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Apparent Temperature Modifies the Effects of Air Pollution on Cardiovascular Disease Mortality in Cape Town, South Africa

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Abstract: Cardiovascular disease (CVD) is the top cause of mortality and a main contributor to disability globally. The evidence so far is varied on whether cold or heat modifies the CVD effects of air pollution. Weather conditions and air pollution sources and levels are different in different countries. Studies in low-and middle-income countries are lacking. Mortality data were obtained from Statistics South Africa. Air pollution and meteorological data were obtained from the South African Weather Service. A time-stratified case–crossover epidemiological design was applied. The association between air pollutants (PM_{10}, NO_2 and SO_2) and CVD mortality was investigated using conditional logistic regression models. Susceptibility by sex and age groups was investigated. In total, 54,356 CVD deaths were included in the 10-year study. The daily PM_{10}, NO_2 and SO_2 levels exceeded the daily WHO guidelines on 463, 421 and 8 days of the 3652 days, respectively. Higher air pollution risks were observed in this study compared to those reported in meta-analyses. In general, the elderly and females seemed to be vulnerable to air pollutants, especially at high and moderate apparent temperature levels. Harvesting effects were observed at longer lags. The results can be used to develop an early warning system for the city.

Keywords: climate change; air pollution; cardiovascular disease; mortality; South Africa; epidemiology

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1. Introduction

Cardiovascular disease (CVD) is the top cause of mortality and a main contributor to disability globally [1]. During the past 30 years, CVD mortality declined in high-income countries; however, there is evidence that the reduction is stalling [2]. In contrast, CVD mortality has increased in low- and middle-income countries (LMIC) over the same period [1]. In South Africa, almost one in five natural deaths were due to CVD from 2016 to 2018 [3]. However, knowledge on the incidence and prevalence of CVD morbidity in South Africa is poor [4], and thus mortality is the tip of the proverbial iceberg. In addition, people in Africa have a poor understanding of CVD, its risk factors and clinical symptoms, which contributes to CVD mortality [5–7].

Evidence is increasing on the short- and long-term CVD effects of outdoor air pollution, one of the many risk factors of CVD [1,8–11]. There are thousands of chemicals that people can be exposed to via inhalation, however, the vast majority of epidemiological studies investigated particulate matter with an aerodynamic diameter less than or equal to 2.5 µm ($PM_{2.5}$), PM_{10}, ground-level ozone (O_3), nitrogen oxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO) and lead [11].

Government air pollution monitoring [12–14] as well as exposure assessment and epidemiological studies are lacking in Africa [14–16], and the true burden of air pollution on human health in Africa is up for debate. A recent meta-analysis summarised the evidence from epidemiological studies that investigated the effects of air pollution on all-cause and cause-specific mortality, such as CVD, during 1992 to 2019 [10]. Only 44 studies were

included in the meta-analysis that investigated the association between CVD mortality and PM_{10}. Studies are lacking for the other common air pollutants and also in LMIC [10]. Few studies investigated susceptibility by sex and age or two-pollutant models [10]. The meta-analysis included only one study from Africa. The latest WHO guideline report also highlighted that more research is needed on the human health effects of NO_2 and SO_2 [11].

Human activities that lead to air pollution emissions also contribute to climate change. Climate change will alter weather conditions such as temperature, humidity, wind speed, atmospheric direction and mixing height [17]. These weather conditions in turn may modify the human health effects of air pollution by altering levels, transboundary movement and chemical transformation and composition [18].

Global rising ambient temperature, one of the key climatic change indicators, is a cause for concern [19,20]. Ambient temperature has direct and indirect effects on CVD [21,22]. Epidemiological studies in Africa and other LMICs on the human health effects of heat and cold are lacking [23–25]. A review highlighted that LMIC populations are more susceptible to health effects of heat and cold [25]. Possible reasons for this include inadequate healthcare services, infrastructure and technology and poverty [25]. It is projected that by 2080, temperature increases greater than 4 °C will be observed across South Africa [26].

The majority of epidemiological studies that investigated air pollution as a risk factor for human health adjusted for ambient temperature as a confounder in regression models. However, fewer studied how the effects of air pollution on human health are modified by temperature [27,28]. Studies report inconsistent results, and there is a paucity of studies in Africa and other LMICs [29,30].

The aim of this study was to investigate CVD mortality during a 10-year study period (2006–2015) in Cape Town, one of the largest cities in South Africa, in order to address the gaps in knowledge regarding the human health effects due to the interaction between ambient air pollution and temperature exposure. We also investigated susceptibility by sex and age.

2. Materials and Methods

2.1. Study Area

Cape Town is the second-most populous city in South Africa and had 3.7 million residents during the last census in 2011, of whom nearly 70% were in the working age group (15–64 years) [31]. Cape Town has a Mediterranean climate and is located in a Csb Köppen–Geiger climatic zone [32]. The city's climate is influenced by both the warm Agulhas current and the cold Benguela current [31]. The city is situated 10–150 m above sea level and has many peaks that are higher than 300 m, such as Table Mountain (1000–1100 m above sea level) (Figure 1).

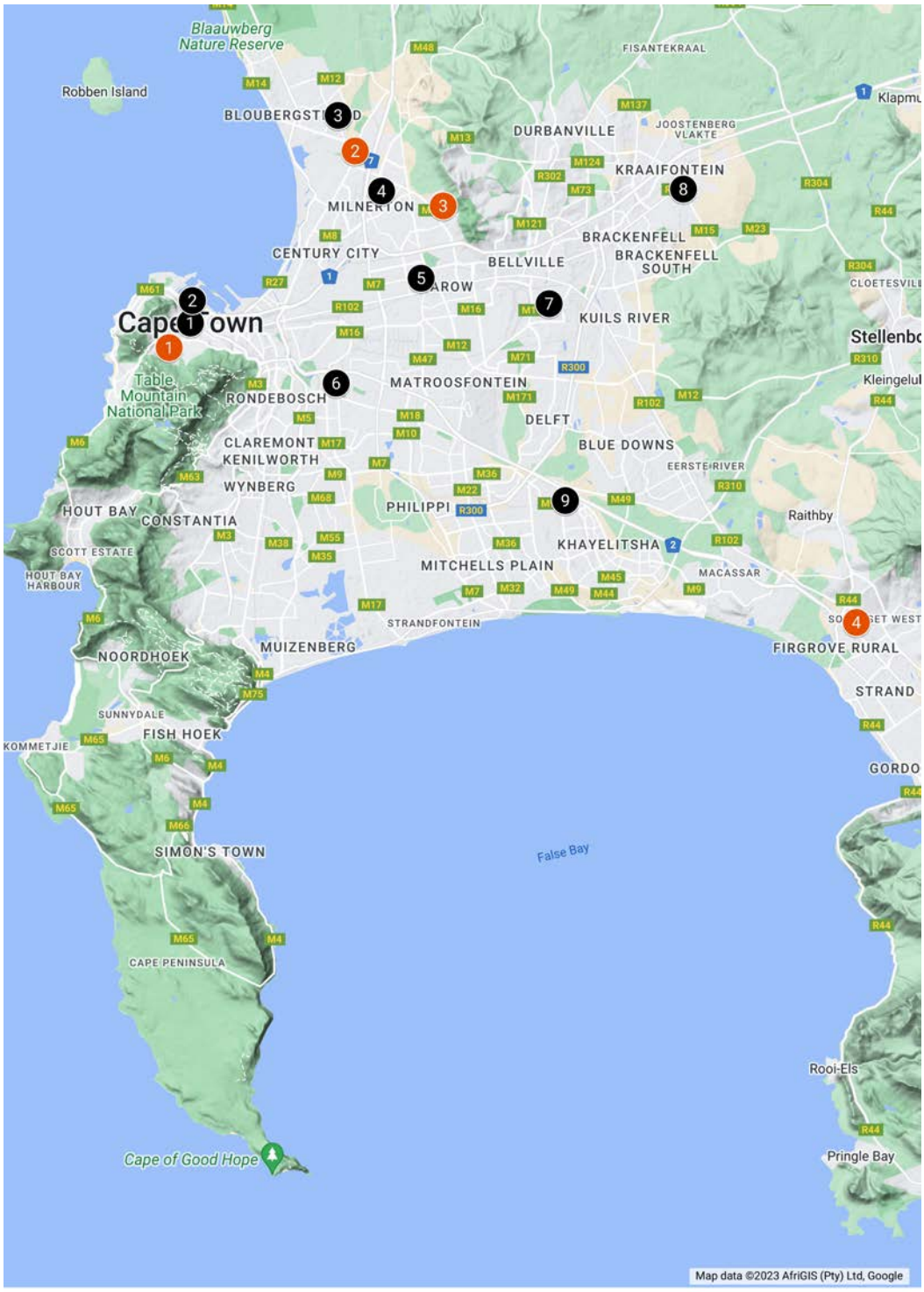

Figure 1. Ambient air quality monitoring stations in Cape Town, South Africa. City Hall (1), Foreshore (2), Tableview (3), Bothasig (4), Goodwood (5), Athlone (6), Bellville South (7), Wallacedene (8) and Khayelitsha (9). Excluded stations in red: Molteno (1), Potsdam (2), Plattekloof (3) and Someset West (4).

2.2. Study Design

A time-stratified case–crossover epidemiological design was conducted, as performed in several studies globally [10,27–30]. This epidemiological study design is a variant of the case–control design and is applied to investigate the effects of short-term exposures on emergency events. In this study design, each person's exposure in a time period just prior

to a case-defining event, such as death, is compared with his/her own exposure at other times [33]. Personal characteristics, such as smoking status, age and co-morbidities, which vary slowly over 24 h, are controlled by the study design if the control days are selected close to the case day (day of death). Control days were selected using the time-stratified approach, e.g., if a death occurred on a Tuesday in September 2007, then this will be the case day, and the control days will be the other Tuesdays in September 2007 [34].

2.3. Mortality Data

Individual-level CVD mortality data (International Classification of Disease, 10th version (ICD-10) (I00–I99)) were requested from Statistics South Africa for the study period 1 January 2006 to 31 December 2015. A large global study used mortality data also obtained from Statistics South Africa [9].

2.4. Air Pollution and Weather Data

Three of the criteria air pollutants were investigated, namely PM_{10}, NO_2 and SO_2. The National Environmental Management: Air Quality Act of 2004 requires the monitoring of criteria air pollutants in the country. A network of air pollution monitors in Cape Town continuously assess real-time concentrations of the criteria air pollutants [31,35] (Figure 1). The US EPA ambient air quality monitoring methods are applied in the operation of the ambient air quality monitoring stations [31].

Hourly air pollution, temperature (°C) and relative humidity (%) data were obtained from the South African Weather Service (SAWS). Other local studies [29,36,37] and a large global study [9] also used air pollution and meteorological data obtained from SAWS. $PM_{2.5}$ was not monitored in Cape Town during 2006–2015. The daily and yearly South African air quality standard for $PM_{2.5}$ only came into effect in June 2012, and there was a delay for the air pollutant to be monitored [38]. Daily averages of the air pollution and meteorological data were based on at least 18 hourly values.

PM_{10}, NO_2 and SO_2 data from nine air quality stations were applied in the study [31]: City Hall, Foreshore, Tableview, Bothasig, Goodwood, Athlone, Bellville South, Wallacedene and Khayelitsha (Figure 1). Data from the Someset West air quality station were excluded, as this site only started operation in 2008 and is 40 km from the city centre of Cape Town [31]. Data from the Molteno, Potsdam and Plattekloof air quality stations were also excluded, as they were mobile stations or did not monitor any of the three air pollutants [31].

NO_2 and SO_2 were monitored with chemiluminescence and UV-fluorescence air quality instruments from Teledyne, respectively, and PM_{10} with Tapered Element Oscillating Microbalance air quality instruments from Thermo Scientific™ [39].

Figure 2 shows a typical air quality station in South Africa along with a photo of the air pollution monitoring instruments.

Figure 2. A typical air quality station in South Africa along with a photo of the air quality instruments [40].

2.5. Statistical Analysis

The sample size (n = 376) for those younger than 15 years was small, so this age group was excluded from the study. Spearman rank correlation analyses were conducted between the air pollutants and the meteorological variables.

Lag0–1 was selected to investigate in this study. Lag0–1 is the mean of lag 0 (same day of exposure as day of death) and lag 1 (day prior to day of death) [27,28].

As conducted in other time-stratified case–crossover epidemiological studies, conditional logistic regression models were applied to investigate the association between the air pollutants (lag0–1) and CVD mortality [10,27–30]. In these models, the repeated measures for each person are taken into consideration (i.e., one case day and 3–4 control days in the same month and year as the case day).

One- as well as two-pollutant models were investigated; the latter included PM_{10} along with NO_2 or SO_2 as linear terms. The majority of studies confirmed a linear association between short-term air pollution exposure and mortality [10]. Strong correlations were not observed between the three air pollutants ($p < 0.05$).

Public holiday (as a binary variable) and lag0–1 of apparent temperature (Tapp) were added as confounders to the models. Sensitivity analyses were conducted to investigate whether Tapp had a linear or non-linear association with CVD mortality. In the models, Tapp was added either as a linear or non-linear term (natural spline with 3 degrees of freedom). Log likelihood ratio tests were conducted to determine whether the non-linear term of Tapp improved the models.

Temperature and relative humidity are used to calculate Tapp in the following equations [41]:

$$\text{Saturation vapour pressure} = 6.112 \times 10^{(7.5 \times \text{temperature } ^\circ\text{C}/(237.7 + \text{temperature } ^\circ\text{C})} \quad (1)$$

$$\text{Actual vapour pressure} = (\text{relative humidity } (\%) \times \text{saturation vapour pressure})/100 \quad (2)$$

$$\text{Dew point temperature } ^\circ\text{C} = (-430.22 + 237.7 \times \ln(\text{actual vapour pressure}))/-\ln(\text{actual vapour pressure}) + 19.08) \quad (3)$$

$$\text{Apparent temperature } ^\circ\text{C} = -2.653 + (0.994 \times \text{temperature } ^\circ\text{C}) + 0.0153 \times (\text{dew point temperature } ^\circ\text{C}) \quad (4)$$

Tapp takes into consideration the joined physiological experience of temperature and humidity. Humidity can reduce the effectiveness of the cooling coping mechanisms of the human body, namely evaporation and perspiration, particularly on warm days. Compared to other weather indicators, such as temperature, dew point temperature, barometric pressure or absolute humidity, Tapp was identified to be the best predictor for heat-related mortality [42]. Several studies applied Tapp [27–30,37,42].

Percent excess risk in CVD mortality per 10 $\mu g \cdot m^{-3}$ increase in an air pollutant level (lag0–1) is applied to indicate association. Other studies also used this approach [9,10,27–30,37].

Stratified analyses were used to investigate effect modification by Tapp. Days with moderate Tapp levels were those when Tapp was equal to or higher than the 25th percentile, but lower than or equal to the 75th percentile during the 10-year study period. Days with high Tapp levels were those when Tapp was higher than the 75th percentile. When Tapp levels were lower than the 25th percentile, days were classified as low Tapp days. Numerous studies applied the same approach [27–30]. Stratified analyses were applied to investigate susceptibility of age groups (15–64 years and $\geq$65 years) and sex (male/female).

A meta-analysis reported no significant difference in the pooled effects of short lags (lag0, lag1 or lag0–1) of PM_{10} on CVD mortality and those of longer lags of up to a week [10]. This means that the deaths of very frail individuals in the population were not merely brought forward by a few days, so no harvesting effects were observed. Sensitivity analyses were therefore conducted for lags of up to a week of the air pollutants (lag0–2, lag0–3, lag0–4, lag0–5 and lag0–6) during the entire study period when all age groups and sexes were combined, as well as separately by the subgroups [10]. The lag of Tapp was the same as that of the air pollutant in these models.

2.6. Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. The Faculty of Health Sciences Research Ethics Committee, University of Pretoria (References 256/2014, 341/2014, 94/2017 and 425/2017), granted approval for the study.

3. Results

3.1. Descriptive Statistics

In total, 54,356 CVD deaths were included in the study. The number of daily CVD deaths ranged from 0 to 33 (Table 1). More CVD deaths occurred amongst males than females. The highest numbers of CVD deaths were observed amongst the elderly (≥ 65-year-olds). Nearly half of the CVD deaths were observed at moderate Tapp levels, followed by low (29%) and high Tapp levels (22%) (Table S1). The CVD deaths displayed well-defined seasonal trends—a higher number of daily deaths during the colder months (May to August) than during the warmer months (September to April) (Figure S1).

Table 1. Daily descriptive statistics of the cardiovascular disease deaths, air pollutants and meteorological conditions in Cape Town, South Africa, 1 January 2006–31 December 2015 (3652 days).

Variable	Mean	Min	P25	Median	P75	Max
Total (n = 54,356)	14.9	2	12	15	18	33
Females (n = 26,167)	7.7	0	6	7	10	20
Males (n = 28,133)	7.2	0	5	7	9	23
15–64-year-olds (n = 20,145)	5.5	0	4	5	7	18
≥65-year-olds (n = 34,164)	9.4	0	7	9	12	26
PM_{10} ($\mu g \cdot m^{-3}$)	29.9	3.8	20.1	27.4	36.8	113.5
NO_2 ($\mu g \cdot m^{-3}$)	16.0	1.4	10.0	14.4	20.5	59.8
SO_2 ($\mu g \cdot m^{-3}$)	9.2	0.6	5.4	8.0	11.7	53.5
Tapp (°C)	16.4	5.1	12.6	16.2	20.3	30.3
Temperature (°C)	17.0	7.5	13.9	16.9	20.2	28.8
Relative humidity (%)	70.0	30.7	62.0	70.7	78.0	100.0

Abbreviations: PM_{10}, particulate matter with an aerodynamic diameter less or equal to 10 μm; NO_2, nitrogen dioxide, SO_2, sulphur dioxide; Tapp, apparent temperature. Low Tapp: <25th percentile (12.6 °C); moderate Tapp: ≥25th and ≤75th percentile; high Tapp: >75th percentile (20.3 °C).

The maximum PM_{10} level was 113.5 $\mu g \cdot m^{-3}$. The daily WHO PM_{10}, NO_2 and SO_2 guidelines of 45 $\mu g \cdot m^{-3}$, 25 $\mu g \cdot m^{-3}$ and 40 $\mu g \cdot m^{-3}$ were exceeded on 463, 421 and 8 days of the 3652 days, respectively (Figures S2–S4) [11]. The mean Tapp was 16.4 °C and ranged between 5.1–30.3 °C (Table 1). Median NO_2 and SO_2 levels (lag0–1) were significantly higher on days with low Tapp levels, followed by those with moderate and high Tapp levels (Table S1). In contrast, the median PM_{10} level (lag0–1) was significantly higher on days with high Tapp levels, followed by those on moderate and low Tapp levels (Table S1).

The broad groups of underlying causes of CVD mortality are presented in Table S2. Ischemic heart disease was the most common type of CVD death (31%), followed by cerebrovascular diseases (27%), as observed globally [1].

The three air pollutants had a moderate correlation (r varying between 0.277 to 0.486) ($p < 0.05$) (Table 2). The gaseous air pollutants (NO_2 and SO_2) had an inverse correlation with Tapp ($p < 0.05$) and no significant correlation with relative humidity. PM_{10} and Tapp had a positive correlation ($p < 0.05$), whereas the air pollutant had an inverse correlation with relative humidity ($p < 0.05$). On days with low Tapp levels, stronger correlations were observed amongst the three air pollutants (Table S3).

Table 2. Spearman rank correlation coefficients between air pollution and weather variables in Cape Town, South Africa, 1 January 2006–31 December 2015 (3652 days).

Variable	NO_2	SO_2	Tapp	Temperature	RH
PM_{10}	0.345	0.277	0.148	0.188	−0.310
NO_2		0.486	−0.387	−0.365	0.016
SO_2			−0.142	−0.131	−0.021
Tapp				0.988	−0.304
Temperature					−0.438

Abbreviations: PM_{10}, particulate matter with an aerodynamic diameter less or equal to 10 μm; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; Tapp, apparent temperature. All correlations were significant ($p < 0.0001$), except between NO_2 and RH ($p = 0.368$) and SO_2 and RH ($p = 0.218$).

3.2. One- and Two-Pollutant Models

The association between PM_{10} or SO_2 and CVD mortality was stronger at low Tapp, although generally not significant, whilst this was the case for NO_2 at moderate Tapp (Table 3). Although more CVD deaths were observed amongst males than females, females were in general more at risk to air pollution exposure. The younger age group was less vulnerable to air pollution exposure than the elderly. The effects of NO_2 were mostly stronger than those of PM_{10} or SO_2, regardless of Tapp level. The highest increase in CVD mortality (7.0% 95% CI 2.6%, 11.6%) was observed for the elderly per 10 $\mu g \cdot m^{-3}$ increase in NO_2 at moderate Tapp, followed by females (5.7% 95% CI 1.0%, 10.7%).

Table 3. One-pollutant model results for the percentage change (95% CI) in daily cardiovascular disease mortality per 10 $\mu g \cdot m^{-3}$ increase in an air pollutant level (lag0–1) in Cape Town, South Africa, 1 January 2006–31 December 2015 (3652 days).

Air Pollutant	Tapp	All	15–64-Year-Olds	≥65-Year-Olds	Females	Males
PM_{10}	Entire range	**1.5 (0.6, 2.4)**	0.9 (−0.6, 2.4)	**1.9 (0.7, 3.1)**	**2.0 (0.7, 3.3**)	0.9 (−0.4, 2.3)
	Low	**1.9 (0.2, 3.6)**	1.7 (−1.1, 4.5)	2.2 (0.0, 4.3)	**2.5 (0.1, 4.9)**	1.4 (−1.0, 3.9)
	Moderate	0.8 (−0.7, 2.4)	0.0 (−2.5, 2.6)	1.4 (−0.6, 3.4)	0.6 (−1.5, 2.8)	1.0 (−1.2, 3.3)
	High	1.3 (−1.1, 3.7)	1.3 (−2.6, 5.3)	1.3 (−1.7, 4.4)	**3.8 (0.4, 7.3)**	−1.3 (−4.7, 2.1)
NO_2	Entire range	**2.7 (0.6, 4.8)**	1.8 (−1.6, 5.3)	**3.3 (0.7, 6.0)**	**3.4 (0.5, 6.4)**	1.9 (−1.1, 5.0)
	Low	3.1 (−0.7, 7.1)	4.2 (−2.2, 11.1)	2.7 (−2.1, 7.8)	4.7 (−0.8, 10.4)	1.7 (−3.8, 7.4)
	Moderate	**4.7 (1.3, 8.3)**	1.0 (−4.4, 6.6)	**7.0 (2.6, 11.6)**	**5.7 (1.0, 10.7)**	3.6 (−1.2, 8.6)
	High	0.6 (−6.3, 8.1)	0.0 (−11.1, 12.4)	1.1 (−7.6, 10.7)	8.7 (−1.6, 20.2)	−7.5 (−16.5, 2.5)
SO_2	Entire range	1.0 (−1.7, 3.9)	−2.4 (−6.8, 2.2)	3.2 (−0.4, 6.9)	1.2 (−2.7, 5.2)	1.1 (−2.9, 5.2)
	Low	4.0 (−2.2, 10.6)	2.4 (−7.6, 13.5)	4.9 (−2.9, 13.2)	7.1 (−1.7, 16.6)	1.6 (−7.1, 11.0)
	Moderate	0.9 (−3.3, 5.3)	−3.3 (−9.9, 3.8)	3.5 (−1.9, 9.2)	3.1 (−2.8, 9.3)	−1.4 (−7.4, 4.9)
	High	−1.3 (−8.3, 6.3)	−8.7 (−19.1, 3.0)	3.5 (−5.8, 13.6)	1.9 (−8.4, 13.3)	−4.4 (−13.8, 6.0)

Low Tapp: <25th percentile (12.6 °C); moderate Tapp: ≥25th and ≤75th percentile; high Tapp: >75th percentile (20.3 °C). Bold text: significant ($p < 0.05$). The median levels of the air pollutants on the low, moderate and high Tapp days are reported in Table S1.

Adjusting for NO_2 attenuated the PM_{10} effects downwards, whilst adding SO_2 to the model increased the PM_{10} risks (Table 4). The effects of NO_2 were in general weaker after adjusting for PM_{10}, except for females, the elderly and all groups combined at moderate Tapp. As in the one-pollutant models, none of the associations were significant for SO_2 after adjusting for PM_{10}. A meta-analysis also reported that weaker and non-significant associations were observed in two-pollutant models [10]. In the two-pollutant models, the highest increase in CVD mortality (7.5% 95% CI 1.5%, 13.8%) was observed for females per 10 $\mu g \cdot m^{-3}$ increase in NO_2 at moderate Tapp, after adjusting for PM_{10}, followed by the elderly (7.4% 95% CI 1.9%, 13.1%).

The associations between the longer lags of the air pollutants and CVD mortality are reported in Table 5. For PM_{10}, the risk reduced gradually for all ages and sexes combined, which is an indication of harvesting. The associations were not significant from lag0–4. In contrast, the risk for PM_{10} was increased at longer lags amongst females, reaching a maximum at lag0–4. The risks due to PM_{10} exposure were similar amongst the elderly for longer lags and only reduced from lag0–4, which is an indication of harvesting. Although

none of the associations were significant for males or the younger age group, the PM_{10} risk disappeared after lag0–3, which is an indication of harvesting effects.

Table 4. Two-pollutant model results for the percentage change (95% CI) in daily cardiovascular disease mortality per 10 $\mu g \cdot m^{-3}$ increase in an air pollutant level (lag0–1) in Cape Town, South Africa, 1 January 2006–31 December 2015 (3652 days).

Air Pollutant	Tapp	All	15–64-Year-Olds	≥65 Year-Olds	Females	Males
PM_{10} adjusted for NO_2	Entire range	1.2 (0.0, 2.5)	0.5 (−1.5, 2.5)	**1.7 (0.2, 3.3)**	**1.9 (0.2, 3.6)**	0.5 (−1.2, 2.3)
	Low	1.8 (−0.8, 4.5)	0.3 (−3.9, 4.7)	2.7 (−0.6, 6.1)	1.8 (−1.8, 5.6)	1.7 (−2.0, 5.6)
	Moderate	−0.8 (−3.0, 1.4)	−1.4 (−4.9, 2.2)	−0.4 (−3.1, 2.4)	−1.6 (−4.5, 1.4)	0.0 (−3.1, 3.2)
	High	1.7 (−1.1, 4.6)	2.1 (−2.4, 6.9)	1.5 (−2.1, 5.2)	**5.3 (1.3, 9.5)**	−1.9 (−5.8, 2.2)
NO_2 adjusted for PM_{10}	Entire range	1.1 (−1.4, 3.7)	1.2 (−2.9, 5.6)	1.1 (−2.1, 4.4)	0.9 (−2.6, 4.6)	1.3 (−2.4, 5.1)
	Low	0.2 (−5.4, 6.1)	3.7 (−5.9, 14.2)	−1.6 (−8.4, 5.8)	1.5 (−6.3, 10.0)	−1.0 (−8.9, 7.6)
	Moderate	**5.7 (1.4, 10.1)**	2.7 (−4.0, 9.8)	**7.4 (1.9, 13.1)**	**7.5 (1.5, 13.8)**	3.6 (−2.3, 9.9)
	High	−0.6 (−7.7, 7.1)	−1.4 (−12.8, 11.4)	0.0 (−8.9, 9.8)	5.6 (−4.8, 17.2)	−6.8 (−16.3, 3.6)
PM_{10} adjusted for SO_2	Entire range	**1.8 (0.8, 2.8)**	**1.8 (0.1, 3.5)**	**1.8 (0.6, 3.1)**	**2.4 (1.0, 3.9)**	1.0 (−0.4, 2.5)
	Low	1.9 (−0.1, 3.9)	1.7 (−1.6, 5.0)	2.2 (−0.3, 4.7)	2.1 (−0.6, 4.9)	1.6 (−1.3, 4.5)
	Moderate	1.3 (−0.5, 3.1)	1.5 (−1.4, 4.5)	1.2 (−1.0, 3.4)	1.0 (−1.4,3.4)	1.6 (−1.0, 4.2)
	High	1.8 (−0.7, 4.3)	2.4 (−1.7, 6.5)	1.4 (−1.7, 4.6)	**4.3 (0.8, 7.9)**	−0.9 (−4.3, 2.7)
SO_2 adjusted for PM_{10}	Entire range	−0.9 (−3.8, 2.1)	−4.5 (−9.1, 0.4)	1.2 (−2.5, 5.1)	−1.4 (−5.5, 2.8)	−0.1 (−4.3, 4.3)
	Low	0.3 (−6.6, 7.8)	−0.9 (−12.1, 11.9)	0.7 (−7.9, 10.2)	3.0 (−6.8, 13.7)	−1.5 (−11.3, 9.3)
	Moderate	−0.4 (−4.8, 4.3)	−4.8 (−11.7, 2.6)	2.4 (−3.3, 8.4)	2.1 (−4.1, 8.7)	−3.0 (−9.2, 3.7)
	High	−1.4 (−8.5, 6.2)	−9.6 (−20.0, 2.2)	3.8 (−5.6, 14.1)	1.1 (−9.2, 12.6)	−3.9 (−13.4, 6.7)

Low Tapp: <25th percentile (12.6 °C); moderate Tapp: ≥25th and ≤75th percentile; high Tapp: >75th percentile (20.3 °C). Bold text: significant ($p < 0.05$). The median levels of the air pollutants on the low, moderate and high Tapp days are reported in Table S1.

Table 5. One-pollutant model results for the percentage change (95% CI) in daily cardiovascular disease mortality per 10 $\mu g \cdot m^{-3}$ increase in an air pollutant level in Cape Town, South Africa, 1 January 2006–31 December 2015 (3652 days).

Group	Lag	PM_{10}	NO_2	SO_2
All ages and sexes combined	Lag0–1	**1.5 (0.6, 2.4)**	**2.7 (0.6, 4.8)**	1.0 (−1.7, 3.9)
	Lag0–2	**1.6 (0.6, 2.7)**	2.3 (−0.1, 4.7)	1.2 (−2.0, 4.5)
	Lag0–3	**1.4 (0.3, 2.6)**	1.2 (−1.4, 3.9)	−0.3 (−3.8, 3.3)
	Lag0–4	1.2 (−0.1, 2.4)	0.8 (−1.9, 3.7)	−1.0 (−4.7, 2.9)
	Lag0–5	1.1 (−0.3, 2.4)	1.2 (−1.8, 4.2)	−0.4 (−4.3, 3.8)
	Lag0–6	0.8 (−0.6, 2.3)	0.7 (−2.4, 4.0)	−0.9 (−5.1, 3.4)
Females	Lag0–1	**2.0 (0.7, 3.3)**	**3.4 (0.5, 6.4)**	1.2 (−2.7, 5.2)
	Lag0–2	**2.4 (1.0, 3.9)**	3.1 (−0.3, 6.5)	0.8 (−3.6, 5.4)
	Lag0–3	**2.6 (1.0, 4.2)**	2.8 (−0.8, 6.6)	−0.5 (−5.3, 4.6)
	Lag0–4	**2.8 (1.0, 4.5)**	3.3 (−0.6, 7.4)	−1.0 (−6.1, 4.4)
	Lag0–5	**2.6 (0.7, 4.5)**	4.1 (−0.1, 8.4)	0.9 (−4.6, 6.8)
	Lag0–6	**2.6 (0.5, 4.7)**	**4.8 (0.3, 9.5)**	0.8 (−5.1, 7.0)
Males	Lag0–1	0.9 (−0.4, 2.3)	1.9 (−1.1, 5.0)	1.1 (−2.9, 5.2)
	Lag0–2	0.8 (−0.7, 2.3)	1.5 (−1.9, 4.9)	1.7 (−2.9, 6.5)
	Lag0–3	0.2 (−1.5, 1.8)	−0.5 (−4.2, 3.2)	0.0 (−5.0, 5.2)
	Lag0–4	−0.5 (−2.3, 1.3)	−1.5 (−5.3, 2.5)	−0.9 (−6.2, 4.7)
	Lag0–5	−0.5 (−2.4, 1.4)	−1.5 (−5.7, 2.8)	−1.6 (−7.2, 4.3)
	Lag0–6	−1.0 (−3.0, 1.1)	−3.2 (−7.5, 1.4)	−2.6 (−8.4, 3.6)
15–64-year-olds	Lag0–1	0.9 (−0.6, 2.4)	1.8 (−1.6, 5.3)	−2.4 (−6.8, 2.2)
	Lag0–2	0.8 (−0.8, 2.5)	1.4 (−2.5, 5.3)	−3.0 (−8.0, 2.3)
	Lag0–3	0.6 (−1.3, 2.5)	−0.1 (−4.2, 4.2)	−4.4 (−9.8, 1.4)
	Lag0–4	−0.1 (−2.1, 2.0)	−0.8 (−5.3, 3.8)	**−6.8 (−12.5, −0.8)**
	Lag0–5	−0.1 (−2.2, 2.2)	0.0 (−4.7, 5.0)	−5.8 (−11.9, 0.7)
	Lag0–6	−0.2 (−2.6, 2.2)	0.0 (−5.1, 5.3)	−5.5 (−11.9, 1.3)
≥65-year-olds	Lag0–1	**1.9 (0.7, 3.1)**	**3.3 (0.7, 6.0)**	3.2 (−0.4, 6.9)
	Lag0–2	**2.2 (0.9, 3.5)**	**3.1 (0.1, 6.2)**	3.7 (−0.3, 8.0)
	Lag0–3	**2.0 (0.5, 3.4)**	2.2 (−1.0, 5.6)	2.2 (−2.2, 6.9)
	Lag0–4	**1.9 (0.4, 3.5)**	2.0 (−1.5, 5.6)	2.6 (−2.2, 7.7)
	Lag0–5	1.7 (0.0, 3.5)	2.8 (−1.0, 6.7)	3.1 (−2.0, 8.5)
	Lag0–6	1.5 (−0.4, 3.3)	2.1 (−1.9, 6.3)	2.1 (−3.3, 7.8)

Models adjusted for public holidays and Tapp (same lag as the air pollutant). Tapp applied either as a linear or non-linear term; refer to Section 2. Bold text: significant associations ($p < 0.05$).

For NO_2, the risk reduced from lag0–3 for all ages and sexes combined, which is an indication of harvesting. For females, the associations weakened for lag0–2 and lag0–3 compared to lag0–1, but then strengthened again, with the strongest association at lag0–6. For the elderly, the associations were weaker from lag0–3, but strengthened again at lag0–5, although not significantly. Harvesting effects were observed after lag0–2 of NO_2 and SO_2 amongst males. Similar results were observed for NO_2 amongst the 15–64-year-old group. Although most of the associations between the lags of SO_2 and CVD mortality were not significant amongst the 15–64-year-old group, harvesting effects may be present, as the risk in general decreased with longer lags.

4. Discussion

Mwase et al. compared PM_{10}, NO_2 and SO_2 levels from various African and global cities [43]. PM_{10}, NO_2 and SO_2 levels in Cape Town during 2006–2015 were similar or even lower than those in cities from developed countries, and markedly lower than those observed in two large South African cities (Durban and Johannesburg), industrial areas in the country or other LMICs in North Africa, Asia and South America [43].

Ischemic heart disease was the most common type of CVD death in Cape Town. Ischemic heart diseases are characterised by narrowed or blocked heart arteries that lead to suboptimal supply of oxygenated blood [44]. The synergistic effects of temperature and air pollution on CVD have a biological plausibility, such as increased clotting risk due to systemic inflammation after air pollution exposure, along with a rise in cholesterol levels and blood viscosity at high ambient temperature [28].

On days with low Tapp levels, significantly higher median NO_2 and SO_2 levels were observed compared to days with moderate or high Tapp levels, although Cape Town is situated in a winter rainfall region [31]. In contrast, the median PM_{10} level was significantly higher on days with high Tapp levels. However, it is probable that during the 10-year study period, drier or wetter months also had days with low and high Tapp levels, respectively. Another explanation for the observed results is that of atmospheric chemistry, as discussed for NO_2 below.

Possible explanations for the observed PM_{10} and NO_2 effects on moderate and high Tapp days may be due to human behaviour, physiology, toxicity of the air pollutants or meteorological factors such as rain or wind. On days with moderate and high Tapp levels people may open windows more, which may result in more outdoor air pollution infiltrating indoors. People may also participate in outdoor activities on such days and this may increase their exposure levels. The source and composition of air pollution may be influenced by ambient temperature. Studies observed that at higher temperature levels higher levels of toxic forms of PM tend to be detected [27,28]. Temperature may thus be an indicator of PM_{10} composition.

A meta-analysis reported that CVD mortality significantly increased by 0.5%, 0.5% and 1.6% at low, moderate and high temperature, respectively, per 10 $\mu g \cdot m^{-3}$ increase in PM_{10}. The meta-analysis included 29 studies, mainly from China, Europe, USA, Australia and India [27]. No results were reported for two-pollutant models in the meta-analysis and no study from Africa was available. The risk for CVD mortality was higher in our study due to exposure to PM_{10} on days with low and moderate Tapp levels, namely 1.9% and 0.8%, respectively, but lower on days with high Tapp levels (1.3%).

PM_{10} effects were attenuated in the two-pollutant models, although the pollutant had weak to moderate correlations with NO_2 and SO_2. The attenuation may not only be due to confounding but may be an indicator of the source-related constituent of PM_{10}, as was proposed by Qian et al. [45].

Evidence is lacking as to what extent temperature modifies the effects of NO_2 or SO_2 on CVD mortality [27,28]. Our observation of a 3.1% and 4.7% increase in CVD mortality per 10 $\mu g \cdot m^{-3}$ increase in NO_2 at low and moderate Tapp levels are higher than results from three Chinese and Taiwanese studies that were included in the meta-analysis [27], but lower at high Tapp (0.6%). The meta-analysis reported significant increases of 1.5%, 1.5%

and 0.9% at low, moderate and high temperature, respectively, per 10 $\mu g \cdot m^{-3}$ increase in NO_2 [27].

We did not observe any significant risks for SO_2 at any Tapp level. Three studies from China found increased CVD mortality of 1.4% and 1.3% at low and moderate temperature, respectively, per 10 $\mu g \cdot m^{-3}$ increase in SO_2, and an insignificant increase of 0.4% at high temperature [27].

NO_2 can be converted to water-soluble nitrate in atmospheric chemical reactions, which can partition to the particulate phase and thereby generate PM [46]. This may be a possible explanation for the higher risks due to NO_2 exposure compared to PM_{10} at low and moderate Tapp. A meta-analysis also reported similar results [27]. A meta-analysis reported that natural-cause mortality increased by 17% per 1 $\mu g \cdot m^{-3}$ increase in nitrate [47], which is much higher compared to a 0.4% increase per 10 $\mu g \cdot m^{-3}$ increase in PM_{10} reported in another meta-analysis [10].

In general, the elderly and females were more vulnerable to air pollution exposure, especially at high and moderate Tapp levels. Reviews highlighted that there is a research need to investigate subgroups of the population [27,28,48]. The elderly tends to be frailer and have more co-morbidities and less physiological resilience [21,48,49]. The inhaled air pollution dose may be larger in females than males, as they have smaller lung tissue and trachea than males [50]. Females also sweat less, have a higher working metabolic rate and may have thicker subcutaneous fat that may weaken thermoregulation [51].

A meta-analysis reported no significant difference in the pooled effects of short lags (lag0, lag1 or lag0–1) of PM_{10} on CVD mortality and those of longer lags of up to a week [10]. This means that the deaths of very frail individuals were not merely brought forward by a few days, so no harvesting effects were observed. Harvesting effects are observed if the risks decrease at longer lags of air pollutants. This indicates that the frail individuals are removed from the population at short lags, leaving fewer frail individuals to be at risk at longer lags [52]. The meta-analysis reported pooled effects for all age groups and sexes combined. Few studies investigated susceptibility by age or sex, as mentioned before. In the current study, it appears that harvesting effects were not uniform for the different air pollutants nor the different subgroups. It was expected that harvesting effects will be clearly observed for females and the elderly, as they were identified to be more at risk from air pollution exposure at lag0–1. Possible reasons for the difference in harvesting effects among males and females may be due to physiology, as mentioned above, or exposure to indoor air pollution such as environmental tobacco smoke or polluting household fuel use for cooking and heating. Clearly, studies are needed in South Africa that investigate air pollution harvesting effects on mortality and hospital admissions. Even though harvesting may be observed in our study, from a public health risk communication perspective, it is beneficial to decrease air pollution levels in Cape Town. Chronic air pollution exposure leads to disease incidence [8,11], which in turn makes individuals in the population frail.

Air pollution and meteorological levels were measured at a few sites, and it was assumed that these levels are the same across the entire city. This may have led to measurement error. All ecological epidemiological studies have this limitation. However, it was shown that this exposure misclassification is non-differential and bias the effect estimates towards the null [53].

Another limitation is that $PM_{2.5}$ was not investigated in this study. The pollutant was not monitored in the City of Cape Town during 2006–2015. $PM_{2.5}$ can penetrate deeper into the respiratory tract than PM_{10}, penetrate the lung barrier and enter the blood system, thus making it more hazardous to human health than PM_{10} [9,11].

The findings of this study can be applied to develop an early warning system for the city, e.g., use of machine learning methods [54]. For example, days can be grouped based on median daily air pollution levels at low, moderate and high Tapp levels. This can be a predictor variable for CVD mortality. It is important to note that the results cannot be extrapolated to other health outcomes such as hospital admissions, other cause-specific mortalities or to other cities in South Africa.

5. Conclusions

The daily PM_{10}, NO_2 and SO_2 levels exceeded the daily WHO air quality guidelines frequently in Cape Town. These air pollution levels were similar to or even lower than those in Western Europe and North America, where most of the epidemiological evidence on the health effects of air pollution and human health are derived. However, the CVD mortality risks due to air pollution exposure were higher in Cape Town compared to those reported in meta-analyses that summarised the evidence. The air pollution effects on CVD mortality were modified by Tapp, with higher risks observed on days with moderate and high Tapp levels. The elderly and females were identified to be more vulnerable to PM_{10} and NO_2 exposure. Harvesting effects were observed and were not uniform for the different air pollutants nor the different subgroups. The results can be used to develop an early warning system for the city.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cli11020030/s1.

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Data Availability Statement: Mortality data: individual-level respiratory disease mortality data (International Classification of Disease, 10th version [ICD-10] (J00–J99) were obtained from Statistics South Africa for the study period 1 January 2006 to 31 December 2015, but restrictions apply to the availability of these data, which were used under a strict signed data agreement, and so are not publicly available. Air pollution, temperature (°C) and relative humidity (%) data were obtained from the South African Weather Service for the study period, after signing a data agreement.

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