	0.944	1.027	1.028	1.005	1.052
Female		0.98	0.937	1.025	1.026	1.001	1.051
Male		0.981	0.942	1.021	1.011	0.986	1.038
All ages and sex	PM_{10} SO_2	0.999	0.973	1.027	1.022	1.006	1.039
Age 15 - 64		0.996	0.96	1.034	1.01	0.984	1.037
Age >65		1.003	0.966	1.04	1.03	1.01	1.051
Female		1.003	0.965	1.043	1.034	1.012	1.056
Male		0.997	0.963	1.033	1.01	0.988	1.033
All ages and sex	PM_{10} O_3	0.999	0.968	1.031	1.028	1.01	1.047

Age 15 - 64		1.005	0.963	1.05	1.008	0.979	1.039
Age >65		0.994	0.952	1.038	1.042	1.018	1.066
Female		0.99	0.946	1.037	1.044	1.018	1.07
Male		1.005	0.964	1.047	1.013	0.987	1.04
All ages and sex	PM_{10} NO_2 SO_2	0.98	0.95	1.012	1.018	0.999	1.037
Age 15 - 64		0.974	0.932	1.018	1.003	0.972	1.035
Age >65		0.986	0.944	1.03	1.028	1.004	1.052
Female		0.975	0.931	1.021	1.028	1.002	1.055
Male		0.984	0.944	1.026	1.007	0.98	1.034
All ages and sex	PM_{10} SO_2 O_3	0.996	0.964	1.03	1.03	1.01	1.05
Age 15 - 64		1.001	0.956	1.048	1.006	0.975	1.038
Age >65		0.994	0.949	1.04	1.046	1.021	1.072
Female		0.988	0.941	1.037	1.048	1.021	1.076
Male		1.002	0.959	1.046	1.013	0.985	1.041
All ages and sex	PM_{10} NO_2 O_3	0.984	0.948	1.023	1.019	0.996	1.042
Age 15 - 64		0.996	0.944	1.05	0.989	0.953	1.026
Age >65		0.973	0.923	1.026	1.038	1.009	1.067
Female		0.983	0.929	1.04	1.03	0.999	1.062
Male		0.984	0.936	1.034	1.007	0.975	1.039
All ages and sex	PM_{10} NO_2 SO_2 O_3	0.985	0.947	1.024	1.02	0.997	1.044
Age 15 - 64		0.996	0.943	1.052	0.984	0.947	1.022
Age >65		0.974	0.922	1.029	1.043	1.013	1.074
Female		0.979	0.924	1.038	1.033	1.001	1.067
Male		0.987	0.937	1.039	1.006	0.973	1.039

Table A3: Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of NO_2 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (11 $\mu g/m^3$)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	NO_2	1.045	1.014	1.076	1.022	1.004	1.041
Age 15 - 64		1.041	0.997	1.085	1.01	0.981	1.041
Age >65		1.049	1.007	1.093	1.031	1.008	1.054
Female		1.049	1.004	1.096	1.026	1.001	1.051
Male		1.042	1.002	1.083	1.019	0.993	1.045
All ages and sex	NO_2 PM_{10}	1.058	1.022	1.095	1.01	0.989	1.031
Age 15 - 64		1.055	1.004	1.108	1.007	0.973	1.042
Age >65		1.061	1.012	1.113	1.013	0.987	1.04
Female		1.063	1.01	1.119	1.012	0.983	1.041
Male		1.054	1.008	1.103	1.009	0.979	1.039
All ages and sex	NO_2 SO_2	1.043	1.011	1.077	1.019	1	1.039
Age 15 - 64		1.042	0.996	1.09	1.007	0.976	1.039
Age >65		1.046	1.001	1.092	1.028	1.004	1.053
Female		1.047	0.999	1.097	1.025	0.999	1.052
Male		1.043	1	1.088	1.013	0.987	1.041
All ages and sex	NO_2 O_3	1.031	0.992	1.07	1.031	1.009	1.054
Age 15 - 64		1.018	0.965	1.074	1.026	0.989	1.063
Age >65		1.042	0.99	1.098	1.038	1.01	1.068
Female		1.003	0.948	1.061	1.039	1.008	1.071
Male		1.053	1.002	1.106	1.027	0.995	1.06

All ages and sex	NO_2 PM_{10} O_3	1.041	0.996	1.088	1.017	0.991	1.044
Age 15 - 64		1.018	0.956	1.084	1.03	0.988	1.075
Age >65		1.063	1.001	1.129	1.013	0.98	1.046
Female		1.015	0.95	1.084	1.021	0.985	1.058
Male		1.063	1.003	1.126	1.016	0.979	1.055
All ages and sex	NO_2 PM_{10} SO_2	1.055	1.018	1.093	1.008	0.987	1.03
Age 15 - 64		1.054	1.002	1.109	1.004	0.97	1.04
Age >65		1.056	1.005	1.109	1.012	0.986	1.04
Female		1.063	1.008	1.12	1.011	0.982	1.041
Male		1.052	1.003	1.102	1.006	0.976	1.036
All ages and sex	NO_2 SO_2 O_3	1.031	0.991	1.074	1.035	1.011	1.059
Age 15 - 64		1.018	0.961	1.078	1.025	0.987	1.065
Age >65		1.043	0.987	1.102	1.044	1.014	1.075
Female		0.999	0.941	1.061	1.045	1.012	1.078
Male		1.059	1.005	1.116	1.027	0.994	1.062
All ages and sex	NO_2 PM_{10} SO_2 O_3	1.04	0.994	1.088	1.021	0.994	1.049
Age 15 - 64		1.017	0.954	1.084	1.031	0.988	1.077
Age >65		1.061	0.997	1.129	1.019	0.985	1.054
Female		1.012	0.946	1.082	1.028	0.991	1.066
Male		1.065	1.004	1.13	1.018	0.98	1.057

Table A4: Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of SO_2 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (6 $\mu g/m^3$)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	SO_2	1.013	0.99	1.036	1.014	1	1.028
Age 15 - 64		1.01	0.979	1.042	1.01	0.988	1.032
Age >65		1.016	0.985	1.047	1.017	0.999	1.034
Female		1.021	0.988	1.055	1.007	0.989	1.026
Male		1.005	0.976	1.035	1.022	1.003	1.041
All ages and sex	SO_2 PM_{10}	1.013	0.99	1.037	1.008	0.993	1.022
Age 15 - 64		1.011	0.978	1.045	1.007	0.984	1.03
Age >65		1.015	0.983	1.048	1.008	0.99	1.026
Female		1.02	0.985	1.055	0.998	0.979	1.018
Male		1.007	0.976	1.039	1.019	0.998	1.039
All ages and sex	SO_2 NO_2	1.002	0.977	1.027	1.01	0.995	1.025
Age 15 - 64		0.997	0.963	1.033	1.012	0.988	1.036
Age >65		1.007	0.973	1.042	1.008	0.989	1.027
Female		1.013	0.976	1.05	1.003	0.984	1.024
Male		0.992	0.96	1.025	1.017	0.997	1.039
All ages and sex	SO_2 O_3	1.002	0.972	1.033	1.007	0.988	1.026
Age 15 - 64		1.007	0.965	1.05	0.999	0.97	1.03
Age >65		0.999	0.958	1.043	1.012	0.988	1.036
Female		1.004	0.959	1.05	1.003	0.978	1.028
Male		1	0.961	1.04	1.012	0.986	1.039

All ages and sex	SO_2 PM_{10} O_3	1.004	0.973	1.037	0.996	0.977	1.016
Age 15 - 64		1.007	0.963	1.053	0.999	0.968	1.03
Age >65		1.003	0.959	1.048	0.995	0.971	1.02
Female		1.008	0.961	1.058	0.987	0.961	1.014
Male		1.001	0.96	1.044	1.007	0.98	1.036
All ages and sex	SO_2 PM_{10} NO_2	1.005	0.98	1.031	1.007	0.992	1.022
Age 15 - 64		1.001	0.966	1.038	1.012	0.988	1.038
Age >65		1.009	0.975	1.045	1.003	0.984	1.022
Female		1.016	0.979	1.055	0.998	0.978	1.019
Male		0.996	0.963	1.03	1.017	0.996	1.039
All ages and sex	SO_2 NO_2 O_3	0.995	0.962	1.03	0.997	0.977	1.018
Age 15 - 64		0.996	0.95	1.045	1.004	0.971	1.037
Age >65		0.996	0.95	1.045	0.993	0.967	1.019
Female		1.011	0.96	1.064	0.991	0.964	1.019
Male		0.983	0.94	1.028	1.004	0.975	1.034
All ages and sex	SO_2 PM_{10} NO_2 O_3	1	0.965	1.036	0.993	0.972	1.014
Age 15 - 64		0.998	0.95	1.049	1.009	0.975	1.044
Age >65		1.002	0.954	1.053	0.982	0.956	1.009
Female		1.015	0.963	1.071	0.984	0.956	1.013
Male		0.988	0.944	1.034	1.003	0.974	1.034

Table A5: Single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of O_3 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant IQR (16 $\mu g/m^3$)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	O_3	1.006	0.965	1.049	1.025	1.002	1.048
Age 15 - 64		1.007	0.951	1.067	1.019	0.982	1.057
Age >65		1.004	0.948	1.063	1.029	1	1.059
Female		0.949	0.894	1.008	1.018	0.987	1.05
Male		1.054	0.998	1.113	1.035	1.002	1.069
All ages and sex	O_3 PM_{10}	1.002	0.961	1.046	1.03	1.006	1.054
Age 15 - 64		1.005	0.947	1.066	1.019	0.982	1.058
Age >65		1	0.943	1.06	1.037	1.008	1.067
Female		0.944	0.887	1.005	1.025	0.993	1.057
Male		1.051	0.993	1.112	1.038	1.004	1.072
All ages and sex	O_3 NO_2	0.998	0.955	1.044	1.025	1.001	1.05
Age 15 - 64		0.989	0.929	1.053	1.02	0.981	1.06
Age >65		1.006	0.945	1.07	1.031	1.001	1.063
Female		0.932	0.873	0.995	1.024	0.991	1.058
Male		1.054	0.994	1.118	1.03	0.996	1.066
All ages and sex	O_3 SO_2	1.006	0.965	1.049	1.022	0.998	1.046
Age 15 - 64		1.005	0.948	1.065	1.014	0.977	1.053
Age >65		1.006	0.949	1.065	1.027	0.998	1.058
Female		0.952	0.896	1.012	1.015	0.984	1.047

Male		1.051	0.995	1.111	1.032	0.998	1.066
All ages and sex	O_3 PM_{10} SO_2	1.002	0.96	1.046	1.027	1.003	1.051
Age 15 - 64		1.001	0.943	1.063	1.014	0.977	1.053
Age >65		1.002	0.944	1.063	1.036	1.006	1.066
Female		0.947	0.889	1.008	1.022	0.99	1.055
Male		1.047	0.989	1.108	1.034	1.001	1.069
All ages and sex	O_3 PM_{10} NO_2	0.993	0.949	1.038	1.027	1.002	1.052
Age 15 - 64		0.983	0.923	1.047	1.018	0.979	1.059
Age >65		0.999	0.939	1.064	1.035	1.004	1.066
Female		0.928	0.868	0.991	1.026	0.993	1.061
Male		1.046	0.985	1.111	1.03	0.996	1.066
All ages and sex	O_3 SO_2 NO_2	0.999	0.955	1.044	1.025	1.001	1.05
Age 15 - 64		0.989	0.928	1.052	1.018	0.979	1.059
Age >65		1.006	0.946	1.071	1.032	1.001	1.064
Female		0.934	0.875	0.997	1.022	0.989	1.056
Male		1.054	0.993	1.118	1.032	0.998	1.068
All ages and sex	O_3 PM_{10} NO_2 SO_2	0.993	0.949	1.039	1.027	1.003	1.052
Age 15 - 64		0.983	0.922	1.047	1.016	0.977	1.057
Age >65		1	0.939	1.065	1.036	1.005	1.068
Female		0.928	0.869	0.992	1.025	0.992	1.059
Male		1.046	0.985	1.111	1.033	0.998	1.069

Table A6: Single and multiple pollutant model adjusted relative risk (RR) for 10 µg/m^3 increase in the two-day moving average of PM_{10} concentrations and mortality due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10 µg/m^3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM_{10}	1.002	0.987	1.017	1.015	1.005	1.024
Age 15 - 64		1.002	0.981	1.024	1.007	0.992	1.022
Age >65		1.002	0.981	1.023	1.02	1.008	1.032
Female		1.006	0.983	1.028	1.02	1.007	1.032
Male		1	0.98	1.02	1.009	0.996	1.022
All ages and sex	PM_{10} NO_2	0.988	0.97	1.007	1.011	1	1.023
Age 15 - 64		0.985	0.959	1.011	1.002	0.984	1.021
Age >65		0.991	0.965	1.017	1.017	1.003	1.031
Female		0.988	0.961	1.015	1.016	1	1.031
Male		0.988	0.964	1.013	1.007	0.991	1.023
All ages and sex	PM_{10} SO_2	1	0.983	1.016	1.014	1.004	1.023
Age 15 - 64		0.998	0.975	1.021	1.006	0.99	1.023
Age >65		1.002	0.979	1.024	1.018	1.006	1.031
Female		1.002	0.979	1.026	1.021	1.007	1.034
Male		0.998	0.977	1.02	1.006	0.992	1.02
All ages and sex	PM_{10} O_3	0.999	0.98	1.019	1.017	1.006	1.029
Age 15 - 64		1.003	0.977	1.03	1.005	0.987	1.024
Age >65		0.996	0.97	1.023	1.025	1.011	1.04
Female		0.994	0.967	1.022	1.027	1.011	1.042
Male		1.003	0.978	1.028	1.008	0.992	1.024

All ages and sex	PM_{10} NO_2 SO_2	0.988	0.969	1.007	1.011	0.999	1.023
Age 15 - 64		0.984	0.958	1.011	1.002	0.983	1.021
Age >65		0.992	0.966	1.018	1.017	1.002	1.032
Female		0.985	0.957	1.013	1.017	1.001	1.033
Male		0.99	0.966	1.016	1.004	0.988	1.021
All ages and sex	PM_{10} SO_2 O_3	0.998	0.978	1.018	1.018	1.006	1.03
Age 15 - 64		1	0.973	1.029	1.004	0.984	1.023
Age >65		0.996	0.969	1.024	1.028	1.013	1.043
Female		0.992	0.963	1.022	1.029	1.012	1.046
Male		1.001	0.975	1.028	1.008	0.991	1.025
All ages and sex	PM_{10} NO_2 O_3	0.99	0.968	1.014	1.012	0.998	1.026
Age 15 - 64		0.998	0.966	1.031	0.993	0.971	1.016
Age >65		0.984	0.952	1.016	1.023	1.005	1.041
Female		0.99	0.956	1.025	1.018	0.999	1.038
Male		0.99	0.96	1.021	1.004	0.985	1.024
All ages and sex	PM_{10} NO_2 SO_2 O_3	0.991	0.967	1.015	1.012	0.998	1.027
Age 15 - 64		0.997	0.965	1.031	0.99	0.967	1.013
Age >65		0.984	0.952	1.018	1.026	1.008	1.045
Female		0.987	0.953	1.023	1.02	1.001	1.04
Male		0.992	0.961	1.024	1.003	0.983	1.024

Table A7: Single and multiple pollutant model adjusted relative risk (RR) for 10 µg/m^3 increase in the two-day moving average of NO_2 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10 µg/m^3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	NO_2	1.042	1.013	1.072	1.021	1.004	1.038
Age 15 - 64		1.038	0.998	1.08	1.01	0.982	1.038
Age >65		1.046	1.007	1.087	1.029	1.007	1.051
Female		1.026	1.002	1.051	1.024	1.001	1.048
Male		1.039	1.002	1.078	1.018	0.994	1.042
All ages and sex	NO_2 PM_{10}	1.054	1.02	1.089	1.009	0.99	1.029
Age 15 - 64		1.051	1.004	1.101	1.006	0.974	1.039
Age >65		1.057	1.011	1.106	1.012	0.988	1.037
Female		1.059	1.009	1.111	1.011	0.984	1.038
Male		1.051	1.007	1.097	1.008	0.981	1.036
All ages and sex	NO_2 SO_2	1.041	1.01	1.072	1.018	1	1.036
Age 15 - 64		1.039	0.996	1.084	1.007	0.978	1.037
Age >65		1.043	1.001	1.086	1.026	1.004	1.05
Female		1.044	0.999	1.091	1.023	0.999	1.048
Male		1.04	1	1.082	1.013	0.988	1.038
All ages and sex	NO_2 O_3	1.029	0.993	1.066	1.029	1.008	1.051
Age 15 - 64		1.017	0.967	1.069	1.024	0.99	1.059
Age >65		1.04	0.99	1.091	1.036	1.009	1.063
Female		1.003	0.951	1.057	1.036	1.007	1.066
Male		1.049	1.002	1.099	1.025	0.995	1.056

All ages and sex	NO_2 PM_{10} O_3	1.039	0.996	1.082	1.016	0.992	1.041
Age 15 - 64		1.017	0.959	1.078	1.029	0.988	1.07
Age >65		1.059	1.001	1.121	1.012	0.981	1.043
Female		1.014	0.953	1.079	1.02	0.986	1.055
Male		1.059	1.003	1.118	1.015	0.981	1.051
All ages and sex	NO_2 PM_{10} SO_2	1.051	1.017	1.087	1.008	0.988	1.028
Age 15 - 64		1.051	1.002	1.102	1.004	0.971	1.037
Age >65		1.052	1.005	1.102	1.011	0.986	1.037
Female		1.059	1.008	1.112	1.011	0.984	1.038
Male		1.048	1.003	1.095	1.005	0.977	1.034
All ages and sex	NO_2 SO_2 O_3	1.029	0.991	1.069	1.032	1.01	1.055
Age 15 - 64		1.017	0.963	1.073	1.024	0.988	1.061
Age >65		1.04	0.988	1.096	1.041	1.013	1.07
Female		0.999	0.945	1.057	1.042	1.011	1.073
Male		1.055	1.004	1.108	1.025	0.994	1.058
All ages and sex	NO_2 PM_{10} SO_2 O_3	1.037	0.994	1.082	1.02	0.995	1.046
Age 15 - 64		1.016	0.957	1.079	1.029	0.988	1.072
Age >65		1.057	0.997	1.12	1.018	0.986	1.05
Female		1.011	0.949	1.077	1.026	0.992	1.062
Male		1.061	1.004	1.121	1.017	0.981	1.053

Table A8: Single and multiple pollutant model adjusted relative risk (RR) for 10 µg/m^3 increase in the two-day moving average of SO_2 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10 µg/m^3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	SO_2	1.021	0.984	1.06	1.023	1.001	1.047
Age 15 - 64		1.017	0.965	1.071	1.016	0.979	1.054
Age >65		1.026	0.975	1.08	1.028	0.999	1.057
Female		1.036	0.981	1.094	1.012	0.982	1.044
Male		1.009	0.96	1.06	1.037	1.004	1.07
All ages and sex	SO_2 PM_{10}	1.022	0.983	1.063	1.013	0.989	1.037
Age 15 - 64		1.018	0.964	1.076	1.012	0.973	1.051
Age >65		1.025	0.972	1.082	1.013	0.983	1.043
Female		1.033	0.975	1.094	0.997	0.966	1.03
Male		1.012	0.961	1.065	1.031	0.997	1.066
All ages and sex	SO_2 NO_2	1.003	0.962	1.046	1.016	0.992	1.042
Age 15 - 64		0.995	0.939	1.056	1.02	0.98	1.062
Age >65		1.012	0.956	1.071	1.013	0.983	1.045
Female		1.021	0.961	1.085	1.006	0.973	1.04
Male		0.987	0.934	1.042	1.029	0.994	1.065
All ages and sex	SO_2 O_3	1.003	0.954	1.056	1.011	0.981	1.043
Age 15 - 64		1.011	0.942	1.085	0.999	0.951	1.05
Age >65		0.999	0.931	1.072	1.02	0.981	1.06
Female		1.006	0.933	1.085	1.005	0.963	1.048
Male		1	0.936	1.068	1.021	0.977	1.066

All ages and sex	SO_2 PM_{10} O_3	1.007	0.955	1.063	0.994	0.962	1.027
Age 15 - 64		1.011	0.939	1.089	0.998	0.947	1.051
Age >65		1.005	0.933	1.082	0.992	0.952	1.034
Female		1.014	0.936	1.098	0.979	0.936	1.024
Male		1.002	0.935	1.074	1.012	0.966	1.06
All ages and sex	SO_2 PM_{10} NO_2	1.009	0.967	1.053	1.012	0.986	1.037
Age 15 - 64		1.002	0.944	1.064	1.021	0.98	1.063
Age >65		1.016	0.958	1.076	1.005	0.973	1.037
Female		1.027	0.965	1.093	0.997	0.964	1.032
Male		0.993	0.939	1.05	1.028	0.993	1.065
All ages and sex	SO_2 NO_2 O_3	0.992	0.937	1.05	0.995	0.962	1.03
Age 15 - 64		0.994	0.917	1.077	1.006	0.952	1.063
Age >65		0.994	0.918	1.076	0.988	0.945	1.032
Female		1.018	0.934	1.109	0.985	0.94	1.033
Male		0.972	0.902	1.047	1.007	0.959	1.057
All ages and sex	SO_2 PM_{10} NO_2 O_3	0.999	0.942	1.06	0.988	0.954	1.023
Age 15 - 64		0.997	0.919	1.083	1.015	0.959	1.074
Age >65		1.004	0.925	1.09	0.971	0.928	1.016
Female		1.026	0.939	1.12	0.973	0.927	1.021
Male		0.98	0.908	1.058	1.006	0.957	1.057

Table A9: Single and multiple pollutant model adjusted relative risk (RR) for 10 µg/m^3 increase in the two-day moving average of O_3 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, age groups and sex, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10 µg/m^3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	O_3	1.004	0.978	1.031	1.016	1.001	1.031
Age 15 - 64		1.004	0.968	1.042	1.012	0.988	1.036
Age >65		1.003	0.967	1.04	1.019	1	1.037
Female		0.967	0.93	1.005	1.011	0.991	1.032
Male		1.034	0.999	1.071	1.022	1.001	1.043
All ages and sex	O_3 PM_{10}	1.002	0.975	1.029	1.016	1.001	1.032
Age 15 - 64		1.003	0.966	1.042	1.013	0.988	1.038
Age >65		1	0.963	1.038	1.02	1	1.04
Female		0.964	0.926	1.003	1.015	0.994	1.037
Male		1.032	0.996	1.07	1.019	0.997	1.042
All ages and sex	O_3 NO_2	0.999	0.971	1.028	1.014	1.002	1.027
Age 15 - 64		0.993	0.954	1.033	1.016	0.996	1.038
Age >65		1.004	0.965	1.044	1.014	0.998	1.031
Female		0.956	0.917	0.997	1.013	0.995	1.03
Male		1.034	0.996	1.074	1.018	1	1.037
All ages and sex	O_3 SO_2	1.004	0.977	1.031	1.014	0.999	1.029
Age 15 - 64		1.003	0.967	1.041	1.009	0.985	1.033
Age >65		1.004	0.967	1.041	1.017	0.999	1.037
Female		0.969	0.932	1.008	1.01	0.989	1.03
Male		1.032	0.997	1.07	1.02	0.999	1.042

All ages and sex	O_3 PM_{10} SO_2	1.001	0.974	1.029	1.017	1.002	1.032
Age 15 - 64		1.001	0.963	1.04	1.009	0.985	1.034
Age >65		1.001	0.964	1.04	1.023	1.004	1.042
Female		0.966	0.928	1.005	1.014	0.994	1.035
Male		1.03	0.993	1.068	1.022	1.001	1.044
All ages and sex	O_3 PM_{10} NO_2	0.995	0.967	1.024	1.017	1.002	1.033
Age 15 - 64		0.989	0.95	1.03	1.012	0.986	1.037
Age >65		1	0.96	1.041	1.022	1.002	1.042
Female		0.953	0.913	0.994	1.017	0.996	1.038
Male		1.029	0.991	1.07	1.019	0.997	1.042
All ages and sex	O_3 SO_2 NO_2	0.999	0.971	1.028	1.016	1.001	1.032
Age 15 - 64		0.993	0.954	1.033	1.012	0.987	1.037
Age >65		1.004	0.965	1.045	1.02	1.001	1.04
Female		0.957	0.918	0.998	1.014	0.993	1.035
Male		1.034	0.995	1.074	1.021	0.999	1.043
All ages and sex	O_3 PM_{10} NO_2 SO_2	0.995	0.967	1.025	1.017	1.002	1.033
Age 15 - 64		0.989	0.949	1.03	1.01	0.985	1.036
Age >65		1	0.96	1.041	1.023	1.003	1.043
Female		0.953	0.914	0.995	1.016	0.995	1.038
Male		1.029	0.99	1.07	1.021	0.999	1.043

Table A10: Warm and dry - Season-specific single and multiple pollutant model adjusted relative risk (RR) for 10 µg/m^3 increase in the two-day moving average of $PM_{10,}$ $NO_{2,}$ SO_2 and O_3 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10 µg/m^3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM_{10}	1.01	0.987	1.033	1.003	0.99	1.016
	NO_2	1.058	1.011	1.107	1.004	0.979	1.03
	SO_2	1.011	0.953	1.072	0.991	0.959	1.023
	O_3	1.02	0.984	1.056	1.002	0.984	1.02
All ages and sex							
	PM_{10} NO_2 SO_2 O_3	1.008	0.966	1.053	1.006	0.982	1.031
	NO_2 PM_{10} SO_2 O_3	1.134	1.044	1.233	1.019	0.972	1.068
	SO_2 PM_{10} NO_2 O_3	0.967	0.876	1.068	0.995	0.94	1.052
	O_3 PM_{10} NO_2 SO_2	0.969	0.922	1.019	1.016	0.991	1.042

Table A11: Cold and wet - Season-specific single and multiple pollutant model adjusted relative risk (RR) for 10 µg/m^3 increase in the two-day moving average of $PM_{10,}$ $NO_{2,}$ SO_2 and O_3 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10 µg/m^3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM_{10}	1	0.984	1.016	1.016	1.007	1.025
	NO_2	1.039	1.01	1.07	1.024	1.006	1.041
	SO_2	1.024	0.985	1.064	1.034	1.01	1.059
	O_3	0.999	0.972	1.027	1.019	1.004	1.034

All ages and sex							
	PM_{10} NO_2 SO_2 O_3	0.991	0.964	1.019	1.015	0.998	1.032
	NO_2 PM_{10} SO_2 O_3	1.021	0.973	1.071	1.017	0.988	1.047
	SO_2 PM_{10} NO_2 O_3	1.012	0.943	1.086	0.985	0.943	1.028
	O_3 PM_{10} NO_2 SO_2	1	0.97	1.032	1.018	1.001	1.035

Table A12: Warm and dry - Season-specific single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of $PM_{10,}$ $NO_{2,}$ SO_2 and O_3 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10 µg/m^3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM_{10}	1.016	0.978	1.054	1.004	0.984	1.026
	NO_2	1.062	1.012	1.114	1.004	0.978	1.032
	SO_2	1.006	0.972	1.042	0.994	0.975	1.014
	O_3	1.031	0.976	1.089	1.003	0.976	1.032
All ages and sex							
	PM_{10} NO_2 SO_2 O_3	1.013	0.944	1.087	1.011	0.979	1.044
	NO_2 PM_{10} SO_2 O_3	1.144	1.047	1.25	1.011	0.978	1.044
	SO_2 PM_{10} NO_2 O_3	0.98	0.924	1.04	0.999	0.974	1.025
	O_3 PM_{10} NO_2 SO_2	0.952	0.881	1.029	1.028	0.999	1.057

Table A13: Cold and wet - Season-specific single and multiple pollutant model adjusted relative risk (RR) for an interquartile range increase in the two-day moving average of PM_{10}, NO_2, SO_2 and O_3 concentrations and mortality due to cardiovascular and respiratory diseases in all ages, Cape Town, South Africa, 1 January 2006 - 31 December 2015.

		Respiratory disease			Cardiovascular disease		
	Pollutant (10 µg/m^3)	Relative risk	95% Confidence interval		Relative risk	95% Confidence interval	
			Lower interval	Upper interval		Lower interval	Upper interval
All ages and sex	PM_{10}	1	0.975	1.026	1.026	1.011	1.042
	NO_2	1.042	1.011	1.074	1.025	1.007	1.044
	SO_2	1.014	0.991	1.038	1.02	1.006	1.035
	O_3	0.999	0.957	1.042	1.029	1.006	1.053
All ages and sex							
	PM_{10} NO_2 SO_2 O_3	0.986	0.942	1.031	1.023	0.99	1.058
	NO_2 PM_{10} SO_2 O_3	1.022	0.971	1.076	1.032	0.992	1.073
	SO_2 PM_{10} NO_2 O_3	1.007	0.965	1.051	0.986	0.955	1.019
	O_3 PM_{10} NO_2 SO_2	1.001	0.954	1.05	1.036	1.006	1.067

Lag structures

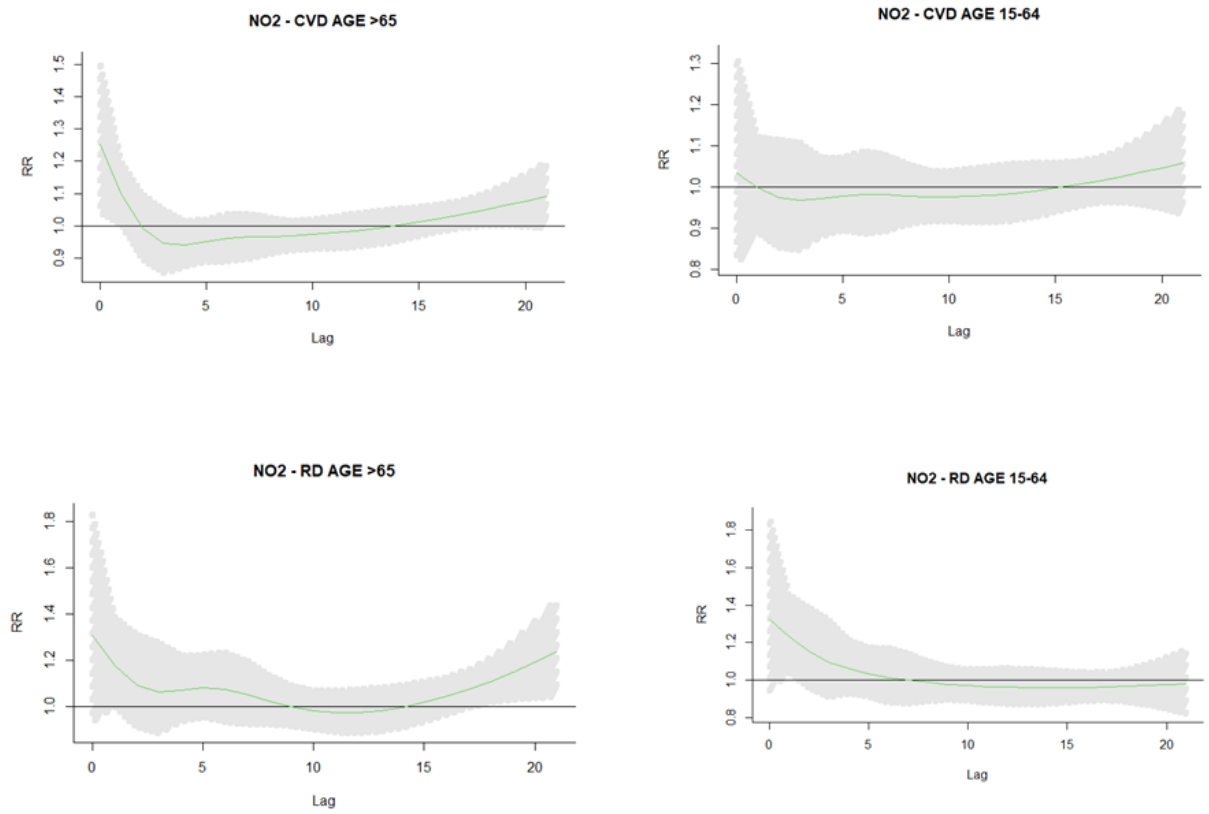

Figure ix: Age-specific Lag structure (0–21) of the estimated effects of a 10 µg/m³ increase in NO_2 concentrations on cardiovascular and respiratory disease mortality in Cape Town, South Africa, 2006–2015. The green curve gives the RR-estimates and the light grey band their 95% confidence intervals.

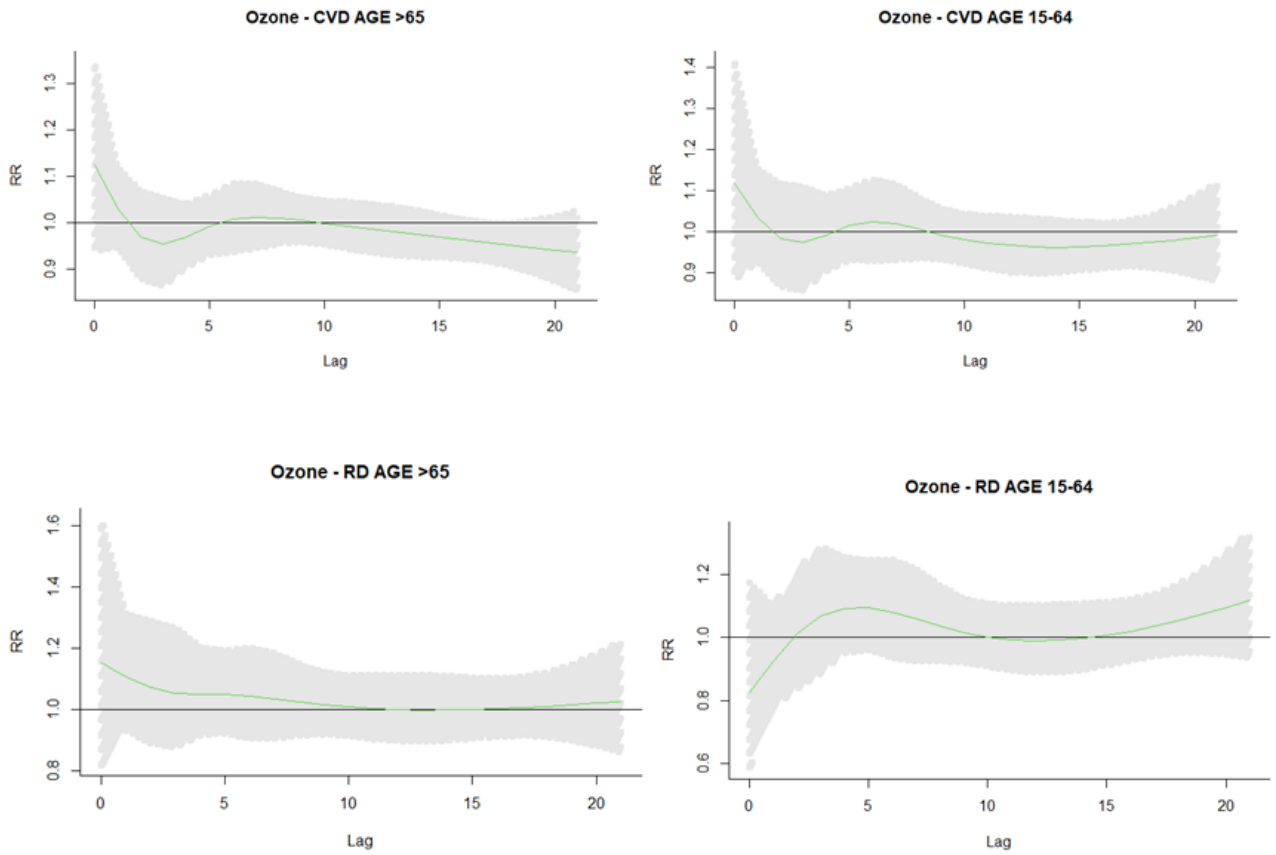

Figure x: Age-Specific lag structure (0–21) of the estimated effects of a 10 µg/m^3 increase in O_3 concentrations on cardiovascular and respiratory disease mortality in Cape Town, South Africa, 2006–2015. The green curve gives the RR-estimates and the light grey band their 95% confidence intervals.

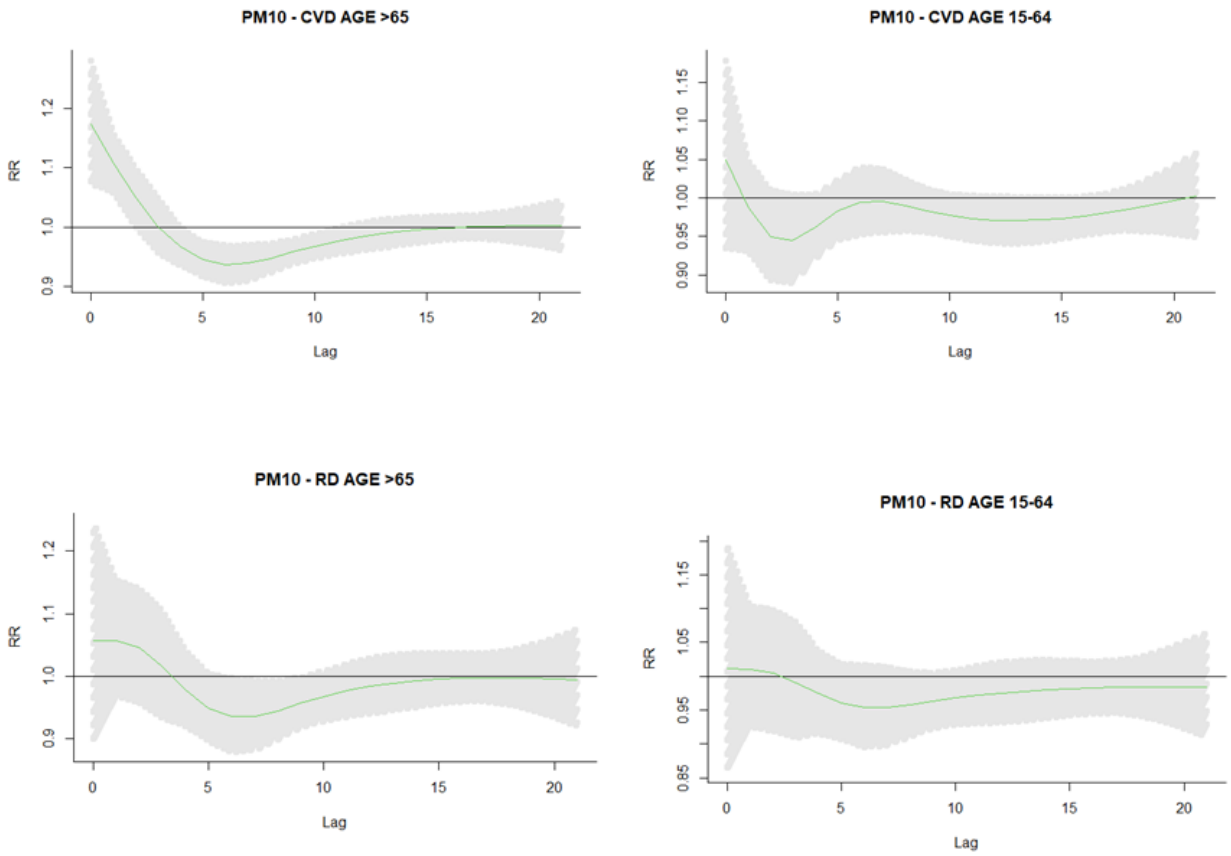

Figure xi: Age-Specific lag structure (0–21) of the estimated effects of a 10 µg/m3 increase in PM_{10} concentrations on cardiovascular and respiratory disease mortality in Cape Town, South Africa, 2006–2015. The green curve gives the RR-estimates and the light grey band their 95% confidence intervals

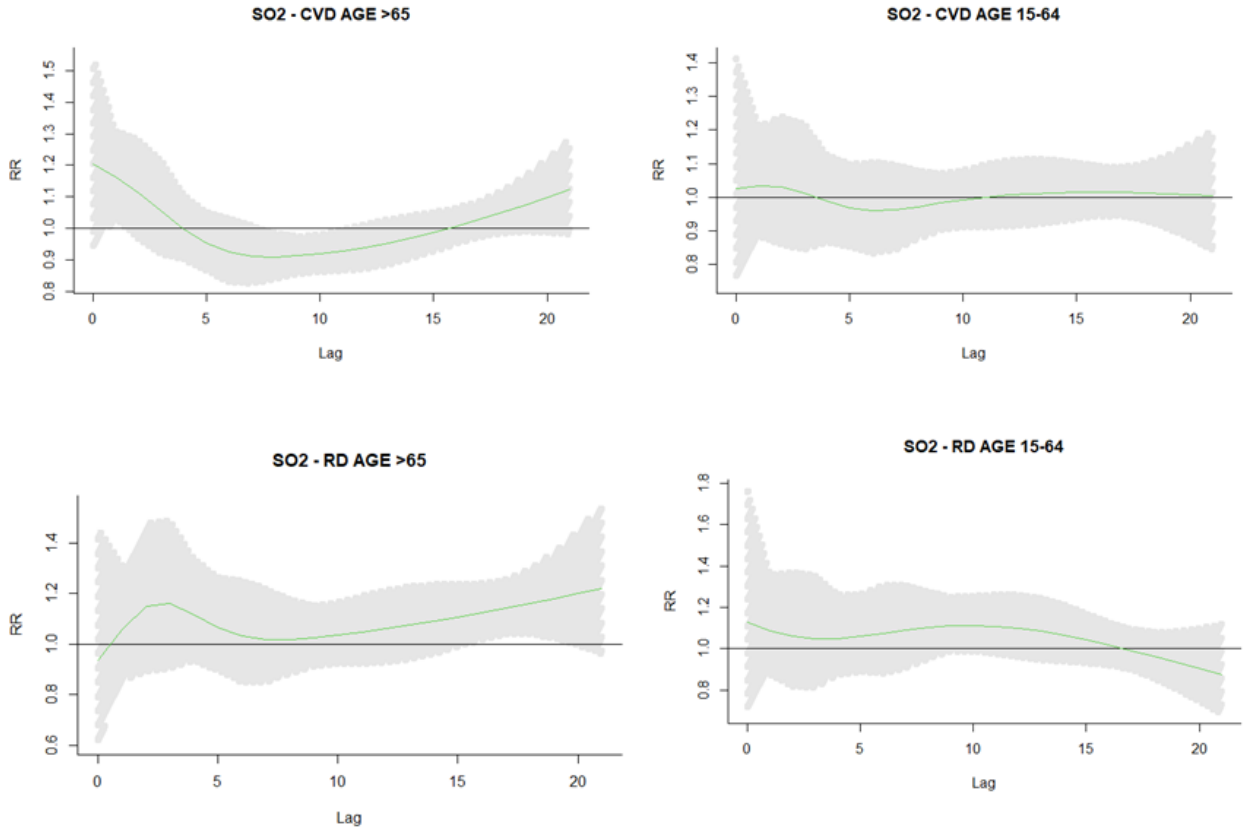

Figure xii: Age-Specific lag structure (0–21) of the estimated effects of a 10 µg/m3 increase in SO_2 concentrations on cardiovascular and respiratory disease mortality in Cape Town, South Africa, 2006–2015. The green curve gives the RR-estimates and the light grey band their 95% confidence intervals

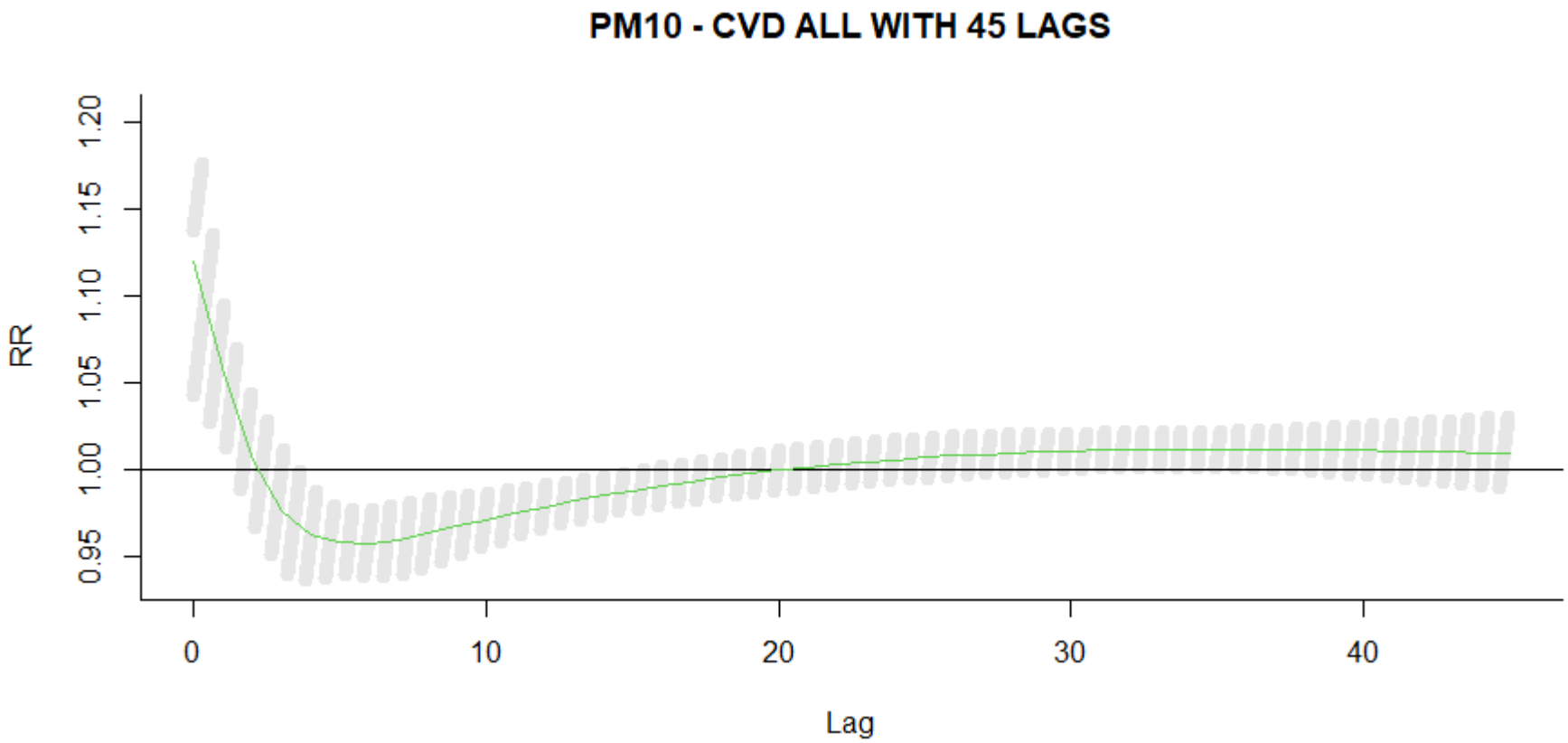

Figure xiii: Overall lag structure (0–45) of the estimated effects of a 10 µg/m³ increase in PM_{10} concentrations on cardiovascular disease mortality in Cape Town, South Africa, 2006–2015. The green curve gives the RR-estimates and the light grey band their 95% confidence intervals.

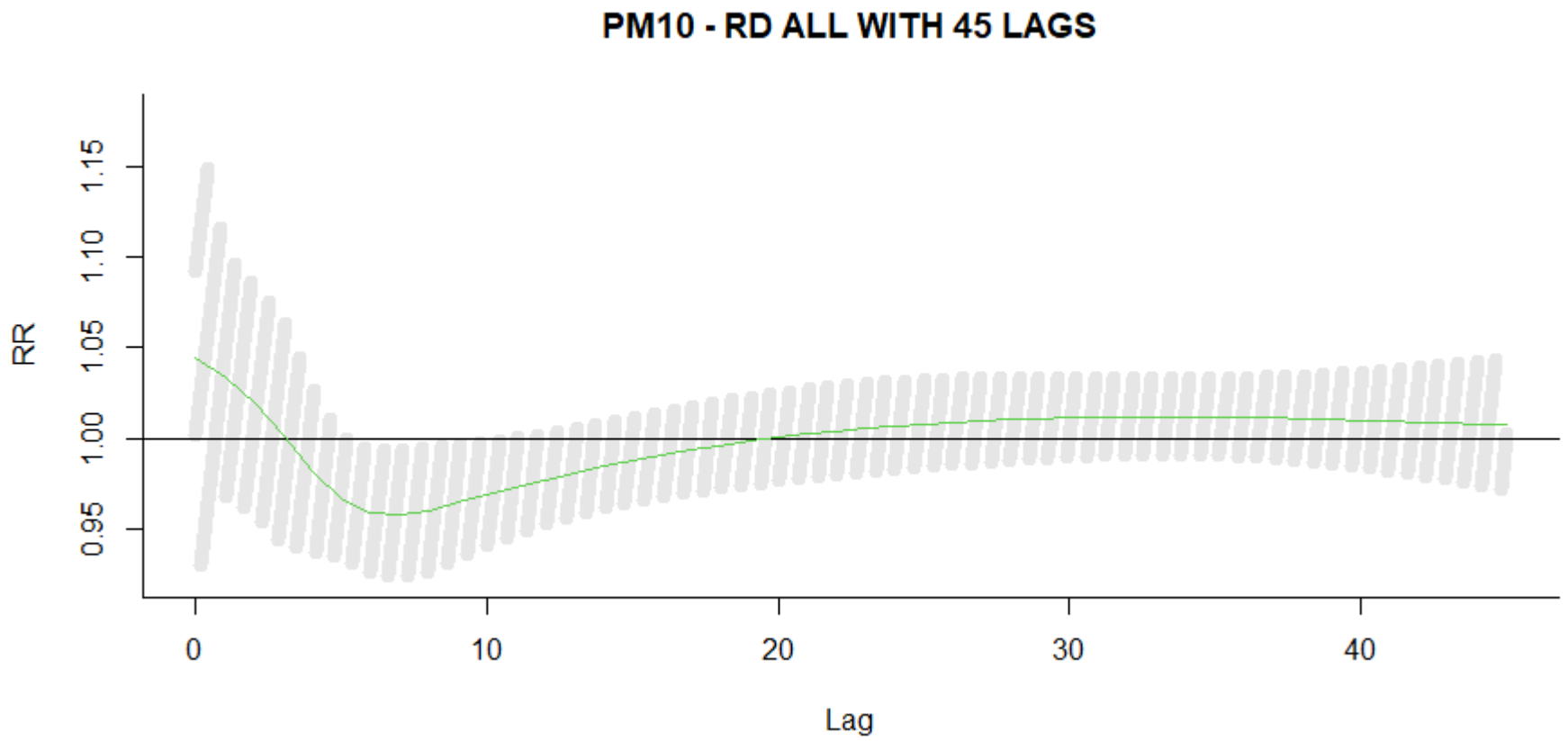

Figure xiv: Overall lag structure (0–45) of the estimated effects of a 10 µg/m^3 increase in PM_{10} concentrations on respiratory disease mortality in Cape Town, South Africa, 2006–2015. The green curve gives the RR-estimates and the light grey band their 95% confidence intervals.

Chapter 4

A new global Air Quality Health Index (AQHI) based on the WHO Air Quality Guideline Values with application in Cape Town.

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A New Global Air Quality Health IndexBased on the WHO Air Quality Guideline Values with Application in Cape Town

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Objectives: This study developed an Air Quality Health Index (AQHI) based on global scientific evidence and applied it to data from Cape Town, South Africa.

Methods: Effect estimates from two global systematic reviews and meta-analyses were used to derive the excess risk (ER) for $PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3. Single pollutant AQHIs were developed and scaled using the ERs at the WHO 2021 long-term Air Quality Guideline (AQG) values to define the upper level of the "low risk" range. An overall daily AQHI was defined as weighted average of the single AQHIs.

Results: Between 2006 and 2015, 87% of the days posed "moderate to high risk" to Cape Town's population, mainly due to PM_{10} and NO_2 levels. The seasonal pattern of air quality shows "high risk" occurring mostly during the colder months of July–September.

Conclusion: The AQHI, with its reference to the WHO 2021 long-term AQG provides a global application and can assist countries in communicating risks in relation to their daily air quality.

Keywords: air pollution, air quality guidelines, health effects, globalized air quality health index, air quality regulations

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INTRODUCTION

In 2012, approximately 50 million South Africans (95%) were exposed to harmful concentrations of ambient particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$) and ozone (O_3) with measurements above the national ambient air quality standards (NAAQS) of 10 μg/m³ and 120 μg/m³, respectively [1]. In South Africa, the total burden of disease attributable to $PM_{2.5}$ was estimated at 19,507 premature deaths, with 463,028 (95% Uncertainty interval (UI): 273,422–632,937) disability-adjusted life years (DALYs); while 1734 premature deaths due to COPD were attributed to O_3 with 61,130 DALYs (95% UI: 25,634–84,605) [1].

The daily communication of air quality to the public has beenin practice since the late nineties with the use of Air Quality Index (AQI) and lately in the early 2000s, the Air Quality Health Index (AQHI).

The AQI is conventionally developed using criteria pollutants of which the short-term average concentrations are compared to the short-term limit values set by the national ambient air quality standards (NAAQS). The pollutant with the highest value relative to its limit value determines the short-term AQI value [2]. This means the AQI is based on reporting the most offending pollutant, while ignoring the "lower levels" of the other pollutants. This is one of the core reasons why the index has received criticism. As countries adopt different NAAQS, air quality indices are not comparable across countries, which is a confusing feature of a tool adopted to communicate the risks related to daily levels of air pollution. In particular, the lowest index values are usually labeled as "green" or "healthy air". Thus, with discrepant AQI scales, the same level of pollution may be communicated as "green" in one city or country but "hazardous" elsewhere. Other limitations of AQIs include their inability to reflect additive or combined effects of multiple pollutants, to capture effects below thresholds and that they are rarely updated when the NAAQS are reviewed or amended [3–5].

In South Africa, the NAAQS of the pollutants are less stringentthan those proposed by WHO in 2005 and, thus, far less stringentthan the new 2021 WHO air quality guideline (AQG) values. Thishas major implications on the way South Africa communicatesshort-term air quality to the public. South Africa's AQI has fivebands on a scale of 1–10 indicating "low," "moderate," "high" "very high" and "hazardous" risk levels of air quality [6]. The bands defining "good" air quality or "low" pollution are enormous, with hourly concentration of $PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3 varying from 0–103 μg/m³, 0–190 μg/m³,0–200 ppb (376 μg/m³), 0–350 ppb (916.7 μg/m³) and 0–80 ppb (157 μg/m³), respectively. Thus, concentrations within these ranges are declared to be "safe" or healthy although they may be far higher than the 2005 WHO Air Quality Guideline values[7]. Therefore, the misclassification of the air quality levels in this index leads to an underestimation of the true risks. In fact, onlyextreme episodes of unusually high levels of air pollution aboveNAAQS can be captured, which, in most parts of the country, arerare as seen on the South African Air Quality Information System(SAAQIS) [8].

In contrast, the health-based multipollutant indices commonly known as AQHI have the primary objective of comprehensively accounting for the short-term health effects of multiple air pollutants. The AQHI reflects the overall influence of different mixtures of air pollutants and the presence of effects at low levels of exposure, which by designis a limitation of the AQI. Cairncross et.al. constructed a health-based multipollutant index a decade before South Africa implemented the AQI. They used relative risks for daily mortality from a WHO health impact assessment conductedin Europe to illustrate the method for developing the index[3]. A well-constructed AQHI must have a few attributes as highlighted by Hewings [2]. These involve the inclusion of criteriapollutants and their synergies, expandable for other pollutants and averaging times; comparability among communities; understandability to the public; and usability as an information and alert system.

We add two other criteria that an AQI or AQHI index should fulfill. First, a health-oriented index should consistently weigh the health impact of each pollutant. Second, the long-term WHO AQG values rather than the short-term values should be a point of reference to properly reflect the scientific evidence in the interpretation of short-term concentrations. WHO does not consider the short-term AQG values as a "healthy" reference but as a concentration that should not be exceeded more than three times a year. Instead, AQI ignore this statistical definition ofshort-term limit values but consider these concentrations as "healthy" irrespective of the number of exceedances. This results in the paradox that daily compliance with the short- term guideline values will define air quality as "healthy" although the annual mean may still be far above the long-term WHO AQG value.

In the 2021 WHO AQG update it has been emphasized, thatthe effect of ambient air pollution on mortality, cardiovascular and respiratory disease hospital admissions can be observed at levels lower than WHO 2005 air quality guidelines and South Africa's NAAQS [9–15], thus, AQG values have been lowered.This calls for a revision of the AQI and we take this as an opportunity to develop a globally generalizable index that addresses the limitations and paradox of current AQI discussed above.

Therefore, this study proposes a revised methodology for the AQI to be of direct relevance for South Africa and beyond. Wedescribe the numeric formulation of the index and its health standardized scaling, which uses the WHO 2021 long-term AQG values as point of reference to define "healthy" air quality. We also propose the translation of the scale into a traffic-color-based scheme (green-yellow–red). Finally, the constructed index is applied to daily air pollution data from Cape Town, 2006–2015.

METHODS

The development of our health-based multiple pollutant index which will be referred to as AQHI for simplicity requires five stepsas illustrated in Figure 1. Each step is described in more detail inthe method section of the Supplementary Material. In summary,the numeric formulation of the AQHI starts with using existing epidemiological concentration-response functions (CRF) for four ambient pollutants, generally a relative risk estimate (RR) per unit increases in the ambient concentrations. These RR from large reviews is used for the derivation of the new WHO AQG (2021)[16, 17]. In the second step we used these CRF's to derive the dailyexcess mortality risks for each of the four pollutants. Third, wescaled the distribution of each pollutant's excess risk (ER) to index values with linear categories from 1 to 10+ in a way that theindex value of 3 corresponds to the ER derived for the concentrations where the WHO long-term AQG values are met. Fourth, the overall AQHI is calculated by taking theweighted average of the four index values. In the last step, we

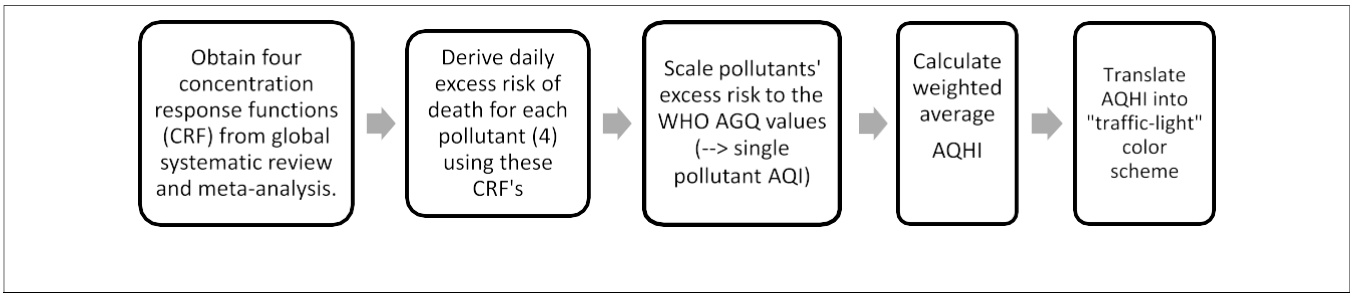


TABLE 1 | Derivation of the weighted average AQHI indices: the single pollutant concentration-response functions (CRF), the related beta coefficient, the chosen WHO AQGreference value, [16, 17] the related daily excess risk (ER) (Eq. 1). In addition, the daily ER%s of the pollutants ER% per index unit are shown. Thus, by design, the single pollutant index value of 3 corresponds to PM_{10}, NO_2, SO_2 and O_3 concentrations of 15 μg/m^3, 10 μg/m^3, 20 μg/m^3, and 60 μg/m^3, respectively. The weights for the average index value are shown for both, the $PM_{2.5}$ and the PM_{10} based AQHI. Cape Town, South Africa 2006 and 2015.

Pollutant p	CRF published in WHO AQG (per 10 μg/m^3)	Beta coefficient per 1 μg/m^3	WHO AQG reference value [1] in μg/m^3 for index value = 3	ER (%) at index value = 3	Average ER (%)per index unit	Inverse weight for $PM_{2.5}$ based AQHI	Inverse weight for PM_{10} based AQHI
$PM_{2.5}$	1.0065	0.00065	5	0.326	0.109	1	—
PM_{10}	1.0041	0.00041	15	0.617	0.206	—	1
NO_2	1.0072	0.00072	10	0.723	0.241	0.451	0.853
SO_2	1.0059	0.00059	20[2]	1.187	0.396	0.275	0.519
O_3	1.0043	0.00043	60	2.614	0.871	0.125	0.236

categorize the 10 index units into the color scheme of traffic lights where "green" will be up to level 3 of the scale, thus in compliance with the excess risk occurring at concentrations up to the long-term WHO AQG values of each pollutant. Therefore, if concentrations of all pollutants remain on all days within the "green" levels, air quality will also be compliant with the long-term AQG values. Concentrations above the index value of 10 all fall into the unbounded upper category of "10+".

In the last section, we will apply the new AQHI to the time series of Cape Town used in the first step to demonstrate the features of the AQHI and the level of compliance of the past air quality in Cape Town with the proposed index.

Due to the high correlation between PM_{10} and $PM_{2.5}$, and given that some authorities restrict the monitoring of PM to only one fraction, we propose to derive the AQHI with either one ofthe two size fractions of PM. Thus, each of the two AQHI willinclude four pollutants, namely the three gaseous pollutants butonly one of the two particulate mass fractions. In our case study,we will apply the PM_{10} based AQHI to our 2006–2015 Cape Town data. The daily ERs were calculated using Eq. 1, therefore, the excessrisk associated with the long-term WHO AQG-value c_i ofpollutant i becomes $100\left(e^{\beta_i c_i} - 1\right)$.

$$pollutant\ i\ excess\ risk\ on\ day\ t = 100\ (e^{\beta_i x_i(t)} - 1) \quad (1)$$

β = *coefficient per* 1 $\frac{ug}{m3}$ *increase of pollutant i,* $x_i(t)$ = *concentration of pollutant on day t)*

We used the ERs associated with an index of 1 (Table 1) to define the weights of the pollutant-specific AQHIs in the overallAQHI. For each pollutant i, the weight W_i is defined as the ratio between the ER of PM_{10} (or $PM_{2.5}$) and the ER of the pollutant i. Thus, the weight of PM_{10} (or $PM_{2.5}$) is defined to be 1. The daily average AQHI value is the weighted mean of the index values of the different pollutants using Eq. 2, rounded to the nearest integer.

$$Weighted\ Average\ AQHI(t) = \frac{1}{\sum W_i} \sum_{i=1\ldots n} W_i * AQHI_i(t) \quad (2)$$

where n = number of pollutants used in AQHI, i = pollutant, $AQHI_i(t)$ *= derived index value for pollutant i on day t and* W_i *= weight of* $AQHI_i(t)$

Given that monitoring stations may occasionally not be functional, authorities will face the challenge of missing data. We propose a simple imputation in the Supplementary Material. Otherwise, the weighted average AQHI may be based on less than four index values.

Using the result from Table 1 we present the final AQHI in Table 2 below:

Application of the Proposed Method to Cape Town

In this section we used the daily air pollution monitoring data from Cape Town from 2006–2015 which was aggregated to city level from all available stations and analyzed for previous publications [10, 11]. We described the distribution of daily concentrations of each pollutant and of the daily ER% in this long-term time-series.

In addition, the total daily ER% was translated into the pollutant-specific daily index values. In the last step, we derived the daily weighted average AQHI, based on PM_{10} and the three gaseous pollutants, as described in the Methods.

RESULTS

The daily averages (standard deviation) of PM_{10}, NO_2, SO_2 and O_3 were 30.4 μg/m³ (13.6 μg/m³), 17 μg/m³ (8.8 μg/m³), 11 μg/m³ (5.5 μg/m³) and 33 μg/m³ (12.3 μg/m³), respectively. These data have been previously described in detail [10]. The 2021 WHO short-term air quality guideline values were exceeded on 497 (13.6%) days of the 3,652-day study period for PM_{10} (>45 μg/m³), 501 (13.7%) days for NO_2 (>25 μg/m³), and 196 (5.4%) days for SO_2 (>40 μg/m³); however, we did not observe any exceedance forOzone (>100 μg/m³). The daily concentrations of PM_{10} and NO_2 exceeded the WHO AQG 2021 long-term values on 93% (n =3,399) and 70% (n = 2,533) of the days of the study period. Thedaily means of each pollutant during the study period of 2006–2015 are shown in (Supplementary Figure S2). Ozone levels after 2010 were below the WHO AQG long-term value while PM_{10} shows a decreasing trend. NO_2 and SO_2 do not show adiscernible trend.

The highest average daily excess risk (ER%) was observed for PM_{10} with an ER% of 1.25%, while SO_2 had the lowest ER% with adaily average of 0.6%; NO_2 and O_3 averaged 1.08% and 1.05% respectively. The number of days on which the individual AQHIs were in agreement with the long-term values of the WHO 2021 AQG, i.e. with an AQHI of 1, 2 or 3 and a "green" color code, was 277 (7.58%), 741 (20%), 3,366 (92.17%) and 2,613 (71.55%) for PM_{10}, NO_2, SO_2 and O_3, respectively. The distribution of the individual pollutants and their AQHIs is shown in Table 3.

AQHI level 3 indicates PM_{10} exceeds on average the WHO long-term value (15 μg/m³ vs. 19 μg/m³) while the means of the other pollutants are below their long-term WHO AQG values.

PM10, with the lowest number of missing days (0.2%) and contributing more weight to the combined index, likely compensated for missing measurements of other pollutants.

Figure 2 shows the air quality in Cape Town. The weighted average AQHI for the combination of all four pollutants during the study period of 3,652 days was "low risk" on 482 days (13%), "moderate risk" on 2,565 days (70%) and "high risk" on 605 days (17%). In the first 2 years, there were 6 "low risk" days each and the last year (2015) had the highest number of "low risk" days (123 days, i.e.,33%). There appears to be an improvement in air quality when comparing the beginning and the end of the study period, but there was no clear trend, as the number of "low risk" days varied in the intervening years. In addition, the first 3 years had more "moderate-high risk" days between April and September. After 2009, however, the seasonal pattern became more pronounced with "high risk" days occurring mostly in the colder months of June–September. We provide an interactive plot showing the single pollutant AQHIs and the weighted average AQHI for the study period in Cape Town, South Africa 2006 and 2015.

DISCUSSION

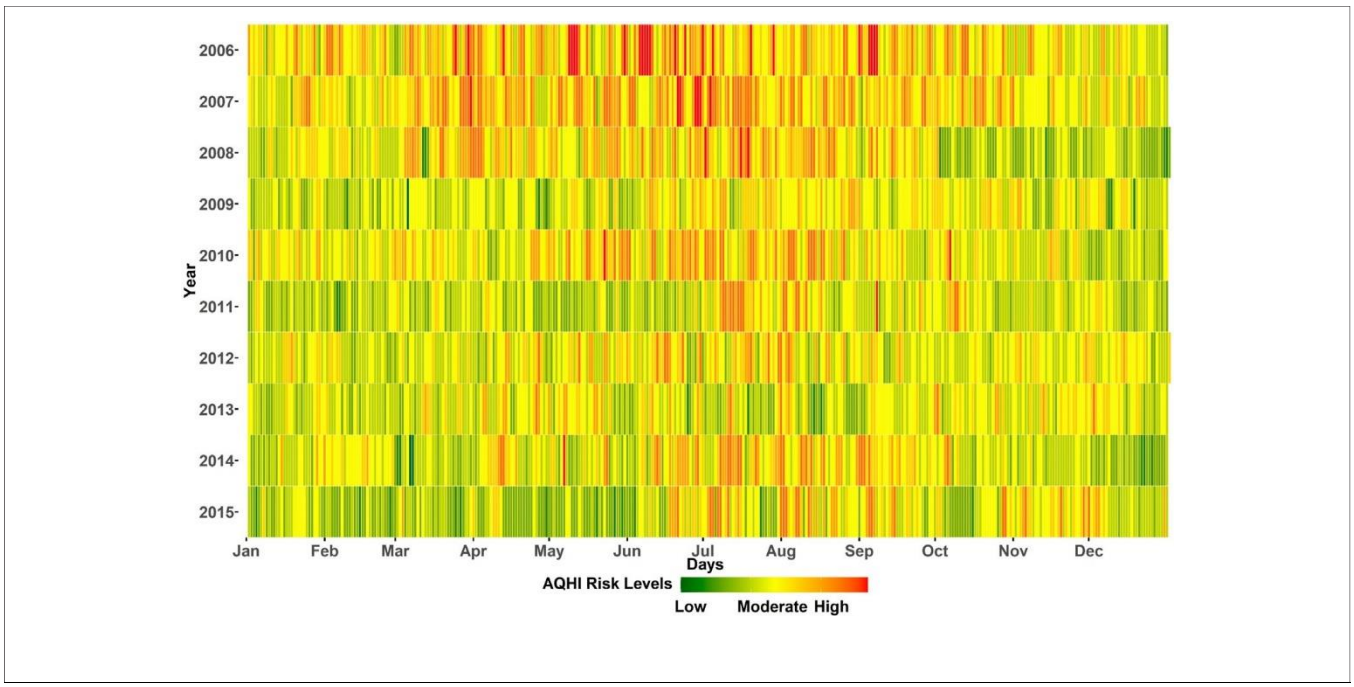
This study constructed a globally applicable Air Quality Health index using concentration-response functions (CRF) obtained from recent global systematic reviews on the short-term effects ofair pollutants on daily mortality [16, 17]. It is the first index to incorporate the newly published long-term WHO Air Quality Guideline values as a reference point to define "healthy" or "low risk" days. Thus, judgments about daily air quality will not contradict current evidence of health effects occurring at concentrations exceeding the long-term AQG values. Indeed, all AQI currently in use can lead to the paradox that all daily means may be labeled "green" or healthy although the annual mean may substantially exceed the WHO reference values.

TABLE 2 | The constructed AQHI showing the range of excess mortality risk per pollutant, levels of risk and the corresponding health messages. Cape Town, South Africa 2006 and 2015.

Single pollutant ER% range						Health messages	
AQHI	PM_{10}	NO_2	SO_2	O_3	Risk levels	General population	Susceptible population
1	<0.21	<0.24	<0.4	<0.87	Low risk (AQHI 1–3)	Ideal conditions for regular outdoor activities	Enjoy your usual outdoor activities
2	>0.21–0.42	>0.24–0.48	>0.4–0.8	>0.89–1.74			
3	>0.42–0.63	>0.48–0.72	>0.8–1.2	>1.74–2.61			Follow your doctor's advice for exercise
4	>0.63–0.84	>0.72–0.96	>1.2–1.6	>2.61–3.48	Moderate risk(AQHI 4–6)	No need to modify your usual outdoor activities	If you have heart or breathing problems, and experience symptoms, consider reducing physical exertion outdoors or rescheduling activities to times when the index is lower
5	>0.84–1.05	>0.96–1.20	>1.6–2	>3.48–4.35			Contact your doctor and follow their advice
6	>1.05–1.26	>1.20–1.44	>2–2.4	>4.35–5.22			
7	>1.26–1.47	>1.44–1.68	>2.4–2.8	>5.22–6.09	High risk (AQHI 7–10+)	Consider reducing or rescheduling strenuous outdoor activities to periods when the index is lower, especially if you experience symptoms	Children, the elderly and people with breathing or heart problems should avoid physical exertion outdoors
8	>1.47–1.68	>1.68–1.92	>2.8–3.2	>6.09–6.96			
9	>1.68–1.89	>1.92–2.16	>3.2–3.6	>6.96–7.83			If you have heart or breathing problems, follow your doctor's advice about managing your condition
10+	>1.89–2.10+	>2.16–2.40+	>3.6–4.0+	>7.83–8.70+			

TABLE 3 | Distribution of daily mean (standard deviation) concentration of pollutants and number of days per weighted average-AQHI value in Cape Town for the period from 2006 to 2015 (in total, 3,652 days) Cape Town, South Africa 2006 and 2015.

Single -AQHI		PM_{10}	NO_2		SO_2		O_3	
μg/m³		Days	μg/m³	Days	μg/m³	Days	μg/m³	Days
1[3]	—	—	—	—	8.3 (4.7)	3 (0.1%)	—	—
2	15.1 (3.2)	33 (0.9%)	3.9 (1.4)	4 (0.1%)	7.2 (2.9)	30 (0.8%)	30.8 (10.3)	24 (0.7%)
3	19.3 (5.6)	419 (11.4%)	7.2 (2.8)	265 (7.3%)	8.0 (4.1)	398 (10.9%)	32.4 (10.9)	308 (8.4%)
4	22.5 (7.8)	1,015 (27.8%)	11.0 (3.8)	916 (25.1%)	8.9 (4.3)	984 (26.9%)	30.9 (12.6)	715 (19.6%)
5	29.1 (10.2)	954 (26.1%)	15.3 (5.1)	875 (24.0%)	10.0 (4.6)	945 (25.9%)	33.9 (12.5)	720 (19.7%)
6	36.2 (10.9)	602 (16.5%)	18.7 (6.1)	601 (16.5%)	11.5 (5.3)	598 (16.4%)	35.2 (12.3)	440 (12.0%)
7	42.8 (11.3)	345 (9.4%)	24.6 (6.6)	345 (9.4%)	12.6 (4.7)	337 (9.2%)	34.7 (12.4)	249 (6.8%)
8	51.6 (11.0)	241 (6.6%)	32.8 (7.1)	214 (6.6%)	16.6 (6.3)	241 (6.6%)	32.5 (11.4)	181 (5.0%)
9	65.1 (13.2)	37 (1.0%)	41.8 (8.3)	37 (1.0%)	26.8 (5.3)	37 (1.0%)	30.7 (11.3)	35 (1.0%)
Missing	—	9(0.3%)	—	368 (10.1%)	—	79(2.2%)	—	980 (26.8%)



Our novel index keeps a methodological similarity with the Canadian AQHI. The latter index was constructed with an assumption of linear, no-threshold associations between the exposure to air pollutants and daily excess mortality. The appropriateness of this approach was also demonstrated inrecent systematic reviews, including a particularly large multicity study on particulate matter and daily mortality also used in the derivation of the new WHO AQG values [18].

The application of our index to data from Cape Town showed that the proposed AQHI would qualify 87% of the days in ourstudy period as "moderate" or "high risk". This strongly contradicts the risk levels communicated via the current South African AQI where the past years would mostly be labeled as "good". A large body of literature endorses the revised qualification of Cape Town's air quality. Previous studies of short-term effects of air pollution on cardiorespiratory health in the study area reported that PM_{10} and NO_2 were positively associated with hospital admissions and at levels far below the average daily concentrations observed in Cape Town during the study period. An interquartile range (IQR) increase of 12 μg/m³ for PM_{10} and 7.3 μg/m³ for NO_2 were associated with a 2% (95% confidence interval (CI): 0.5%–3.2%) and 2.3% (95% CI: 0.6%–4%) increased risk of respiratory disease hospitalizations, respectively [11]. In addition, the same increment in PM_{10} was associated with a 2.1% increased risk in cardiovascular hospitalization [11]. Another study on CVD and RD mortality showed a 4.5% increased risk of CVD mortality (95% CI: 1.4%–7.6%) for an IQR change of 10.7 μg/m³ in NO_2. In addition, an IQR change of 16 μg/m³, 11 μg/m³, and 16 μg/m³ in PM_{10}, NO_2 and O_3 was associated with an increased risk of 2.4% (95% CI:0.9%–2.2%), 2.2% (95% CI: 0.4%–4.1%) and 2.5% (95% CI: 0.2%–4.8%) in RD mortality, respectively [10]. During our study period,

the ER% for the average PM_{10} (30.3 μg/m³) and NO_2 (16.6 μg/m³) levels would correspond to 1.25 ER% (AQHI 10) and 1.2ER% (AQHI 6) of death, respectively. Thus, it is appropriate to label the air quality to which the population of Cape Town was exposedto as poor rather than as "low risk".

There is no universal method for constructing an AQHI; most authors have developed their index using the methods of Cairncross and Stieb, but the indices differ in the number of pollutants, averaging times and breakpoints for risk classification [3, 5]. Our use of established effect estimates is similar to Cairncross' air pollution index, but these authors used estimates from a European study whereas ours are from a global systematic review. Ideally, an AQHI would communicate the combined effects of the pollution mixture. The approach of Stieb et.al. [5] to develop an AQHI based on multi-pollutant time-series analyses, was indeed an intriguing proposal along these lines. However, the number of multi- pollutant studies is very limited, thus, the derivation of mutually adjusted effect estimates would rely on thin data,usually from high income countries. Moreover, most multipollutant studies evaluated only two-pollutant models whereas mutually adjusted models with three or even all four pollutants used in our AQHI are not available [16]. Thus, we consider our approach based on single-pollutant CRFs as adequate.

Our approach challenges though the derivation of a combined AQHI summary measure. If the four AQHI were based on mutually adjusted CRF's, the sum of the four estimates would be an adequate measure of the overall AQHI. However, the sumof single-pollutant ERs would clearly overestimate the true totalER given the substantial correlation between single pollutants such as PM and NO_2 or SO_2. Without proper knowledge of thedegree of overlap it is impossible to properly adjust the sum of single-pollutant based ERs. Thus, to nevertheless integrate information of four pollutants into one single AQHI, we derived a weighted average AQHI. Inevitably, this will underestimate the total risk to the extent that at least part ofthe effects of single pollutants are additive, i.e. independent of those estimated for the other pollutants. Indeed, for PM and ozone, risk assessors agreed to treat those as independent effects, thus, the Global Burden of Disease integrates the sum of both into the assessment of the total air pollution related burden [19]. Instead for the other three pollutants, combined models are notyet available. In fact, a recent study made valuable first efforts tointegrate mutually adjusted risk estimates for two pollutants, namely, $PM_{2.5}$ and NO_2 [20].

As mentioned, a novelty of our AQHI is the full alignment with the WHO AQG values. AQHI values 1 to 3 (green) all comply with daily concentrations up to the long-term mean guideline values. Our method reveals an interesting feature of the AQG values, which plays a key role in the derivation of the overall average index value. As emphasized in the WHO AQG (2021) [9], the Guideline Development Group did not define any "acceptable" health burden to derive the guideline values. Instead, the lowest concentration for which effects could be observed withsufficient confidence were taken to define the long-term AQGvalues. This contrasts with the prevailing risk management concept for carcinogens where "acceptable risks"—e.g., 1 case per 1 million lives—are defined as "acceptable" policy target [21]. The WHO AQG emphasize also the lack of evidence for any "thresholds of no effect" for the pollutants used in the AQHI, thus, concentration below the guideline values is not considered "healthy" but the shape of the CRF is not yet defined below those levels. If one estimates the excess risk for the concentrations proposed by WHO as the guideline values as compared to zero pollution, one obtains in essence the implicitly defined "acceptable risks" as shown in Table 1. Those ER vary substantially across the four pollutants. E.g., the ER% at the limit value of ozone is 4.23 times higher than the ER% at the new guideline value of PM_{10}. In other words, the WHO AQG hasthe inherent inconsistency of tolerating a much higher health burden due to ozone than due to PM_{10}. Thus, taken at the sameindex level (e.g., 3), the arithmetic means of four ER% would bedominated by the burden due to ozone.

As a consequence of the dominance of the ER% scaling of ozone and of the much more likely compliance of ozone with the AQG values the arithmetic mean of the four index values would often mask "high risk" days of PM_{10} (and NO_2) as "low risk" days.Such bias jeopardizes the intention of the AQHI, namely to coherently communicate the daily health risks due to air pollution. Thus, instead of using the arithmetic mean we derive the weighted mean AQHI using the inverses of the ER

% at the WHO AQG reference values as the weights. As shown in Table 3, as a consequence of this weighting, the measured concentrations of the four pollutants are mostly below the long-term AQG values on days when the derived overall AQHI results at level 1, 2 or 3. However, in case of PM10 the long-term AQG value is exceeded on 296 days (8%) of the study period partly due to its weight.

Our proposal for a globally adopted AQHI is an innovative approach as it offers a fresh perspective on the long-standing issues of AQIs. It fully standardizes the science-based communication of risk levels irrespective of the local policies and pollution. It endorses the "right to know" on a global scale, inan equitable manner. On the other side, it forces authorities in regions with very high levels of air pollution to label air quality on most if not all days as "red" or "high risk." Globally harmonized AQHI facilitate the comparison of air quality across geographical locations (within or between countries). A standardized index could provide additional value in tracking air quality trends over time, which can help authorities to evaluate their efforts and policies to achieve clean air.

For the reporting of the AQHI, authorities may adopt various approaches. The index could be reported for each monitoring station or for the mean values of each pollutant across all stations of a geographical location. Such regional mean AQHI could also help to reduce exposure misclassification as people are exposed at different levels of air pollution as they move within the region (e.g. for work). Authorities may also opt for the reporting of all four single-pollutant AQHI and the related weighted average. This would transparently disclose problematic pollutants. However, for the users of the AQHI,it may be confusing to deal with five different values. Thus, thereporting of the weighted average AQHI might be the preferable

choice. In addition, sensitivity analysis of PM_{10}-and $PM_{2.5}$- based indices and simple imputation for missing pollutantsare discussed in the Supplementary Material.

We propose to replace currently used AQI with our new scheme. The communication messages of current AQI are, however, still adequate (see Table 2). As shown in the literature [5], the communication of AQI values and related health information assists the general population to keep track of the air quality and possibly subscribe to receiving notifications for when the risk level exceeds a certain threshold, e.g., when it goes beyond green for people at risk.A study in Canada showed that air quality alert programs led toa 25% (95%CI 1%–47%) reduction in asthma-related emergency department visits [22]. Another study in Chile, reported a reduction in deaths among the elderly (age >64 years) following the announcement of above-average pollutionepisodes; the Chilean authorities accompanied their announcements with mandatory measures such as driving restrictions to reduce car emissions, shutting down of certain large stationary emitters, and other protocols, which resulted ina further 20% reduction in air pollution compared to days without alerts [23]. This shows that mandatory measures, such as those implemented in Chile, could be more effectivein reducing pollution and protecting human health if accompanied by air quality alert at a certain threshold—for example, when the AQHI risk level approaches "high risk." We recognize though, that making people aware of their air quality and the associated risks may not be sufficient to change their behaviour. At the very least, it could help susceptible people to self-calibrate if they understand the levels of the index at which they experience symptoms and discomfort.

Conclusion

This study has constructed a global air quality health indexas an effective tool for communicating air quality to the public on a daily basis. The alignment of our index scale with the science based excess risks attributable to the daily concentrations of the four pollutants used in our index guarantees global comparability of local air quality levels and fosters a coherent understanding of the related health effects. This, in turn, may foster public support for the adoption of stringent clean air policies.

AUTHOR CONTRIBUTIONS

Conceptualization TA-O, JW, and NK; Methodology TA-O and NK; Data collection, TA-O and JW; Analysis TA-O and NK; Writing TA-O; all authors including OA, CS, and NP-H contributed and reviewed the article prior to submission. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.ssph-journal.org/articles/10.3389/ijph.2023.1606349/full#supplementary-material

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Paper 3 Appendix

A new global air quality health index based on the WHO Air Quality Guideline Values with application in Cape Town.

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Conflict of interest: The authors declare they have nothing to disclose.

This document outlines the methods used for constructing the air quality health index (AQHI) in detail and presents additional results.

Online supplementary material

Method

The construction of the AQHI follows five steps as shown in Figure S 1. The detail of each step is outlined below.

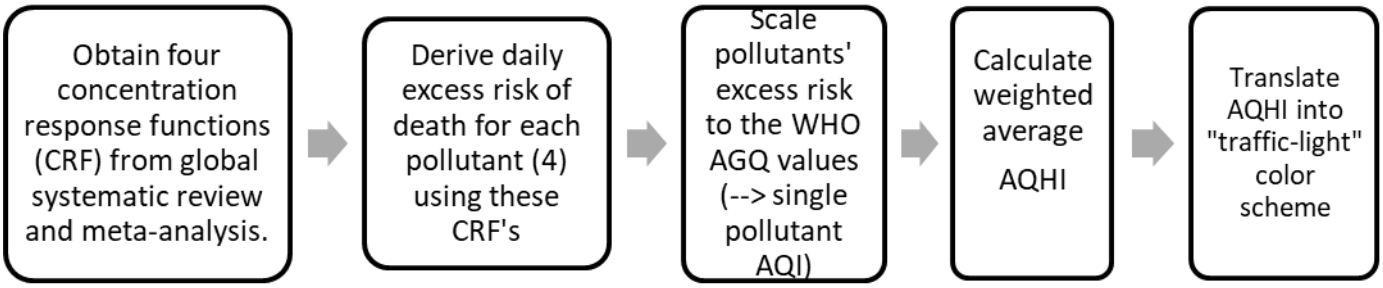


Figure S 1: A four-step guide for constructing an Air Quality Health Index (AQHI)

Obtain concentration response functions (CRF)

Many CRF for the association between daily mean concentrations and mortality are available. We opted for the CRFs from the global systematic review of 263 studies for $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 and all-cause mortality that guided the development of the 2021 WHO AQG values.[1,2] These reviews published pooled effect estimates from single-pollutant analyses. Two of the studies in the review were large multi-city studies of 652 and 406 cities, six of which were South African, conducted by the Multi-country-multi-city (MCC) collaborative research network.[3,4] These estimates are considered to be more stable than those reported from single city study analyses and are thus suitable for constructing an index for global use. The CRFs from the review are shown in Table 1 of the main manuscript, repeated here also in Table S 1.

Derivation of daily excess risk for each pollutant

Next, we used these all-cause mortality CRF coefficients shown in Table S 1 to derive the excess risk (ER) for each pollutant in our study. As first point of reference for this ER we used the concentrations of each pollutant that corresponds to the WHO AQG long-term values published in 2021.[5] Given the WHO AQG 2021 methodology, air quality is expected to be complying with those long-term values if the short-term values defined by WHO AQG are not exceeded more than three times a year.

In case of SO_2, 2021 WHO AQG did not propose a long-term value but only the daily mean of 40µg/m^3 not to be exceeded more than three times a year.

Thus, WHO AQG have not derived the statistical relationship between the number of exceedances and the annual mean for SO_2 as in case of the other pollutants.

However, in the second edition of the WHO AQG (2000), an annual mean value of 20 µg/m^3 was proposed to protect natural ecosystems.[6] The value has been scientifically derived as critical load to protect the vegetation in the long run.[7] Many legislators require environmental conditions that protect human health, vegetation, crops and animals alike. Thus, we consider this a suitable point of reference for the derivation of the ER and assume that compliance with this annual mean to correspond to only a few daily means above the WHO AQG 2021 value.

We calculated the excess risk associated with each pollutant i's coefficient β_i where c_i is the long-term concentration defined in the WHO AQG as shown in Equation S 1.

	$pollutant\ i\ excess\ risk\ on\ day\ t = 100\left(e^{\beta_i c_i} - 1\right)$	*Equation S 1*

$$\beta_i = coeffcient\ per\ 1\frac{ug}{m3}\ increase\ of\ pollutant\ i,\ c_i(t) = long - term\ WHO\ AQG\ concentration\ of\ pollutant\ i\ )$$

$PM_{2.5}$ standards were implemented in 2012 and $PM_{2.5}$ measurements were introduced only in 2018 according to SAAQIS report with more stations added in 2019 and 2020.[8] Thus, the AQHI in this study uses PM_{10} data from 2006 – 2015. However, the derivation of a $PM_{2.5}$ based AQHI is identical.

Scaling the pollutant excess risk in context of the WHO AQG values

In line with concepts of previous AQI or AQHI, our linear scale ranges from 1 to 10+. For each pollutant, the percent increase per unit of the index was chosen in such a way that the index value of 3 corresponds to the ER at the WHO long-term reference values as derived above. The ER per 1 unit index as shown in Table S 1 of the main manuscript, were rounded to two decimal places and used to produce categories for 10 index values. The daily ER% of each index value, thus, corresponds for each pollutant to the ranges as presented in Table 2 of the main manuscript, for example, a PM_{10} index value of 1 corresponds to up to 0.21% excess mortality risk whereas larger ER% up to 0.42% are contained in level 2 and so on.

Calculate overall AQHI

The previous step derived a daily index value for each pollutant. For communication purposes, it would be informative to provide one single index value that summarizes the impact across pollutants. The sum of the four estimates is not a valid summary measure of the impact as it would assume fully independent excess risks attributable to each pollutant. Although this may be defendable for O_3 and PM, there is agreement that single-pollutant CRFs capture partly correlated, thus, overlapping effects of e.g., PM and NO_2 or SO_2.[9] However, at this stage this overlap is not well defined given the paucity of estimates of multipollutant CRFs.

Instead, we propose the derivation of an "average index value" to reflect the expected daily mean health impact of the pollutants used in the index. However, the arithmetic mean of the single values has problematic features. As shown in Table 1, although the WHO AQG values are derived to protect health, the mortality ER% at the long-term AQG value grossly varies across the pollutants. Moreover, as shown in the case study later on, the ability to comply with the AQG values differs substantially across the pollutants used in the index. E.g., the new $PM_{2.5}$ AQG are extremely ambitious for most regions in the world, compliance with the SO_2 AQG may already be achieved in many places. Thus, the arithmetic means of the four AQI values and the average excess risk – would be unequally influenced by this inherent discrepancy. Therefore, we propose a weighted average index value to harmonize the discrepant ER% at the WHO AQG levels. Methodological details are shown in the main text

Translate AQHI into "traffic-light" colour scheme

In the last step, the AQHI is constructed by using the scaled index and translating it into "traffic-light" colour scheme. The levels of risk in the index ranges from 1 to 10+. We define "low risk" or "green" as 1 – 3, "moderate risk" or "yellow" as 4 – 6, and "high risk" or "red" as 7 – 10+. Authorities might communicate the colours for each single pollutant AQHI or the derived weighted average or both. This is a simple communication tool to enable the public understand the continuum between healthy and unhealthy air quality.

The AQHI is also accompanied with health messages for the general population and population at risk, which is presented in Table 1 of the main manuscript. By design, if all four pollutants complied with the WHO AQG reference value shown in Table 1, the overall AQHI for such day will be "green".

The health messages corresponding to the risk levels were adapted from the Canadian AQHI[10]*;* the Canadian authors were methodical in the process of developing the communication material which involved multiple stakeholders and audiences. The materials were tested and evaluated through qualitative interviews to assess knowledge, attitudes and behaviors related to air pollution and particularly to the air quality index. Therefore, we consider these messages to be well suited for our constructed AQHI. However, we did not consider the index value 10+ as separate category and therefore did not distinguish between "very high" and "high" risk.

Sensitivity analysis

As mentioned, we propose to build the AQHI either with PM_{10} or $PM_{2.5}$. The question arises whether these two options would lead to the same result. To assess the sensitivity of the index for choosing between the two options, we used 2019 data from Table view monitoring station as we had both PM_{10} and $PM_{2.5}$ data for this year. In total, 83.5%, 90%, 97% and 97% of daily values of SO_2, NO_2, PM_{10} and $PM_{2.5}$, respectively, were available for 2019. In addition, we used the O_3 data from Atlantis where 71.5% of the data were available. This is an urban background station and thus provides an adequate estimation for the general O_3 conditions. For the days with missing concentrations for these pollutants, their values were also missing at other stations, thus we could not perform the simple imputation as proposed in this supplementary material. In total, data for at least two gases and both PM_{10} and $PM_{2.5}$ were available for 330 days in 2019. The total ER% was calculated for those days, separately for PM_{10} and $PM_{2.5}$. First, we assigned the index values to each day of these two-time series and the gases based on the daily ER%. Thereafter, the weighted average AQHI was derived for the PM_{10} and the $PM_{2.5}$ based AQHI as shown in Table S1. The linear association between the PM_{10}- and $PM_{2.5}$ based weighted average AQHI was assessed in addition with the Spearman correlation coefficient.

Results

Table S 1: Derivation of the weighted average AQHI indices: *the single pollutant concentration-response functions (CRF), the related beta coefficient, the chosen WHO AQG reference value, the related daily excess risk (ER) (Equation S 2). In addition, the daily ER%s of the pollutants ER% per index unit are shown. Thus, by design, the single pollutant index value of 3 corresponds to PM_{10}, NO_2, SO_2 and O_3 concentrations of 15 µg/m³, 10 µg/m³, 20 µg/m³, and 60 µg/m³, respectively. The weights for the average index value are shown for both, the $PM_{2.5}$ and the PM_{10} based AQHI.*

Pollutant p	CRF published in WHO AQG (per 10 µg/m³)	Beta coefficient per 1 µg/m³	WHO AQG reference value [a] in µg/m³ for index value = 3	ER (%) at index value = 3	Average ER (%) per index unit	Inverse weight for $PM_{2.5}$ Based AQHI	Inverse weight for PM_{10} Based AQHI
$PM_{2.5}$	1.0065	0.00065	5	0.326	0.109	1	-
PM_{10}	1.0041	0.00041	15	0.617	0.206	-	1
NO_2	1.0072	0.00072	10	0.723	0.241	0.451	0.853
SO_2	1.0059	0.00059	20[b]	1.187	0.396	0.275	0.519
O_3	1.0043	0.00043	60	2.614	0.871	0.125	0.236

The CRFs published in the reviews commissioned by WHO[1,2] estimated risks using the 2-day mean of the pollutant measurements. We found a strong positive correlation ($r > 0.87$) between the daily measurements and the 2-day means of each pollutant. Thus, we propose to derive the AQHI based on daily mean data. This is easier to implement and less affected by missing data than the reliance on measurement series of 2-day means.

Table S 2: The constructed AQHI for PM2.5 showing the range of excess mortality risk and risk levels.

AQHI	1	2	3	4	5	6	7	8	9	10
ER% range	<0.11	>0.11-0.22	>0.22-0.33	>0.33-0.44	>0.44-0.55	>0.55-0.66	>0.66-0.77	>0.77-0.88	>0.88-0.99	>0.99-1.10+
Risk level	Low risk AQHI 1 – 3			Moderate risk AQHI 4 – 6			High risk AQHI 7 – 10+			

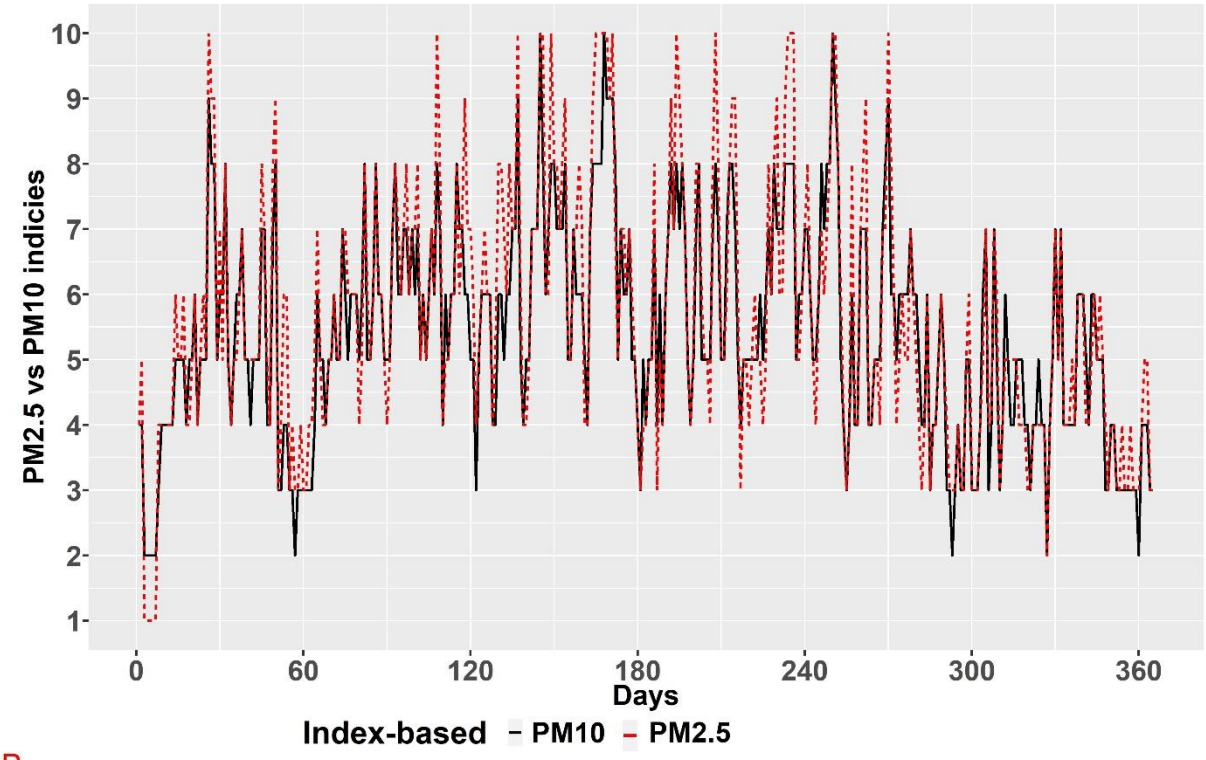
[a] The ambient concentration for each pollutant is the WHO long-term AQG values.
[a] WHO 2021 AQG did not include a long-term value for SO2, thus we used the value from the 2000 WHO AQG. The rationale for this is provided in the "derivation of excess risk" section of the method

Figure S 2: Daily mean concentrations of PM10, NO2, SO2 and O3 in Cape Town, 2006 – 2015. The horizontal lines show the WHO AQG 2021 values for short-term (black) and long-term (orange) of each pollutant.

Sensitivity analysis (PM_{10} versus $PM_{2.5}$ based index)

The means of the weighted average AQHI for $PM_{2.5}$ and PM_{10} using data from 2019 (365 days) were similar, 5.6 and 5.4, respectively. There was no statistically significant difference between the daily weighted average indices using the Welch t-test, (t = 1.61, 95% CI: -0.05; 0.48). There was a strong and positive correlation (r = 0.92, p-value <0.001) between the two weighted average indices. The linear association had an intercept of 1.01 (95% CI: 0.9-1.1) and slope=0.8 as shown in the supplementary material. The two indices differed in the higher AQHI, at index 10 where the $PM_{2.5}$-based index classified more days as high compared to the PM_{10}-based index (20 vs 3). The Plots in panel A of Figure S 3 presents the daily weighted average of $PM_{2.5}$- and PM_{10}-based AQHIs; while the table in panel B shows the daily distribution of each index level for $PM_{2.5}$ and PM_{10} based indices, where 39 and 47 days were "low risk", respectively. The two also had a similar number of days with "moderate risk" 215 and 220, respectively, while the difference was largest in the "high risk" category, with 111 days for the $PM_{2.5}$ based and only 98 days for the PM_{10} – based index; $PM_{2.5}$-based index classified more days as high (index 9 and 10) compared to PM_{10}-index.

A



B

AQHI	1	2	3	4	5	6	7	8	9	10
PM10	0	9	38	62	90	68	53	35	7	3
PM2.5	5	1	33	76	80	59	45	32	14	20

Figure S 3: Daily plot of PM10-based and PM2.5-based AQHI with the three gaseous pollutants (NO2, SO2 and O3) in 2019. Panel B shows the number of days each level of the PM10- and the PM2.5-based AQHI occurred.

This shows that one can derive an average AQHI based on either PM_{10} or $PM_{2.5}$, whatever may be available in the monitoring networks. The question arises which one to use in case both are available. In light of the dominance of $PM_{2.5}$ in the scientific literature and its particular dependence on anthropogenic sources of air pollution, $PM_{2.5}$ might be the preferred choice. As shown for Cape Town, the two options lead, on average, to rather similar judgments of air quality.

The observed departure from the line of identity tended towards higher index values (9 and 10+) for PM2.5 in the 14-49 µg/m3 range of pollution. The wide range is because concentrations with ER% above 1.1% for $PM_{2.5}$ are classified as 10+. However, such distributional properties may be different in other regions and possibly depend on seasonal factors as well.

Table S 3: Distribution of daily mean (standard deviation) concentration of pollutants and number of days per average single-AQHI value in Cape Town for the period from 2006 to 2015 (in total, 3652 days)

Single- AQHI	PM_{10}	Days	NO_2	Days	SO_2	Days	O_3	Days
1[c]	-	-	3.03(0.2)	26(0.71%)	5.34(1.10)	841(23.03%)	14.39(4.51)	374(10.24%)
2	9.06(1.06)	19(0.52%)	5.29(0.97)	255(6.98%)	9.58(1.88)	1948(53.34%)	30.68(5.24)	1612(44.14%)
3	13.47(1.39)	258(7.06%)	8.46(0.95)	460(12.6%)	16.10(1.91)	602(16.48%)	47.12(5.25)	627(17.17%)
4	18.07(1.45)	630(17.25%)	11.65(0.94)	613(16.79%)	23.36(2.01)	128(3.50%)	65.29(4.58)	54(1.48%)
5	23.02(1.46)	672(18.4%)	14.84(0.94)	596(16.32%)	29.22(1.80)	31(0.85%)	83.57(3.71)	5(0.14%)
6	27.98(1.48)	626(17.14%)	18.18(0.96)	370(10.13%)	35.68(1.32)	10(0.27%)	-	-
7	32.95(1.43)	433(11.86%)	21.39(0.95)	325(8.9%)	42.71(1.88)	10(0.27%)	-	-
8	37.95(1.49)	327(8.95%)	24.68(0.96)	219(6%)	48.30(0.70)	3(0.08%)	-	-
9	42.97(1.44)	203(5.56%)	27.97(0.98)	140(3.83%)	-	-	-	-
10	57.13(10.81)	475(13.01%)	36.79(6.64)	280(7.67%)	-	-	-	-
Missing	-	9(0.25%)	-	368(10.08%)	-	79(2.16%)	-	980(26.83%)

[c] Empty cells show there are no ER% calculated for those days, either because the data was missing or the pollutant concentrations did not fall with the ER% range for the AQHI

Table S 4 demonstrates the derivation of the average index using an example of a typical day as observed in the Cape Town case study. The index value shown for each pollutant approximates the average index observed during the year 2015. As shown, the arithmetic mean AQHI for such a day would be 3, thus, lower than the weighted average of 4. The arithmetic mean AQHI is biased toward low values, given the mostly low index values for SO_2 and O_3, masking the impact of PM_{10} and NO_2.

Table S 4: derivation of weighted average PM10-based AQHI for a typical day in Cape Town in comparison to the arithmetic average

Pollutant		PM_{10}	NO_2	SO_2	O_3	AQHI
Single AQHI		5	4	2	2	
Arithmetic mean AQHI	$(5+4+2+2)/4 = 3.25 \sim 3$					3
Weighted Average AQHI	$((1*5)+(0.85*4)+(0.52*2)+(0.24*2))/2.61 = 3.8 \sim 4$					4

Missing data and AQHI

The current practice in South Africa is to derive and report the AQI for each station using measurements of available pollutants, thus the proposed new index can be derived in a similar fashion. However, authorities will face the challenge of missing pollutant data on certain days. In case of the weighted average, summary measures may be derived across the non-missing pollutants only, which in turn may lead to biased averages given the distributional properties discussed above. Alternatively, we have proposed a simple imputation of missing data using measurements from other stations as this would minimize biased weighted averages. The approach uses the monthly mean of the missing station for imputation, as well as measurement data for the same pollutant at other sites.

For the sites with measurements on day t, the ratio between the respective daily mean and the last calendar monthly mean of day t is computed; ratios from these sites are then averaged. Finally, the missing daily mean is calculated by multiplying the monthly mean of the station with the missing value by the computed average ratio as shown in Equation S 2.

	$$X_t = V_t * \frac{1}{n} \sum_{i=1,\ldots,n} \frac{D_{i,t}}{M_{i,t}}$$	*Equation S 2*

$where\ t = day\ of\ missing\ value\ of\ the\ respective\ pollutant\ at\ the\ given\ station,$
$X_t = imputed\ \ mean\ of\ pollutant\ at\ the\ given\ station\ on\ day\ t,$
$V_t = mean\ of\ pollutant\ at\ the\ given\ station\ in\ the\ month\ of\ day\ t,$
$D_{i,t} = mean\ of\ pollutant\ at\ station\ i\ on\ day\ t,$
$M_{i,t} = \ mean\ of\ pollutant\ at\ station\ i\ in\ the\ month\ of\ day\ t,$
$n = number\ of\ stations\ with\ measurements\ of\ the\ pollutant\ on\ day\ t$

The linear regression between PM_{10}- and $PM_{2.5}$ based indices in Cape Town for 365 days had a slope of 0.78, intercept of 1.01 (95% CI: 0.9 – 1.1) and an adjusted R^2 of 0.85.

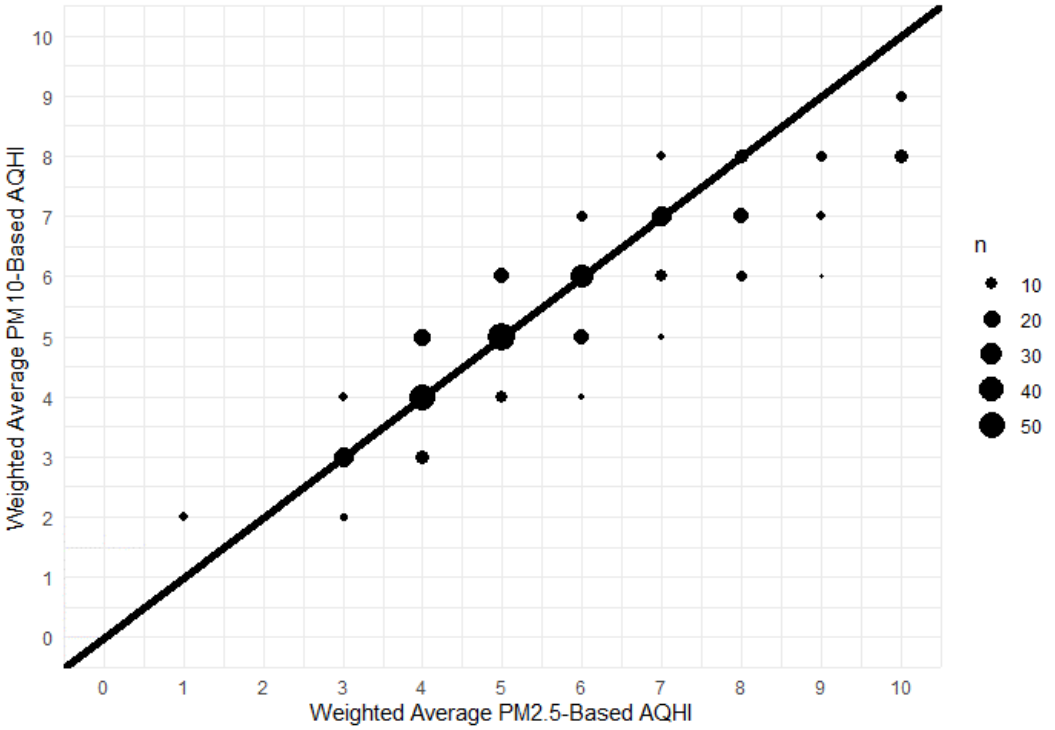


Figure S 4: Linear regression between PM_{10}- and $PM_{2.5}$ based indices in Cape Town, South Africa, 2019. Plot shows the number of days, adjusted R^2, intercept and its 95% confidence interval and the slope with the size of points representing the number of respective days, as well as the identity line.

Table S 5: The 2021 WHO Air Quality Guideline values and South Africa's National Ambient Air Quality Standard (NAAQS)

Guidelines	Averaging time	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3 (8-hour)
WHO	Short-term[a]	15	45	25	40	100
South Africa	Short-term	40	75	200 (1 hr)	125	120
WHO	Annual	5	15	10	-	60 [b]
South Africa	Annual	20	40	40	-	-

[a] Short-term is 24-hours for all pollutants (i.e. 3-4 exceedance days per year) and

[b] Average of daily maximum 8-hour O_3 concentrations in the six consecutive months with the highest six-month running-average O_3 concentration.

The figure below shows the current Air Quality Index in South Africa. The concentrations for each band and their corresponding descriptions such as "good" air quality and "moderate" air quality.

Proposes AQI for South Africa based on NO2, SO, O3, PM10, PM2.5 and CO														
			NO2	NO2 (SA)	SO2(SA)	SO2 (SA)	Ozone (SA)		PM10 (SA)	PM10 (SA)	PM2.5 (SA)	PM2.5 (SA)	CO (SA)	
Colour Bands		NAAQS	200 (Hourly)						ug/m3	ug/m3	ug/m3	ug/m3		
		Bands	ppb	ppb	ppb	ppb	ppb	ppb	188(1hr)	188(1hr)	100 (1hr)	100 (1hr)	ppb	ppb
Air Quality Statu	Summary Message		NO2 Bands	NO2	SO2 Bands	SO2	Ozone Bands	Ozone	PM10 Bands	PM10	PM2.5 Bands	PM2.5	CO	CO Bands
		1	0-66	0	0-115	0	0-26	0	0-65	0	0-33	0	0	0-10000
Low	Good	2	67-133	67	116-231	116	27-53	27	66-128	65	34-68	33	10000	10001-20000
		3	133-200	133	232-350	232	54-80	54	129-190	128	69-103	68	20000	20001-30000
Moderate	Moderate	4	201-267	201	351-400	351	81-107	81	191-215	190	104-128	103	30000	30001-35000
		5	268-334	268	401-450	401	108-134	108	216-240	215	129-153	128	35000	35001-40000
High	Unhealthy	6	335-400	335	451-500	451	135-160	135	241-265	240	154-178	153	40000	40001-45000
		7	401-467	401	501-550	501	161-187	161	266-290	265	179-203	178	45000	45001-50000
Very High	Very Unhealthy	8	468-534	468	551-600	551	188-213	188	291-315	290	204-228	203	50000	50001-55000
		9	535-601	535	601-650	601	214-240	214	316-340	315	229-253	228	55000	55001-60000
Hazardous	Hazardous	10	>602	602	>651	651	>241	241	>341	340	>254	253	60000	>60000

Figure S 5: South Africa AQI bands presented in 2018[11]

Parts per billion conversions to µg/m^3 for NO_2, SO_2 and O_3 using concentrations within the "Good" band of SA's AQI:

NO_2 1 ppb = 1.88 µg m^{-3}; SO_2 1 ppb = 2.62 µg m^{-3}; O_3 1 ppb = 1.96 µg m^{-3}

The figure below shows the air pollution index (API) developed by Cairncross[12], the excess risk range for each AQI level and the corresponding risk levels.

Table 8
Proposed breakpoints for health-risk warnings

Total	1–	1.015–	1.031–	1.046–	1.061–	1.077–	1.092–	1.107–	1.123–	1.138–	>
Mortality RR	1.014	1.030	1.045	1.060	1.076	1.091	1.106	1.122	1.137	1.153	1.153
API value	0	1	2	3	4	5	6	7	8	9	10
Colour code											
RGB values	0 255 0	154 205 50	255 255 0	255 215 0	255 165 0	255 99 71	255 0 0	139 35 35	205 96 144	139 28 98	139 0 139

LOW (1–3): low risk of increased mortality: 1.5–6.0%.
MODERATE (4–6): moderate risk of increased mortality: 6.1–10.6%.
HIGH (7–9): high risk of increased mortality: 10.7–15.3%.
VERY HIGH (10): very high risk of increased mortality: more than 15.3%.

Figure S 6: API constructed by Cairncross 2007[12]

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CHAPTER 5:

General discussion

This first objective of this thesis was to examine the association between short-term effects of multiple air pollutants and hospital admissions and mortality due to cardiorespiratory disease from 2006 to 2015 in Cape Town, South Africa. The exposure-response relationship from these analyses provided in-depth knowledge of the short-term effect of air pollution on cardiorespiratory outcomes in addition to effect modification by sex, age groups and season. The second objective, was to develop a novel Air Quality Health Index (AQHI) aligned with the WHO 2021 long-term Air Quality Guideline values – and then use Cape Town as a case study.

These short-term effect studies have presented in Chapters 2 and 3, while Chapter 4 shows the construction of the global AQHI and its application. This section provides a general discussion of the findings presented in this thesis, followed by personal reflections on their overall public health relevance, policy implications and recommendations for future studies. This research contributes to the growing body of evidence on the relationship between air pollution and health in South Africa (SA).

5.1 What influence does air pollution have on cardio-respiratory health in Cape Town?

In Chapter 2 of this thesis, the overall short-term effect estimates showed a positive association between PM_{10} and NO_2 for respiratory disease (RD) and an independent effect for the same pollutants after adjustment for SO_2. There was no statistically significant evidence of effect modification, although these associations were stronger in children (age 0-14 years) for PM_{10} and NO_2; and in males for PM_{10} exposure only. We further observed robust associations between PM_{10} and cardiovascular diseases in single- and multi-pollutant models. An important key finding of this study was that the overall effect of PM_{10} exposure on RD was driven by the effects observed in children as reflected by the lag-response model. Studies have shown that infants' susceptibility to respiratory infections may be increased by exposure to air pollution during prenatal period. Results from a prospective cohort study of 214 children showed that maternal exposure to elevated levels of outdoor $PM_{2.5}$ (24hr average > 35 $\mu g/m^3$) during pregnancy was associated with a 120g reduction in infant birth weight.(164) In addition, infants born to mothers who were exposed to a daily mean of $PM_{2.5}$ greater than 45.9 35 $\mu g/m^3$ were

found to have a higher incidence of recurrent bronchitis and pneumonia during a 7-year follow-up period compared with those born to mothers in the lower tertiles.(164) This suggests that prenatal exposure to air pollution may lead to a disadvantaged start in life for children, as harmful pollutants passed from mothers to fetuses during pregnancy may have lasting effects on respiratory health. In addition to outdoor sources, particulate matter (PM) is also generated indoors by the use of solid fuels for heating, lighting, and cooking. This can increase the risk of respiratory illnesses for children who spend time indoors with their mothers. According to the WHO, air pollution contributes to an estimated 900,000 deaths of children under five year, primarily due to pneumonia.(165)

This study highlights the harmful effects of air pollution particularly PM_{10} and NO_2 on children and emphasizes the urgent need to adopt of clean air policies.

Chapter 3 showed the overall effect on CVD for PM_{10}, NO_2, SO_2 and O_3; these effects differed by sex and age group. Females and the elderly showed a higher risk for PM_{10} and NO_2, while males had a higher risk for SO_2 and O_3. There was robust evidence for an independent short-term effect of O_3 on RD and NO_2 on CVD. Exposure to O_3 showed evidence of effect modification for sex; where we observed a higher risk in males compared to females, which could have been due to chance as sex-specific findings are inconsistent in the existing literature. The effect estimates for O_3 in this study were higher than in previous studies, even though the levels were below the short- and long-term WHO 2021 AQG values.

A particularly interesting finding was the evidence of harvesting amongst the elderly for PM_{10} exposure; air pollution, especially PM_{10} appeared to advance the death in the frail population. In both chapters, the effect estimates were higher when compared to other studies, and the underlying factors characterizing these differences were discussed. The impact of air pollution on health in Cape Town is well established and remains consistent using data spanning 15 years (2001 – 2015).(13) PM_{10}, NO_2 and O_3 appear to be the main pollutants associated with ill health. Therefore, an air pollution control strategy with a particular focus on reducing PM_{10} and NO_2 levels could result in improved air quality with the co-benefit of reducing other pollutants e.g., O_3.

5.2 Another index? Yes, a Global Air Quality Health Index

The work in chapter 4 developed a global health-based air quality index using concentration-response functions from the largest systematic review and meta-analysis to date on short-term

effect of air pollution and all-cause mortality. This index was constructed for the two mass fractions of particulate matter, PM_{10} and $PM_{2.5}$, and applied to local data in Cape Town, South Africa.

Our results showed that the weighted average for the PM10-based AQHI was above 3 ("low risk" for 87% of the study period, so only 13% of the days would have been classified as having good air quality. The current AQI in South Africa uses a wide range of pollutant concentrations to classify the "good" air quality level. *Table 2* shows the ER%, single pollutant AQHI, and weighted average AQHI for the concentrations at SA's Level 3 AQI and long-term NAAQS are derived using our constructed AQHI method. The lowest ER% is 7% for $PM_{2.5}$ with a single pollutant AQHI of 10+. This is high and should not be classified as "good air quality". Excess risk here refers to the percentage risk of non-accidental deaths above that observed on "typical" pollution days. This suggests that high air pollution levels on days, authorities may need more hospital staff, beds, mortuary cold rooms and even burial sites to accommodate the excess deaths. For both PM-based indices, these values are 10, which means to "high risk".

There are two issues with the current AQI "good air quality" pollution concentration ranges: firstly, there is no epidemiological evidence to support it, and secondly, these values are at least two-folds higher than the short-term NAAQS to which they are being compared. The short-term NAAQS are the tolerable levels of daily air pollution, so the range of pollution concentration that constitutes 'good air quality' should not exceed these levels. Therefore, the current AQI should be replaced by an index based on epidemiological evidence and benchmarked against the WHO 2021 AQG long-term values.

Furthermore, seasonally, our result for 2006-2015 shows that air quality was worse in the colder months with more days at "moderate level" risk compared to the warmer months. In the context of SA, it has been reported that air pollution levels are higher in the colder months compared to the warmer months, although the effects are worse in the warmer months. This can be partly explained by the increased use of solid fuels to heat homes, the winter inversion which traps air closer to the ground, and less favourable meteorological conditions such as wind speed and direction that result in less dispersion of air pollution.

Table 2: Derivation of single pollutant AQHI and weighted average $PM_{2.5}$*-based AQHI for SA current level 3 AQI and long-term concentrations.*

Concentrations	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3
SA AQI Level 3 (µg/m^3)	0-103	0-190	0-376	0-916.7	0-157
ER (%)	6.9	8.1	31.1	73.3	7
Single-AQHI ER%	0.11 – 1.1%	0.21 – 2.1%	0.24 – 2.4%	0.39 – 3.9%	0.87 – 8.7%
Single-AQHI	10+	10+	10+	10+	9
Weighted average PM2.5-AQHI	$(4 * 1 * 10) + (4 * 0.45 * 10) + (4 * 0.27 * 10) + (4 * 0.12 * 9)/7.36 = 9.9 \sim 10$				
Long-term NAAQS[4]	20	40	40	-	-
ER (%)	1.31	1.65	2.92	-	-
Single AQHI	10+	7	8	-	-

As presented in Chapter 2 and 3, PM_{10} and NO_2 are the main drivers for the AQHI increased risk levels while the WHO AQG values were not exceeded for SO_2 and O_3.

A study complied an inventory of countries that adopted the WHO 2005 AQG values or had an air quality standard – of the 170 WHO member states with information, 60% had standard for at least one pollutant while 24% were without standards.(166) It was also reported that NO_2 was the most regulated pollutant but particulate matter and SO_2 were not in compliance with the WHO 2005 AQG. Therefore, countries with fewer pollutant standards can use our proposed single pollutant AQHI in the interim while they update their air quality management plans and monitor more pollutants.

5.3 How is this relevant for public health?

The evidence on acute effects presented in this thesis shows that people are at a greater risk from exposure to air pollution, especially children, females and the elderly. Therefore, an index that informs the public about air quality levels and their risks in real-time could be helpful for the general and vulnerable population. Depending on the message, they may be able to reduce their exposure to air pollution, which in turn could reduce their risk of adverse health effects.

The AQHI has been constructed using a standardized health-based scaling system – the WHO 2021 AQG. This means that, from a global perspective, the index means the same everywhere

[4] There are no long-term NAAQS for SO2 and Ozone.

in the world and can therefore be an excellent tool for promoting cooperation and collaboration between countries and regions to tackle transboundary air pollution. The index can benefit the economy by reducing the costs associated with air pollution-related illnesses, such as lost productivity and medical costs. It can be used by the Department of Forestry, Fisheries and the Environment (DEFF) for preemptive measures and urgent actions such as early warning and emergency response in the event of wildfires and sudden increases in air pollution levels. Cape Town is prone to wildfires and Johannesburg has experienced episodes of hydrogen sulphide (H2S) in the air, known as "smelly air pollution", with levels reaching 100 $\mu g/m^3$ above the threshold. This pollution comes from the oil company Sasol, and is routine and fully authorized.(167) It can also identify areas of consistently high risk of poor air quality and support the pursuit of environmental justice to reduce the environmental inequalities and promote health equity. Finally, the index has the potential to promote a culture of air quality awareness among citizens and empower them to advocate for the implementation, re-evaluation and strengthening of policies to achieve clean air and protect public health.

5.4 What are the policy implications?

The findings from this thesis have implications for public health strategies and policy revision to prevent risk of morbidity and mortality due to cardiorespiratory diseases in people.

The current NAAQS are less stringent. They do not protect the health of the people of Cape Town and South Africa. Therefore, the NAAQS should first be revised given the consistent epidemiological evidence of risks occurring at levels below the current NAAQS. South Africa announced that the current NAAQS would not be amended in line with the WHO 2021 AQG. By January 2030, the only values set to change are the short- and long-term values for $PM_{2.5}$ – from 40 $\mu g/m^3$ to 25 $\mu g/m^3$ and 20 $\mu g/m^3$ to 15 $\mu g/m^3$, respectively. The reason provided was that South Africa has many strong and varying natural sources of pollution such as dust, biomass burning, biogenic and marine sources.(168) On the one hand, I can appreciate that the WHO 2021 AQGs are ambitious, especially for $PM_{2.5}$. On the other hand, I find it rather disingenuous to use natural sources of air pollution as an excuse for not implementing stricter NAAQS when the most dominant source are anthropogenic. An inventory emissions study reported that in SA, the total black carbon emission were predominately from waste burning which contributed 42% (18% residentially and 24% in dump locations), followed by residential (42%), industry (24%), energy (13%) and traffic (9%).(169) In addition, SA is the highest

contributor of SO_2 emissions in Africa by approximately 62% due to its coal-fired power plants while locally it constitutes 95% of the country's emission (51% from power plants, 31% from industry, 4% from residential sector and the remainder from other sectors).(169)

South Africa has an ambitious long-term goal to decarbonise its energy sector and reach net-zero emissions by 2050, with an initial investment plan for the five-year period 2023 – 2027, for which it has received a loan of US$8.5 billion from the International Partners Group.(170) Therefore, such ambitious goal requires more than a 'business as usual' approach.

In the short-term, the country needs to implement its existing policies that can make a tangible difference. For several years, certain industries in South Africa have been delaying the implementation of minimum emission standards and the DFFE has been lenient with them.(46) The NAAQS will not be attained if industry is continually in breach of its agreement. This means that the status quo of the current air pollution levels could be maintained or worsened, resulting in increased health risk to the public. Authorities must also effectively reduce pollution from other sources such as domestic burning, vehicle emission, industry emissions, and unauthorized waste burning. There must also be an equitable distribution of resources and infrastructure to reduce the dependence on dirty fuels and introduce clean energy.

In addition, as discussed above, the ER% for the "good" air quality band of the current AQI is unacceptably high and calls for the adoption of our proposed AQHI. This will allow for transparent and honest communication of the country's air quality.

Public awareness, education, and training, especially for mothers and the elderly on the health effects of indoor and outdoor air pollution needs to be increased. Public participation is an important measure that needs to be taken to increase the chances of achieving improved air quality targets. It should be noted that it is the government's responsibility to ensure people's right to clean air that does not harm their health. However, the public's interest in air pollution can be enhanced through appropriate education.

5.5 Further research

Although investigating the knowledge and attitudes towards air pollution in Cape Town was not a primary objective of this thesis, a mixed-method study that collects data through questionnaires and interviews could yield valuable insights for the scientific community and policy makers. The study could address important questions such as the level of public awareness regarding air pollution, whether people consider it to be a significant problem, and

the extent to which individuals have been affected by air pollution. Additionally, the study could assess whether people are aware of the existing air quality index and whether they use it regularly. Further questions could explore whether individuals modify their behavior based on information from the index, whether they are satisfied with the index, and what actions they take in response to health messages. It would also be relevant to investigate whether individuals have consulted with their doctor to discuss the potential impact of air pollution on their health.

It would also be useful to examine the short- and long-term association between the criteria pollutants and health outcomes at the national level. Where air pollution data are not available, an ensemble averaging approach can be used to model the spatio-temporal concentration of pollutants using remote sensed data for sparsely monitored parts of the country, as demonstrated in four South African provinces.(171) In addition, government involvement and funding will be crucial for such research, particularly for the long-term effects study, as this will require the establishment of a cohort.

In addition, source apportionment studies to identify the sources and components of the criteria pollutants can be informative for health risk assessment. Such studies are currently scarce and require further research.

5.6 Conclusion and Outlook

Some issues: Data quality and access

We were confronted with two main challenges while conducting this research, one of which was access to data. Accessing data was a bureaucratic process that involved obtaining permission to use the air pollution and mortality data, even though ethical clearance had been acquired, still, the data were sent in parts and it took over a year to collect the full set of data needed for chapters 2 and 3.

The other challenge was the varying quality of the data, which required multiple imputations using different technique. The gaps in exposure data did not substantially bias our estimates for a few reasons. Firstly, the pattern of missingness in the air pollution series occurred over a period of consecutive days rather than on isolated days, which shows the missingness were systematic and not random. Secondly, missing data on isolated days were imputed by using available same day data from other stations for the same pollutants. A few reasons for the systematic missing data include malfunctioning monitoring equipment or decommissioned equipment, data logging errors, interrupted power supply, and problems with the server. Thirdly, this missing data were independent from other predictors (temperature and relative

humidity) and the outcome variables. Finally, provided there were collinearity between the missing air pollution data and time, the smoothing function of time in the time-series models would have properly accounted for it.

Our experience with accessing quality data highlighted the importance of having reliable and sufficient data for epidemiological studies. On one hand, the disease burden of air pollution could be underestimated due to poor air quality data and lack of such studies, while on the other hand –not having data for monitoring and evaluation could hinder the progress towards achieving the sustainable development goals.

In conclusion, this thesis achieved it objectives and demonstrated that air pollution at levels lower than the NAAQS and the WHO 2021 AQG poses significant health risks to the people of Cape Town. It also provided a revised and globally applicable health-based air quality index that should be adopted by the DFFE for South Africa, as the current AQI is inadequate for air quality communication.

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