Case-crossover study for the association between increased hospital admissions for respiratory diseases and the increase in atmospheric $PM_{2.5}$ and $PM_{2.5}$-bound trace elements in Pretoria, South Africa

Chantelle Howlett-Downing[a]*, Johan Boman[b], Peter Molnár[c], Joyce Shirinde[a], Janine Wichmann[a]

[a]*School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria, Gezina 0031, South Africa*

[b]*Department of Chemistry and Molecular Biology, Atmospheric Science Division, University of Gothenburg, SE-412 96 Göteborg, Sweden*

[c]*Department of Occupational and Environmental Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, SE-405 30 Göteborg, Sweden*

ORCiD

Chantelle Howlett-Downing: http://orchid.org/0000-0002-9398-586X

Johan Boman: http://orchid.org/0000-0001-9862-4126

Peter Molnár: http://orchid.org/0000-0003-1259-5649

Joyce Shirinde: http://orchid.org/0000-0002-3467-1043

Janine Wichmann: http://orchid.org/0000-0002-3008-3463

*Correspondence to:

Chantelle Howlett-Downing

School of Health Systems and Public Health

Faculty of Health Sciences

University of Pretoria

Pretoria

0001

South Africa

Email: u14233551@tuks.up.ac.za; chowlett@gmail.com

Abstract:
Outdoor $PM_{2.5}$ was sampled in Pretoria, 18 April 2017 to 28 February 2020. A case-crossover epidemiology study was associated for increased $PM_{2.5}$ and trace elements with increased hospital admissions for respiratory disorders (J00-J99). The results included a significant increase in hospital admissions, with total $PM_{2.5}$ of 2.7% (95% CI: 0.6, 4.9) per 10 $\mu g \cdot m^{-3}$ increase. For the trace elements, Ca of 4.0% (95% CI: 1.4%−6.8%), Cl of 0.7% (95% CI: 0.0%−1.4%), Fe of 3.3% (95% CI: 0.5%−6.1%), K of 1.8% (95% CI: 0.2–3.5) and Si of 1.3% (95% CI: 0.1%−2.5%). When controlling for $PM_{2.5}$, only Ca of 3.2% (95% CI: 0.3, 6.1) and within the 0–14 age group by 5.2% (95% CI: 1.5, 9.1). Controlling for a co-pollutant that is highly correlated with PM2.5 does reduce overestimation, but further studies should include deposition rates and parallel sampling analysis.

Keywords: respiratory disorders, $PM_{2.5}$, case-crossover, Pretoria, Tapp, sources

Introduction

Ambient air pollution exposure has been associated with human health effects ranging from symptoms resulting in hospital admissions to mortality.[1] According to the World Health Organization, air pollution poses the highest level of environmental risk.[2-4]

Africa is undergoing a developmental, household and ambient air pollution transition.[5] In the northern regions of Africa, Ethiopia, Ghana and Rwanda, air pollution is improving with the introduction of better domestic energy systems and supply.[5] This trend may not be taking place in the Southern African regions.[6] Increased development, urban sprawl and failing fossil fuelled power stations pose the greatest risk to human wellbeing.

In South Africa, nearly 1.8 million deaths were reported during 2015 to 2018. Of these, nearly 10% were due to respiratory diseases.[7] Locally, Wichmann and Voyi[5] reported an increase of 1.3% and 2.0% in respiratory disease mortality per inter-quartile range increase in PM_{10} (12 $\mu g.m^{-3}$) and NO_2 (12 $\mu g.m^{-3}$), respectively in Cape Town, South Africa during 2001-2006. A follow-up study by Thabethe et al[6] using data from 2006-2010 of three large South African cities, namely Cape Town, Durban and Johannesburg. In the meta-analysis, an overall excess mortality risk of 0.4% and 1.2% was observed for respiratory disease

mortality following a 10 $\mu g.m^{-3}$ increase in PM_{10} and NO_2, respectively. These studies did not investigate $PM_{2.5}$.

Impediments to health studies include inadequate government air pollution monitoring networks and comprehensive air quality laws at domestic levels.[8] Health management systems in various countries may also lack an electronic health registry data system.[3, 4] Researcher-initiated exposure assessment studies are not evenly distributed across Africa and not sustained over long study periods.[9] Studies may include questionnaire-based exposure indicators only.[10] Another challenge for health studies is when the total dataset from the South African Air Quality Monitoring Stations (SAAQIS) is of low quality due to missing values.[11]

It is commonly recognised that $PM_{2.5}$ is more hazardous to human health than PM_{10}, as it can penetrate deeper into the respiratory tract than PM_{10}, penetrate the lung barrier and enter the blood system.[12]
$PM_{2.5}$ is a complex mixture of numerous constituents, each with different physicochemical properties and toxicity. The proportion of which over the total particle mass varies by location, source and season.[13] Although the first epidemiology study reporting on acute health effects and some constituents of $PM_{2.5}$ occurred in 1996, there is still uncertainty as to which PM components are the most harmful.[14] In 2000, the first epidemiology study reported on the risk of acute exposure to $PM_{2.5}$ trace elements on mortality.[15] In the meantime, numerous studies were conducted globally on the health effects of $PM_{2.5}$ composition, but none in Africa.[4]

This is the first attempt to investigate the effects of $PM_{2.5}$, its trace element composition and identified sources on respiratory hospital admissions in the capital city of South Africa, Pretoria.

Materials and Methods

Study area and population

Pretoria is situated in central South Africa and has an overall population of about 2.6 million in 2020.[16] It is located approximately 50 km north of Johannesburg in the north-

east of South Africa. With an altitude of about 1 350 m above sea level, the city enjoys a moderate climate surrounded by hills of the Magaliesberg range. The sampling site was the School of Health Systems and Public Health, University of Pretoria (S25° 43' 57" E28º 12' 10"). (Fig. 1) There is a main road (Steve Biko road) running alongside the campus and an industrial area north of the campus. The hospital data is collected from three Mediclinics (Medforum, Meulmed and Kloof). (Fig. 1) Sources of the $PM_{2.5}$ air pollutant include Secondary S (significantly higher during the summer months, $p<0.001$), biomass burning (significantly higher during the winter months, $p<0.001$), industrial burning, vehicular emissions, mining and resuspended dust matrix.[17]

Sampling and data analysis

$PM_{2.5}$ sampling, gravimetric and chemical analyses

Briefly, the sampling of ambient $PM_{2.5}$ by gravitational methods, followed the EPA MLD 055 SOP as used in the ULTRA studies. Outdoor $PM_{2.5}$ filter samples were collected manually, every third day from 16 April 2017 to 28 February 2020. Samples were collected on 37 mm PTFE membrane filters (Zefon International, Florida, USA) using GilAir-5 personal air samplers (Sensidyne, Schauenburg Electronic Technologies Group, Mulheim-Ruhr, Germany). The GilAir-5 pump flow rates were maintained at 4 $l.min^{-1}$. Sampling started 9 a.m. and ended 9 a.m. the next day. The sampling method follows previous studies in South Africa utilising gravimetric sampling methods.[18]

The $PM_{2.5}$ filter samples were weighed at the SHSPH in batches of 20 before and after sampling. An ultra-micro-balance (Mettler-Toledo XP6) was used under climate-controlled conditions (temperature: 20.1-22.0 °C, relative humidity: 43-54%). The filter samples were stored in a refrigerator at 4 °C.

A XEPOS 5 energy-dispersive X-ray fluorescence (EDXRF) spectrometer (Spectro analytical instruments GmbH, Germany) at the Atmospheric Science Division, University of Gothenburg, was used to analyse the elemental composition of the aerosol particles on all filters. The EDXRF spectra were processed and quantified using the Spectro XRF Analyzer Pro software. All $PM_{2.5}$ filter samples were analysed using a total time of 3000 seconds, automatically divided between the four analytical setup conditions. The concentrations of the following 21 elements were analysed for: As, Ba, Br, Ca, Cl, Cu, Fe, K, Mn, Ni, P, Pb, S, Sb, Se, Si, Sr, Ti, U, V and Zn. The mean analytical precision was 15% to 20%, as calculated from repeated analysis (n=7) of two randomly selected filters, one having a low and the other, a high mass loading. A good correlation between $PM_{2.5}$ levels measured on filter samples using a GilAir-5 pump and those obtained using a continuous real-time instrument (Aeroqual) during May 2018 to May 2019 is observed. (Supplementary Fig 1).[19]

The duplicate sample values were averaged. Precision was estimated using the root mean square method on the duplicate sample concentration.[20] Results will only be reported for nine of the 21 trace elements as these had levels above the limit of detection LoD. Br, Ca, Cl, Fe, K, S, Si, Ti and Zn. (Table 1) Measurements below the (LoD) were treated as missing.

Hospital admissions data (Mediforum, Meulmed and Kloof)

In total, 15 155 respiratory disease hospital admissions were included in this study (Table 2). This data was obtained from three Medi clinics (ethics 300/2020). Meulmed Hospital is situated 3.56 Km Southeast as the crow flies, Mediforum Hospital is 1.73 Km Southerly as the crow flies. Finally, Kloof Hospital is approximately 10.27 Km in the Southerly direction. Approximately 1000 fewer male (n=7 095) than female (n=8 060) patients were

admitted (Table 2). At most, 114 patients were admitted for respiratory disease in a day. The respiratory hospital admissions had clear seasonal trends with more hospital admissions per day during winter than in summer, $p<0.001$. (Fig. 2)

In terms of average admissions per age group; the 0 - 14 age group had an average of 11 admissions per day over the study period. More boys than girls were admitted with an average of 13 admissions per day for all respiratory diseases. The highest number per day was 38 for girls and 49 for boys for all respiratory diseases. The highest number of admissions for a respiratory disease was for pneumonia with a mean of 7 girls and 8.5 for boys. Boys seemed to be more vulnerable at this age. (Table 3)

For the 15 – 64 years age group, there was nearly double the number of admissions for females than males with an average of 9.8 and 5.4 admissions per day, respectively. The highest mean was for asthma for females (4.2) and 1.6 for males. For the elderly (>65 years) the highest number of admissions due to pneumonia with an average of 2.5 for females and 1.6 for males. For the >65 age group, the average number of admissions was 3.9 and 3.5 respectively.

The average number of admissions for asthma for the 15 – 64 age group was 4.2 for females and 1.6 for males. For the >14 age group, the average number was 1.6 for females and 2.4 for males. For the >64 age group, 1.4 for females and 0.96 for males. Lifestyle, occupational exposure, and outdoor activities could account for the trend. There were no admissions for emphysema for children and a very low average for the 15 – 64 age group for both females and males, (0.06 and 0.12 respectively). The average increases for the elderly (0.29 and 0.48 respectively). (Table 3)

Study design and statistical method for case-crossover epidemiology study

Ambient temperature is a well-established confounder for an air pollution-morbidity association. Tapp incorporates temperature, humidity and sometimes wind speed. Most studies considered temperature alone as the confounder and did not take relative humidity into account, even though relative humidity plays a significant role in health effects. Tapp is a better indicator of health effects rather than temperature alone.[21] (Table 4)

The following equations were used to calculate the Tapp

Saturation vapour pressure = 6.112 × 10 (7.5 × temperature °C/ (237.7 + temperature °C) (1)

Actual vapour pressure = (relative humidity (%) × saturation vapour pressure)/100 (2)

Dew point temperature °C = (−430.22 + 237.7 × ln (actual vapour pressure))/−ln (actual vapour pressure) + 19.08) (3)

Apparent temperature °C = −2.653 + (0.994 × temperature °C) + 0.0153 × (dew point temperature °C) (4)

The statistical analysis for the case-crossover study was performed in SAS where the daily number of hospital admissions (frequency) usually has a quasi-Poisson distribution, i.e., over-dispersed, meaning very few days with a low number of hospital admissions. The distribution has a long tail as the frequency declines, i.e., very few days have a large number of hospital admissions. Tables 5 and 6

$$Yt \sim \text{Poisson}(\mu t) \quad (5)$$

The statistical model for investigating the association between $PM_{2.5}$ sources and respiratory disease hospital admissions is:

$$\log(\mu t) = \alpha + \beta SOURCEt + \gamma Tappt + \eta pubholt + \eta DOWt + \lambda Stratat \quad (6)$$

where:

t is the day of the hospital admission;

Yt is the hospital admission count on day t;

α is the intercept;

SOURCEt is a is a categorical variable and indicates the source type of $PM_{2.5}$ on day t,

β is a vector of coefficients for SOURCE,

Tappt is the linear tem of apparent temperature;

γ is a vector of coefficients for Tapp;

DOWt is is a categorical variable and indicates the day of the week on day t and

pubholt is a binary variable for public holidays.

η indicates the vector of coefficients for DOW and pubhol.

Stratat is a categorical variable of the year and calendar month used to control for long-term trend and seasonality and λ is a vector of coefficients for Strata.

SOURCEt is a categorical variable and not a continuous variable. The reference level of the SOURCEt variable was selected once the sources of $PM_{2.5}$ have been identified.

The association between respiratory disease hospital admissions and $PM_{2.5}$, soot, BC and UV-PM was also determined by means of the same model replacing SOURCEt for POLt. POLt is the linear term for $PM_{2.5}$, soot, BC or UV-PM. $PM_{2.5}$. Soot, BC and UV-PM usually have a very strong correlation. Only single pollutant models were therefore investigated. The lag0 of the air pollutant ($PM_{2.5}$, soot, BC or UV-PM) and Tapp was utilised in the models. Lag0 refers to the air pollution or Tapp level on the day of hospitalisation. This method follows on previous studies as no default method was found. [22-24]

Susceptibility of age groups (<15 years, 15–64 years and ≥65 years) and sex (male/female) was investigated by stratified analyses. The associations between hospital admissions and air

pollutant level were presented as the percentage excess risk in hospital admissions per specific unit increase in an air pollutant level, in line with previous studies. The specific unit of increase for each pollutant is indicated below Tables 5 and 6.

Results

Results of analysis of the case-crossover association between air pollutants ($PM_{2.5}$, BC, UV-PM, soot and trace elements) and hospital admissions

Two models where performed. Model 1 using a full dataset including total $PM_{2.5}$, soot, BC, UV-PM and nine trace elements. This model controlled for Tapp, public holidays and monthyear (weekends). Tapp was seasonal with the highest mean in summer, 23.8 ± 2.9 ^{o}C. (Table 4)

Results for model 1, respiratory hospital admissions increased significantly by 2.7% (95% CI: 0.6, 4.9) per 10 $\mu g.m^{-3}$ increase in $PM_{2.5}$. (Table 5) For the trace elements. an increase in respiratory hospital admissions increased significantly with an increase in Ca by 4.0 % (95% CI: 1.4% - 6.8% per 124.4 $ng.m^{-3}$ increase), for Cl by 0.7 % (95% CI: 0.0% - 1.4%) per 29.2 $ng.m^{-3}$ increase, Fe (3.3 % 95% CI 0.5% - 6.1% per 150.8 $ng.m^{-3}$ increase), K (1.8% 95% CI 0.2 – 3.5 per 162.2 $ng.m^{-3}$ increase and Si (1.3 % 95% CI 0.1% - 2.5% per 256.1 $ng.m^{-3}$ increase).

Respiratory hospital admissions increased significantly for females with increased soot of 5.8% (95% CI: 0.6 – 11.3) per 1 m^{-1} x 10^{-5} $ng.m^{-3}$ incremental increase. When stratified for age, the ≥65 years age group, although not significant, tended to experience adverse effects as the percentage change in respiratory hospital admissions > 0%

When stratifying for sex, hospital admissions was significantly increased by an increase of Br by 2.6 % (95% CI; 0.2% - 5.2%) with an IQR of 11.6 per 1 $ng.m^{-3}$, of Ca by 3.8 % (95% CI: 0.5% - 7.3%) with an IQR of 124 per 1 $ng.m^{-3}$, of Cl by 0.9 % (95% CI: 0.1% - 1.8%) with an IQR of 29 per 1 $ng.m^{-3}$ and by Fe of 3.6 % (95% CI: 0.1% - 7.2%) with an IQR of 151 per 1 $ng.m^{-3}$. For males, a significant increase of Ca by 4.3 % (95% CI: 0.8% - 7.9%) with an IQR of 11.6 per 1 $ng.m^{-3}$.

After controlling for $PM_{2.5}$ in model 2, fewer significant associations were observed between respiratory hospital admissions and the trace elements. Respiratory hospital admissions increased significantly for total Ca by 3.2 % (95% CI: 0.3, 6.1) and for the 0 – 14 age group by 5.2 % (95% CI: 1.5, 9.1) per 10 $ng.m^{-3}$. Overall, the associations were slightly weaker compared to model 1. (Table 6)

Association between with sources of $PM_{2.5}$ (lag0) and hospital admissions

The association between $PM_{2.5}$ and the following six sources (resuspended dust matrix (16%), mining (27), exhaust (11%), industry (21%), biomass burning (12%) and vehicular emissions (14%) was performed.[17] The model was controlled for Tapp, public holidays and monthyear (weekends). The respiratory hospital admissions significantly increased with an increase in resuspended dust matrix by 2.9 % (95% CI: 0.1% - 5.7%) and for biofuel burning by 1.6 % (95% CI: 0.1% - 3.2%) per 1 $ng.m^{-3}$ sources.

City of Tshwane air quality monitoring stations

The covariate data for the case crossover study was provided by the City of Tshwane air monitoring stations in the immediate surrounds. Supplementary table S1 reports the descriptive statistics for the $PM_{2.5}$, PM_{10}, NO_2 and SO_2 levels, as measured at the nine ambient air pollution monitoring stations on the 350 days when $PM_{2.5}$ was sampled at the SHSPH study site. The 'missingness' of the data varied from 2% for SO_2 monitored at the Rosslyn monitoring station to 97% for PM_{10} monitored at the Tshwane Market monitoring station. The citywide mean for $PM_{2.5}$ was 29.2 $\mu g.m^{-3}$, which is based on 168 out of the 228 days that had available data. The signed rank test indicated that the median $PM_{2.5}$ level (18.6 $\mu g.m^{-3}$) recorded at the SHSPH study site was significantly lower than that of the citywide level (26.8 $\mu g.m^{-3}$) ($p<0.001$).

During the 350-day study period, the PM_{10} levels exceeded the daily WHO guideline (50 $\mu g.m^{-3}$) on 50 days out of 210 recorded days, whilst SO_2 levels exceeded the daily WHO guideline (20 $\mu g.m^{-3}$) on 78 days out of 119 recorded days.

The timeseries for PM_{10}, NO_2 and SO_2 for the study period were also shown in Supplementary fig. S2 to S4. PM_{10} and NO_2 had a significant positive correlation (rho = 0.31, $p<0.001$), and PM_{10} and NO_2 had a negative correlation with Tapp (rho = -0.18, -0.31,

-0.14, $p<0.001$). Also, SO_2 had significantly positive correlation with NO_2 (rho = 0.83, $p<0.001$). (Supplementary table S2)

No significant associations were observed between $PM_{2.5}$, PM_{10}, NO_2 and RD hospital admissions when using this dataset.

Discussion

Total $PM_{2.5}$ is composed of constituents including organic matter, soot, black carbon and secondary constituents. The yearly average total $PM_{2.5}$ concentration for the 34-month study period was 23.2 ± 17.3 $\mu g.m^{-3}$ with a range of 0.69 – 139 $\mu g.m^{-3}$. The sum of the trace elements was 0.99 $\mu g.m^{-3}$ and makes up 12.1 % of the total $PM_{2.5}$ over the entire 34-month study period. (Table 1) The average yearly concentration was above the yearly WHO guideline (5 $\mu g.m^{-3}$) and the yearly South African NAAQS (20 $\mu g.m^{-3}$). During the study period, the 24-hour WHO guideline of 15 $\mu g.m^{-3}$ was exceeded on 217 out of the 350 samples and the 24-hour South African NAAQS of 40 $\mu g.m^{-3}$ was exceeded on 53 days. [4] The average $PM_{2.5}$ levels were significantly higher during autumn and winter compared to spring and summer ($p<0.001$).

In total, there were 15 155 reported hospitalisations due to pneumonia, bronchitis, chronic obstructive disorder, asthma, respiratory disorder syndrome, respiratory and other related respiratory disorders over the 34-month period. As mentioned, two models were applied in the case-crossover study using lag0 (exposure for the same day as hospitalisation).

The increase in respiratory hospital admissions was significantly increased by an increase in total $PM_{2.5}$ of 2.7% (95% CI: 0.6, 4.9) per 10 $\mu g/m^3$ increase. Achilleos et al[13] reported that respiratory mortality significant increased by 1.10% (95% CI: 0.59, 1.62) per 10 $\mu g.m^{-3}$ increase in total $PM_{2.5}$ in a multi city study.

When assessing the individual trace elements, respiratory hospital admissions significantly increased for Ca by 4.0 % (95% CI: 1.4% - 6.8%), Cl by 0.7 % (95% CI: 0.0% - 1.4%), Fe by 3.3 % (95% CI: 0.5% - 6.1%), K by 1.8% (95% CI: 0.2 – 3.5) and Si by 1.3 % (95% CI: 0.1% - 2.5%) per IQR of 10 $ng.m^{-3}$. (Supplementary table 1)

When assessing the association with BC and UV-PM, the increase in hospital admissions was found to be not significant but tended to have adverse effect on health when the percentage change in respiratory hospital admissions were larger than 0% for all age groups. This could imply that peaks of BC and UV-PM could influence the onset of respiratory outcomes. When stratified for age, hospital admissions did not significantly increase for the three age groups.

In contrast, the review by Atkinson et al,[25] noted that both EC and secondary inorganic aerosols were associated with adverse health effects.[25] Furthermore, Achilleos et al[13] determined that the strongest associations were found with combustion sources which produced EC and K.[13] All-cause mortality significantly increased the most with an increase in carbon compounds, 1.30% (95% CI: 0.17%, 2.43%) with an increase per 1 $\mu g.m^{-3}$. Achilleos et al[13] also found the combustion elements EC (BC in this project) and K to have the most associations with mortality.

A caveat was proposed by Achilleos et al[13], whereby constituent tracer elements that are more strongly correlated with $PM_{2.5}$ may appear to be more closely related to adverse health outcomes due to total $PM_{2.5}$.[13] After controlling for $PM_{2.5}$ in the model 2 (Supplementary table 2), fewer significant associations were observed between respiratory hospital admissions and the trace elements. Respiratory hospital admissions increased significantly for total Ca by 3.2 % (95% CI: 0.3, 6.1) and for the 0 – 14 age group by 5.2 % (95% CI: 1.5, 9.1). The associations were slightly weaker compared to model 1.

Achilleos et al[13] determined that mortality due to respiratory diseases in adults significantly increased with increased exposure to soot, EC, OC, Na, Mg, Si, Cl, K, Ca, Ti, V, Mn, Fe, Ni, Cu and Zn in 148 studies. Although Cu was 32% below the LoD for the 34 – month study,[26] when run for models 1 and 2 there was a significant increase in hospital admissions. In model 1, when stratified for age, there was a significant increase in RD due to increasing Cu by 0.5% (95% CI: 0.1% – 0.9%) and by 0.7% (95% CI: 0.1 – 1.3) for 15- to 64-year-olds. There is a significant increase for hospital admission by an increase of 0.7% (95% CI: 0.1 – 1.2) for >65 year olds. A similar outcome was found in model 2, with an increase of 0.6% (95% CI: 0.1 – 1.2) for 15- to 64-year-olds and by 0.6% (95% CI: 0.1 – 1.1) for >65 year olds. As with this study, Cu is a tracer for vehicular emissions in source apportionment studies.

Beelen et al[27] expanded on the number of models in *An Analysis of 19 European Cohorts within the Multi-Centre ESCAPE Project*. Four models were utilised, model 1 stratified for sex and timeframes similar to our model 1, but model 2 and 3 utilised more individual data. Model 4, interestingly, utilised two pollutants with a correlation <0.7.[27] Although the average yearly concentration varied considerable between cities and regions, the largest inter cohort variation occurred for S and the smallest for Si. S and Si were the two highest yearly concentrations for this project. In model 1, positive HRs were estimated for almost all single pollutant exposures, with a statistically significant association for $PM_{2.5}$ S (HR = 1.14; 95% CI: 1.06, 1.23 per 200 $ng.m^{-3}$). Borderline statistically significant associations ($p > 0.05$ and ≤ 0.10) were found for model 4, $PM_{2.5}$ Si (HR = 1.09; 95% CI: 0.99, 1.09 per 100 $ng.m^{-3}$), PM_{10} Ni (HR = 1.09; 95% CI: 1.00, 1.19 per 2 $ng.m^{-3}$), and PM_{10} K (HR = 1.03; 95% CI: 1.00, 1.06 per 100 $ng.m^{-3}$).[27] As in this project, Zn, was not found to be significant. Ni and V which are excluded in this project were also found to be poorly correlated in low concentrations.

This finding corresponds with model 4 in Beelen et al[27], where two pollutants were analysed, the HR for $PM_{2.5}$ was closer to the null and statistically nonsignificant when adjusted for $PM_{2.5}$ S (HR = 1.07; 95% CI: 1.02, 1.13 vs. HR = 1.02; 95% CI: 0.96, 1.09 per 5 $\mu g.m^{-3}$). Furthermore, the two-pollutant model resulted for $PM_{2.5}$ Si, PM_{10} K, and PM_{10} Ni because the single pollutant associations for those elements were borderline statistically significant. After adjustment for $PM_{2.5}$ S, associations with PM_{10} Ni (HR = 1.09; 95% CI: 0.98, 1.22 vs. HR = 1.06; 95% CI: 0.95, 1.18 per 2 $ng.m^{-3}$) were slightly reduced. The combined effect estimate for $PM_{2.5}$ S from the two-pollutant model adjusted for $PM_{2.5}$ did not differ from the single-pollutant model estimate.[27]

Similar outcomes were found in Wang et al[28] where in a study of eight pooled European cohorts, the study utilised the Cox proportional analysis and additional personal information. The hazard ratio (HR) for death was 1.021 (95% confidence interval: 1.019–1.022) per one $\mu g.m^{-3}$ increase in annual $PM_{2.5}$, the risk associated with $PM_{2.5}$ increased with relative concentration of elemental carbon, vanadium, copper, calcium, and iron and decreased with nitrate, organic carbon, and sulphate.

In this project, Br had a positive HR, 2.6% (95% CI: 0.2, 5.2) and an IQR (11.6) for females in model 1, and not in model 2 when controlled for $PM_{2.5}$. Of interest, Br as a strong

positive correlation with $PM_{2.5}$ (rho = 0.81, p<0.001).[26] The same would apply for the following 4 trace elements which were found to be positively associated for model 1, but not for model 2, Cl (rho = 0.55, p<0.001), Fe (rho = 0.67, p<0.001), K (rho = 0.55, p<0.001) and Si (0.39, p<0.001). Cl and K were correlated for the 34 – month study (rho=0.72, p<0.001) and were tracers for biomass burning. These were determined to be not significantly associated in the second model. (Supplementary table S3)

Association with the sources of $PM_{2.5}$ and hospital admissions

The model is controlled for Tapp, public holiday and monthyear. There was a significant increase in hospital admissions with an increase in resuspended dust matrix by 2.9 % (95% CI: 0.1% - 5.7%) and for the biofuel burning, by 1.6 % (95% CI: 0.1% - 3.2%) sources. Ca is a tracer for course particulates in source apportionment. This includes resuspended dust and for biofuel and coal burning. In model 2, when controlling for $PM_{2.5}$, Ca was the only significantly associated trace element when modelled. Vulnerable ages, 0-14 and >65 are also determined to be significantly associated with increase in Ca.

This was in line with a review by Hopke et al[29], which found that hospital admissions increased significantly with the same sources. Here an increase of 2.5% (95% CI: 0.0% 5.1%) for road dust and an increase of 3.0% (95% CI 0.3%, 5.7%) by biofuels by incremental increase of 1 $\mu g.m^{-3}$. The study took place in New York from 2005 to 2016.

Hospital admission did not significantly increase with an increase in factors allocated to mining and vehicular emissions but had a tendency to have adverse effect as % change in respiratory hospital admissions tended to 0%. The factor allocated to exhaust resulted in not being significant, but with a tendency to not to have adverse effect as % change in RD hospital admissions tended to 0%. This too was similar to the Hopke et al[29] study as the source allocated to ignition fumes and emissions, brake pad particulates and fuel additives was also allocated in the same way for the Pretoria study. The road dust and residual oil factors resulted in an increase in IQR for asthma but a decrease in COPD.[30] The protective nature of the result could be due to the lag time being longer than 3 days or in the Pretoria study lag0 as well as the complex nature of the constituents of $PM_{2.5}$ and the factor allocation.

The outcome was further supported by two other studies where, in a study by Karakatsani et al[31] , in four European cities, a 10 μg/m^3 increase in previous day coarse particles concentrations was positively associated with most symptoms (an increase of 0.6 to 0.7% in average) (OR= 1.076, 95% CI: 1.026-1.128). In Bachwenkizi et al[32] various models were utilised for the health study. In the single-constituent model, for an IQR increase in pollutant concentrations, the odds ratio (OR) of infant mortality was 1.03 (95 %CI; 1.01, 1.06) for PM2.5 total mass, and was 1.04 (95 %CI: 1.02, 1.06), 1.04 (95 %CI: 1.02, 1.05), 1.02 (95 %CI: 1.00, 1.03), 1.04 (1.01, 1.06) for BC, OM, SO_4^{2-}, and dust, respectively.

In Croft et al[33], where the rate of respiratory infection was associated with increased concentrations of source-specific $PM_{2.5}$ in New York found that increased rates of emergency room visits for influenza were associated with interquartile range increases in concentrations of spark ignition vehicle emissions (excess rate = 9.2%; 95% CI: 4.3%, 14.3%) and diesel (excess rate = 3.9%; 95% CI: 1.1%, 6.8%) for lag days 0-3.

In a recent health risk assessment using the same dataset, it was found that the hazard quotient (HQ) for total $PM_{2.5}$, Cl, K, Si and Ti was above 1 for all year for infants and children and above 1 for S and Si for adults.[26]

When analysing the influence of sources of $PM_{2.5}$, the confounding was treated differently in methods 3 and 4 where residuals were included. This approach accommodated confounding by pre-empting the possibility of certain factors appearing to be more toxic than another due to $PM_{2.5}$ being related to both constituent concentration and health outcomes.[34] The results were the same as in model 2. This was slightly in contrast to the Hopke et al[30] study where the model run with the $PM_{2.5}$ residuals was slightly lower for all factors. The size of the New York dataset (10 years) was much larger than the Pretoria study (34 months) which could play a role in the outcome when utilising residuals.

For the criteria air pollutants (PM_{10}, NO_2 and SO_2), we utilised the data from the City of Tshwane (CoT) monitoring station database. (Supplementary table S1 and S2) PM_{10} and NO_2 had a significant positive correlation (rho = 0.31, p<0.001), and PM_{10} and NO_2 had a negative correlation with Tapp (rho = -0.18, -0.31, -0.14, p<0.001). Also, SO_2 had significantly positive correlation with NO_2 (rho = 0.83, p<0.001). In Supplementary table S2, the summary statistics of the CoT dataset for 350 days notes that there is 55% missing

datapoints for the calculated citywide total $PM_{2.5}$, 60% of PM_{10}, 88% of NO_2 and 90% of SO_2. All the correlation were significant between CoT data, Tapp, windspeed, temperature and relative humidity. (Supplementary table S4)

No significant association was observed between $PM_{2.5}$ and PM_{10} and respiratory hospital admissions. In addition, there was increase in respiratory hospital admissions for NO_2 and SO_2. This was contrary to what was reported in other studies conducted in urban areas. The results may have been influenced by the amount of missing data in the dataset.

In contrast, Thabethe et al[35] studied the association between PM_{10}, NO_2 and SO_2 and CVD and respiratory deaths where daily mean concentrations of PM_{10}, NO_2, and SO_2 in Cape Town were 32.7, 17.5, and 10.4 $\mu g.m^{-3}$, respectively, during the 5-year study period. In Cape Town, an inter-quartile range (IQR) of 17 $\mu g/m_3$ increase in the CA2 (2-day cumulative average) of PM_{10} increased RD mortality for all ages by 0.8% (95% CI:$_{2.5}$%, 4.1%). The association between PM_{10} and RD mortality was stronger for women than men. In a similar study by Wichmann *et. al.,* (2014) in Gothenburg between 1990 and 2000, found a very strong association between hospitalisations due to acute myocardial infarction and PM_{10} (4.1%, 95% CI 0.2% − 8.2%). In a review by Ab Manan et al[9] hospital admissions for respiratory diseases in 28 studies resulted in a pooled estimate of an increased risk of hospitalization by $PM_{2.5}$ (1.1 to 1.8); PM_{10} (1.007 to 1.13); NO_2 (1.08 to 1.94) and SO_2 (1.02). A reason for the discrepancy with our estimates may be that the above studies took place in Europe, the USA and Australia. Cape Town has similar PM and priority chemical compound yearly concentrations to Europe, but Pretoria is currently higher.[23]

Although no association was found in the Karakatsani et al[31] study for NO_2, in Goeminne et al[36], a case-crossover study was done for the association between bronchiectasis and outdoor air pollutants in Dundee, UK. For each 10 $\mu g/m^3$ increase in PM_{10} and NO_2, the risk of having an exacerbation that same day increased significantly by 4.5% (95% CI: 0.9–8.3) and 3.2% (95% CI: 0.7–5.8), respectively. The overall (lag 0-4) increase in risk of exacerbation for a 10 $\mu g/m^3$ increase in air pollutant concentration was 11.2% (95% CI: 6.0–16.8) for PM_{10} and 4.7% (95% CI: 0.1–9.5) for NO_2. Sub analysis showed higher relative risks during spring (PM_{10} 1.2 (95% CI: 1.1–1.3), NO_2 1.146 (95% CI: 1.0–1.3)) and

summer (PM_{10} 2.1 (95% CI 1.8–2.6), NO_2 1.4 (95% CI: 1.1–1.6)) when outdoor air pollution exposure would be expected to be highest.

Conclusion

In the initial model where the association was controlled for Tapp and (weekends) monthyear, the result was a significant increase in respiratory hospital admissions with an increase in Ca, Cl, Fe, K and Ti (IQR 10μg.m^{-3}). When controlling for $PM_{2.5}$ too, increase in hospital admission is significant with an increase in Ca (IQR 10μg.m^{-3}) exposure only. By considering strong the presence of positive associations with $PM_{2.5}$, one can avoid overestimation albeit a very conservative result. The cause of this strong association may be due to Pretoria being situated in a region which experiences dry winters and wet summers. In winter the average total $PM_{2.5}$ is five times higher than in summer. The sources attributed to the mean concentration of $PM_{2.5}$ were both ubiquitous and seasonal. Trace elements are tracers for flue gas emissions from coal fuelled power stations as well as biomass burning during the winter months. The increase in respiratory hospital admissions is significantly increased with and an increase in $PM_{2.5}$ allocated to resuspended dust matrix and biofuel burning sources. It is recommended that urban areas consider the sources (both seasonal and ubiquitous) when updating the Municipal Air Quality Management Plans.

Funding details

Sampling during the study period 16 April 2017 to 31 December 2019 was funded by the National Research Foundation under grant [CPT160424162937]. Sampling during the study period 1 January to 28 February 2020 was funded by the University of Pretoria, South Africa [no grant number].

Disclosure statement

The authors report there are no competing interests to declare.

Availability of data and material

Upon request, but then the authors want to be co-authors on the other study's manuscript.

Ethics approval

Ethics approval was done through the University of Pretoria Research Committee, number 300/20

Acknowledgements

The authors would like to thank the South African Weather Services for the air pollution data of the City of Tshwane and for the meteorology data.

Reference

1. Wichmann J, Sjöberg K, Tang L, Haeger-Eugensson M, Rosengren A, Andersson E, Barregard L, Sallsten G: The effect of secondary inorganic aerosols, soot and the geographical origin of air mass on acute myocardial infarction hospitalisations in Gothenburg, Sweden during 1985–2010: a case-crossover study. Env Health **2014**, *13*(1):61-77.

2. Prevention and Control of Noncommunicable Diseases: Guidelines for primary health care in low resource settings [https://apps.who.int/iris/bitstream/handle/10665/76173/9789241548397_eng.pdf]

3. World Health Organization: The cost of a polluted environment: 1.7 million child deaths a year, says WHO. **2019**.

4. World Health Organization: WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organisation; 2021.

5. Fisher S, Bellinger DC, Cropper ML, Kumar P, Binagwaho A, Koudenoukpo JB, Park Y, Taghian G, Landrigan PJ: Air pollution and development in Africa: impacts on health, the economy, and human capital. The Lancet Planetary Health **2021**, *5*(10):e681-e688.

6. Thabethe NDL, Voyi K, Wichmann J: Association between ambient air pollution and cause-specific mortality in Cape Town, Durban, and Johannesburg, South Africa: any susceptible groups? Environ Sci Pollut Res **2021**, *28*:42868-42876.

7. SASTATS: Mortality and causes of death in South Africa:

Findings from death notification P0309.3. In.; 2018.

8. Agbo EP, Ekpo CM, Edet CO: Analysis of the effects of meteorological parameters on radio refractivity, equivalent potential temperature and field strength via Mann-Kendall test. Theor Appl Climatol **2021**, *143*(3):1437-1456.

9. Ab Manan N, Noor Aizuddin A, Hod R: Effect of Air Pollution and Hospital Admission: A Systematic Review. Ann Glob Health **2018**, *84*(4):670-678.

10. Pope III CA, Lefler JS, Ezzati M, Higbee JD, Marshall JD, Kim S-Y, Bechle M, Gilliat KS, Vernon SE, Robinson AL: Mortality risk and fine particulate air pollution in a large, representative cohort of US adults. Environmental health perspectives **2019**, *127*(7):077007.

11. Wichmann J, Voyi K: Ambient Air Pollution Exposure and Respiratory, Cardiovascular and Cerebrovascular Mortality in Cape Town, South Africa: 2001–2006. Int J Environ Res Public Health **2012**, *9*(11):3978-4016.

12. Shezi B, Wright CY: Household air pollution exposure and respiratory health outcomes: A narrative review update of the South African epidemiological evidence. Clean Air J **2018**, *28*(1):43-56.

13. Achilleos S, Kioumourtzoglou M-A, Wu C-D, Schwartz JD, Koutrakis P, Papatheodorou SI: Acute effects of fine particulate matter constituents on mortality: A systematic review and meta-regression analysis. Environ Int **2017**, *109*:89-100.

14. Sah D, Verma PK, Kumari KM, Lakhani A: Chemical partitioning of fine particle-bound As, Cd, Cr, Ni, Co, Pb and assessment of associated cancer risk due to inhalation, ingestion and dermal exposure. Inhal Toxicol **2017**, *29*(11):483-493.

15. Lee ES, Koh HL, Ho EQ, Teo SH, Wong FY, Ryan BL, Fortin M, Stewart M: Systematic review on the instruments used for measuring the association of the level of multimorbidity and clinically important outcomes. BMJ Open **2021**, *11*(5):e041219.

16. Stats S: Mid-year population estimates 2020: STATISTICAL RELEASE P0302. Pretoria: Stats SA **2020**.

17. Howlett-Downing C: Associations of PM2.5 and respiratory diseases in Pretoria, 2017-2020. In. Edited by Pretoria Uo, Dissertation for PhD edn. Pretoria; 2022: 375.

18. Howlett-Downing C, Boman J, Molnár P, Shirinde J, Wichmann J: PM2.5 Chemical Composition and Geographical Origin of Air Masses in Pretoria, South Africa. Water Air Soil Pollut **2022**, *233*(7):1-13.

19. Mwase N: Human health risks of inhalable exposure to PM2.5 Pretoria, South Africa. MSc (Epidemiology) Dissertation. University of Pretoria; **2020**.

20. Hyslop NP, White WH: Estimating precision using duplicate measurements. J Air Waste Manag Assoc **2009**, *59*(9):1032-1039.

21. Zhang Y, Wang SG, Ma YX, Shang KZ, Cheng YF, Li X, Ning GC, Zhao WJ, Li NR: Association between Ambient Air Pollution and Hospital Emergency Admissions for Respiratory and Cardiovascular Diseases in Beijing: a Time Series Study. Biomedical and Environmental Sciences **2015**, *28*(5):352-363.

22. Wichmann J, Sjöberg K, Tang L, Haeger-Eugensson M, Rosengren A, Andersson EM, Barregard L, Sallsten G: The effect of secondary inorganic aerosols, soot and the geographical origin of air mass on acute myocardial infarction hospitalisations in Gothenburg, Sweden during 1985–2010: a case-crossover study. Env Health **2014**, *13*(1).

23. Wichmann J, Voyi K: Ambient air pollution exposure and respiratory, cardiovascular and cerebrovascular mortality in Cape Town, South Africa: 2001-2006. IJERPH **2012**, *9*(11):3978-4016.

24. Ueda K, Yamagami M, Ikemori F, Hisatsune K, Nitta H: Associations Between Fine Particulate Matter Components and Daily Mortality in Nagoya, Japan. J Epidemiol **2016**, *26*(5):249-257.

25. Atkinson RW, Mills IC, Walton HA, Anderson HR: Fine particle components and health—a systematic review and meta-analysis of epidemiological time series studies of daily mortality and hospital admissions. Journal of Exposure Science & Environmental Epidemiology **2015**, *25*(2):208-214.

26. Howlett-Downing C, Shirinde J, Wichmannn J: Health risk assessment of PM2.5 and PM2.5-bound trace elements in Pretoria, South Africa. In: ISEE Conference Abstracts: 2022.

27. Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, Wolf K, Samoli E, Fischer P, Nieuwenhuijsen M: Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. The lancet **2014**, *383*(9919):785-795.

28. Wang Y, Shi L, Lee M, Liu P, Di Q, Zanobetti A, Schwartz JD: Long-term Exposure to PM2.5 and Mortality Among Older Adults in the Southeastern US. Epidemiology (Cambridge, Mass) **2017**, *28*(2):207-214.

29. Hopke PK, Dai Q, Li L, Feng Y: Global review of recent source apportionments for airborne particulate matter. Science of The Total Environment **2020**, *740*:140091.

30. Hopke PK, Croft DP, Zhang W, Lin S, Masiol M, Squizzato S, Thurston SW, van Wijngaarden E, Utell MJ, Rich DQ: Changes in the hospitalization and ED visit rates for respiratory diseases associated with source-specific PM2.5 in New York State from 2005 to 2016. Environ Res **2020**, *181*:108912.

31. Karakatsani A, Analitis A, Perifanou D, Ayres JG, Harrison RM, Kotronarou A, Kavouras IG, Pekkanen J, Hämeri K, Kos GPA et al: Particulate matter air pollution and respiratory symptoms in individuals having either asthma or chronic obstructive pulmonary disease: a European multicentre panel study. Env Health **2012**, *11*(1):75.

32. Bachwenkizi J, Liu C, Meng X, Zhang L, Wang W, van Donkelaar A, Martin RV, Hammer MS, Chen R, Kan H: Fine particulate matter constituents and infant mortality in Africa: A multicountry study. Environ Int **2021**, *156*:106739.

33. Croft DP, Zhang W, Lin S, Thurston SW, Hopke PK, van Wijngaarden E, Squizzato S, Masiol M, Utell MJ, Rich DQ: Associations between source-specific particulate matter and respiratory infections in New York State adults. Environ Sci Technol **2019**, *54*(2):975-984.

34. Mostofsky E, Schwartz J, Coull BA, Koutrakis P, Wellenius GA, Suh HH, Gold DR, Mittleman MA: Modeling the Association Between Particle Constituents of Air Pollution and Health Outcomes. AJE **2012**, *176*(4):317-326.

35. Thabethe NDL, Voyi K, Wichmann J: Association between ambient air pollution and cause-specific mortality in Cape Town, Durban, and Johannesburg, South Africa: any susceptible groups? Environ Sci Pollut Res **2021**.

36. Goeminne PC, Cox B, Finch S, Loebinger MR, Bedi P, Hill AT, Fardon TC, de Hoogh K, Nawrot TS, Chalmers JD: The impact of acute air pollution fluctuations on bronchiectasis pulmonary exacerbation: a case-crossover analysis. European Respiratory Journal **2018**, *52*(1).

Figures and tables

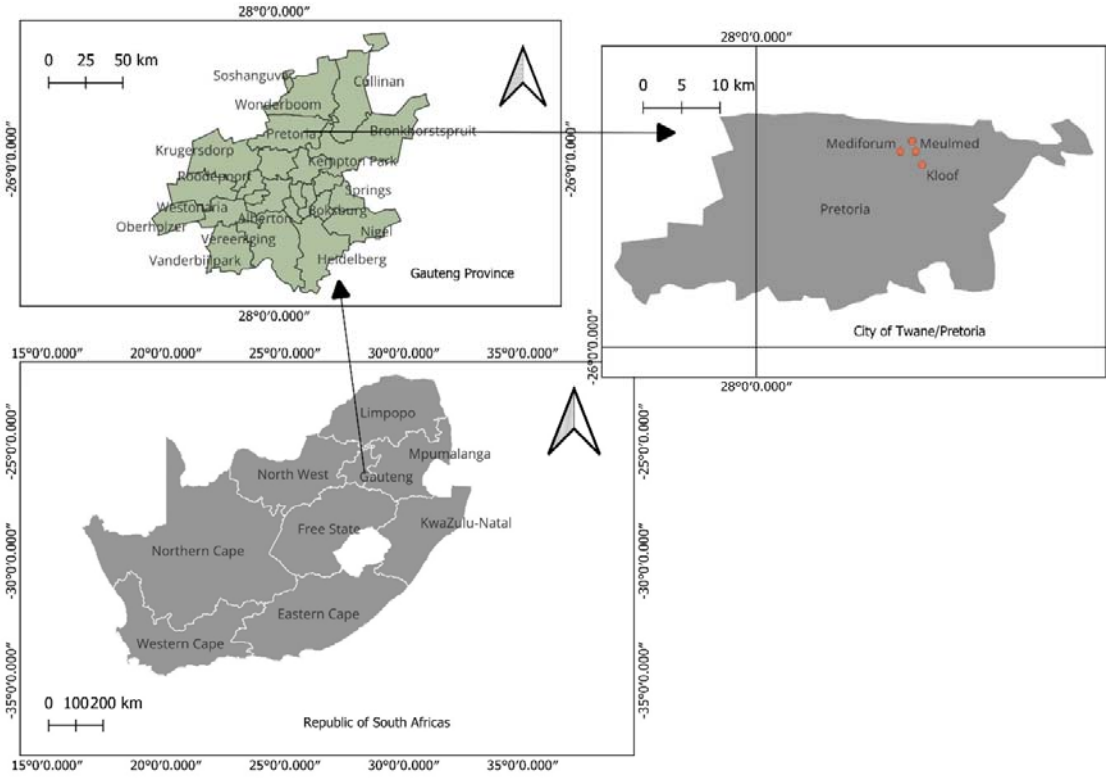


Fig 1.

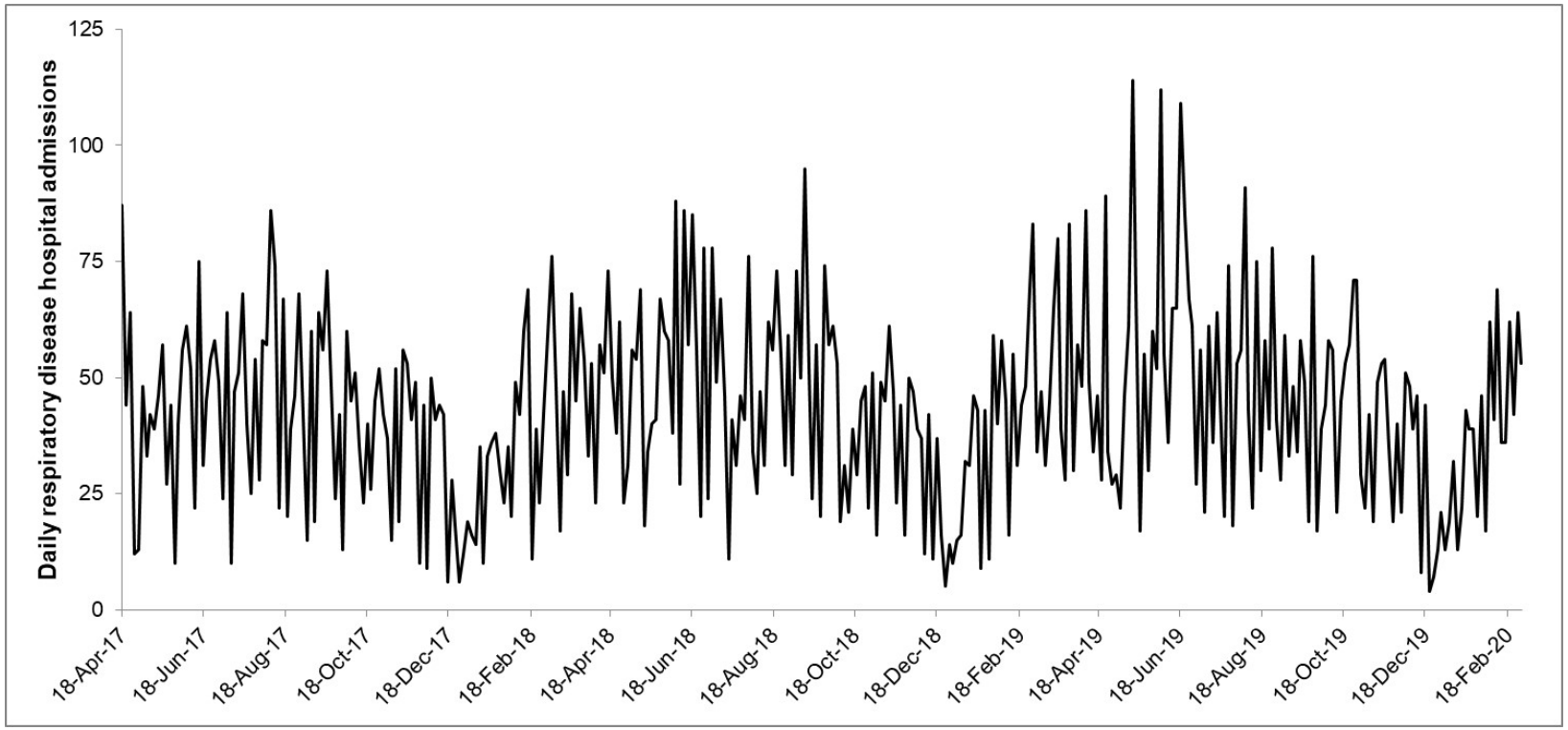
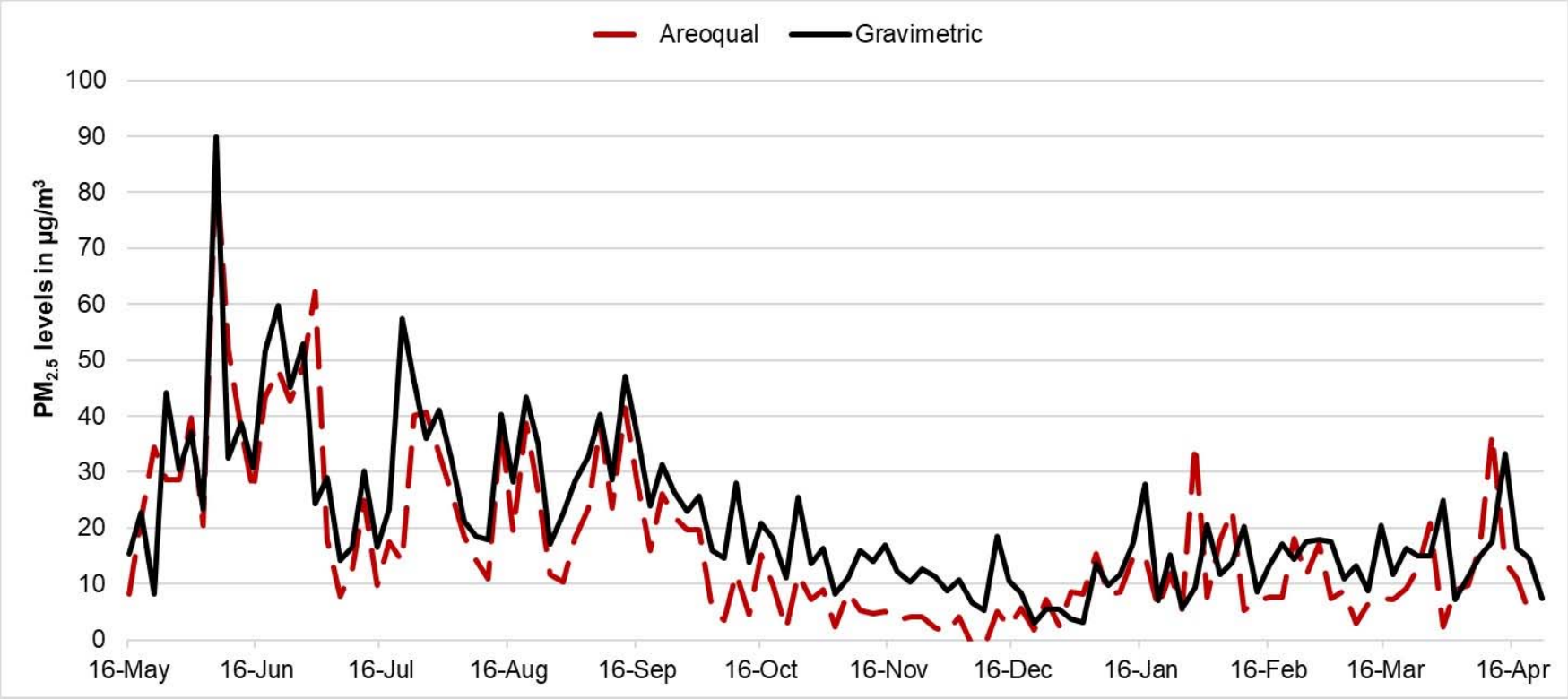
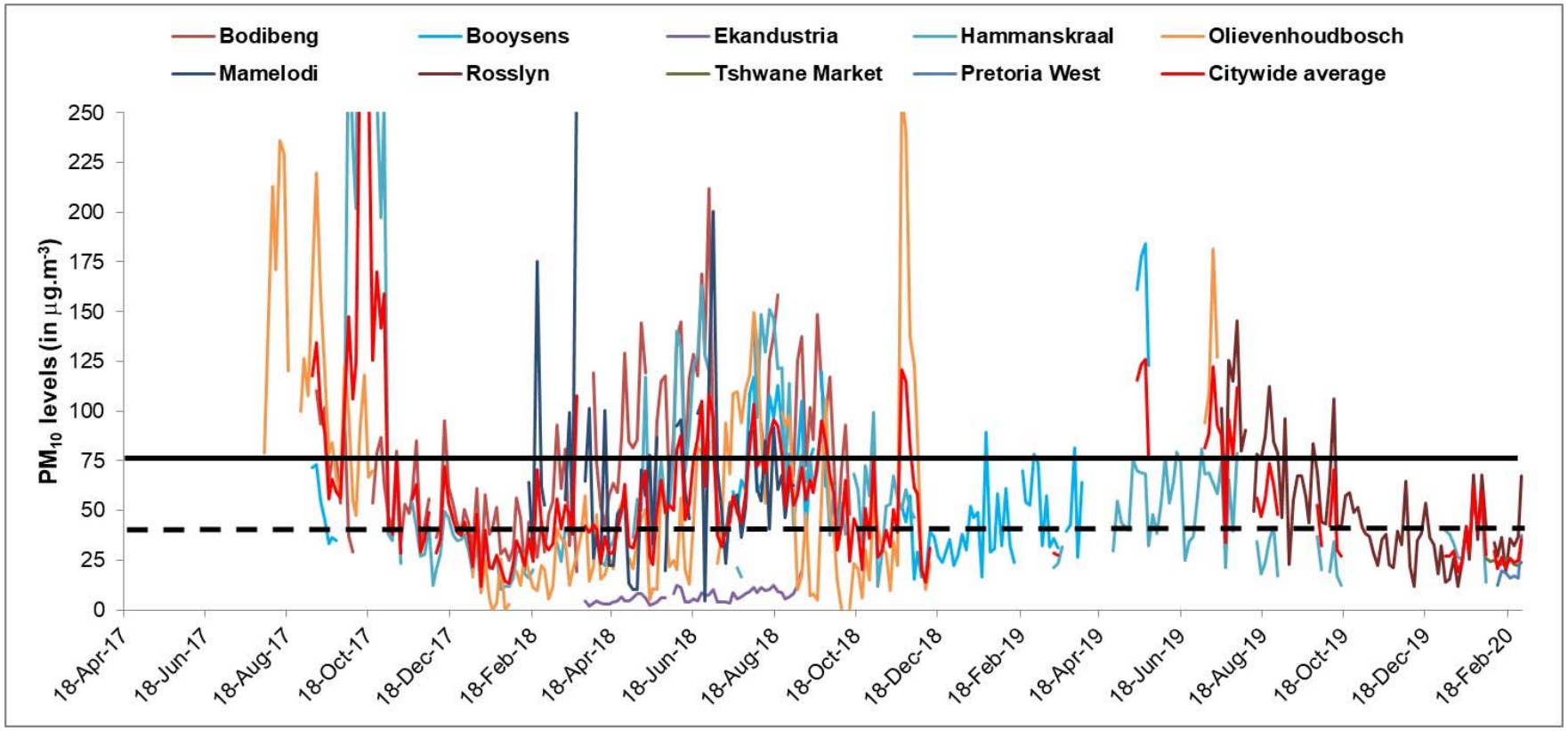

Daily respiratory disease hospital admissions
125
100
75
50
25
0
18-Apr-17
18-Jun-17
18-Aug-17
18-Oct-17
18-Dec-17
18-Feb-18
18-Apr-18
18-Jun-18
18-Aug-18
18-Oct-18
18-Dec-18
18-Feb-19
18-Apr-19
18-Jun-19
18-Aug-19
18-Oct-19
18-Dec-19
18-Feb-20

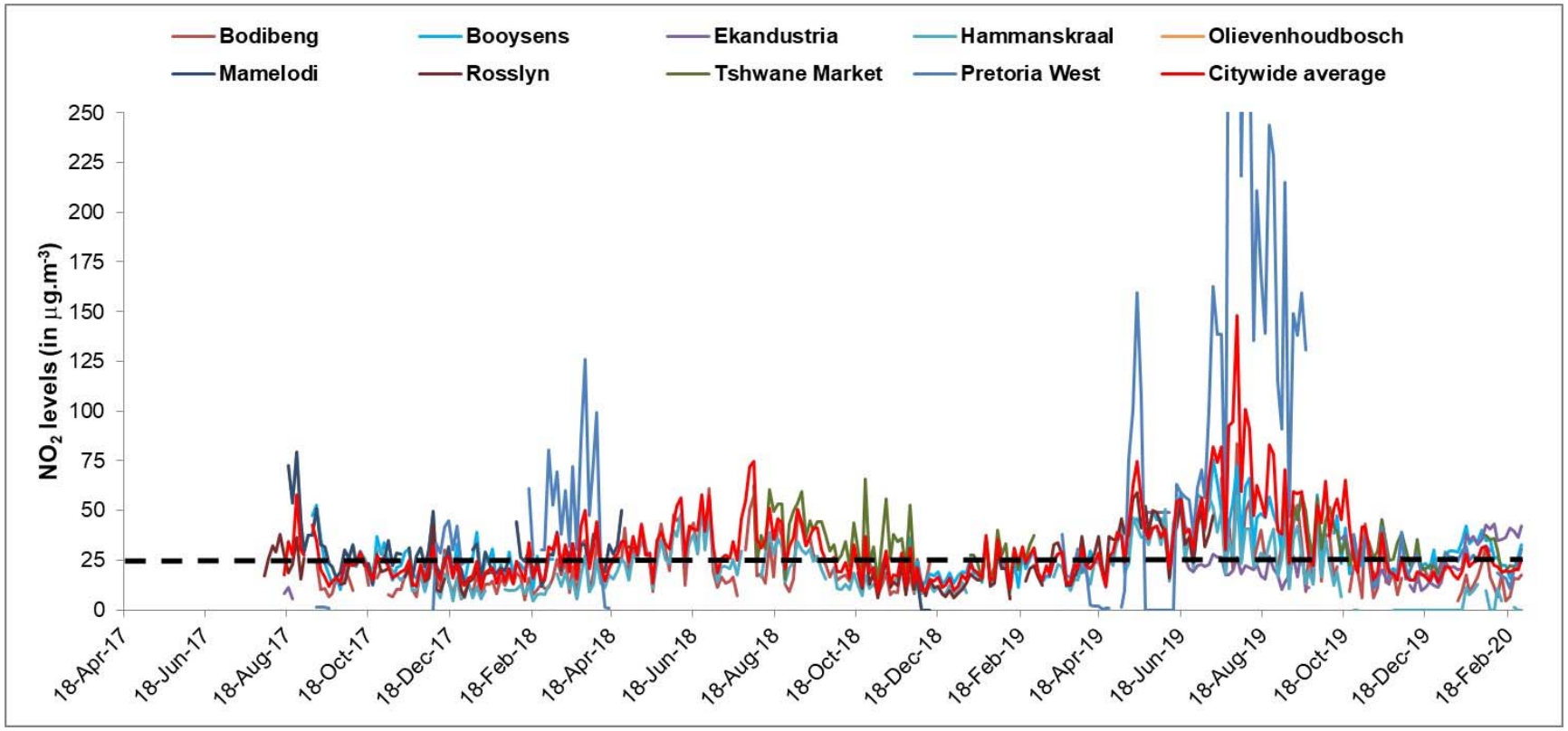
Fig.2:



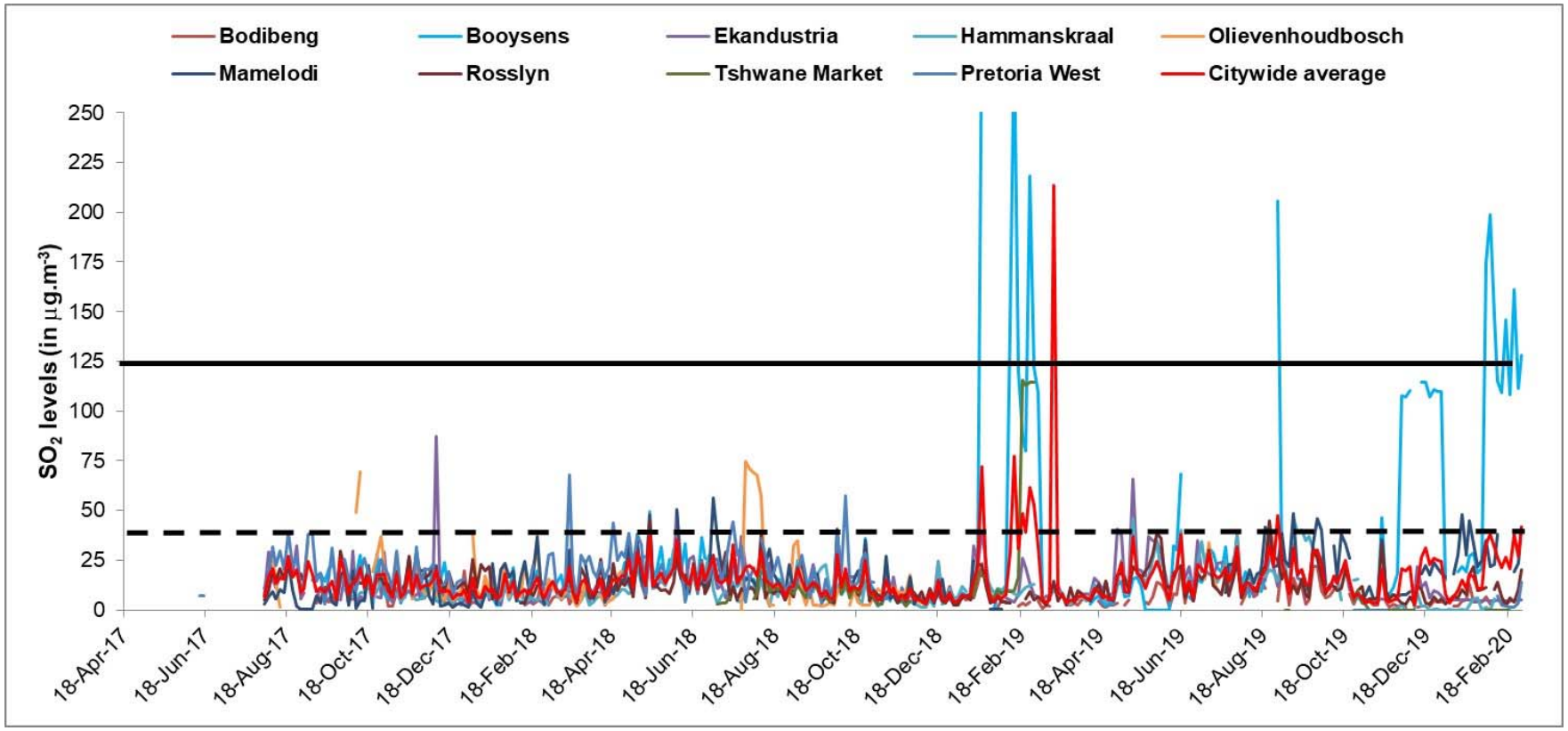
Supplementary Fig. S1



Supplementary Fig. S2



Supplementary Fig. S3



Supplementary Fig. S4

Table 1: Summary statistics for 24-hour $PM_{2.5}$ and the trace elements measured at the School of Health Systems and Public Health, University of Pretoria during 18 April 2017 and 28 February 2020 (350 days).

Variable	Mean	Std Dev	Median	Min	Max
$PM_{2.5}$	23.2	17.3	17.7	0.7	139
Soot	1.8	1.7	1.0	0.0	11.0
BC	3.1	2.5	2.1	0.2	11.4
UV-PM	2.5	1.7	2.1	0.1	7.6
Temperature	19	4	20	9	27
Relative humidity	59	17	61	13	99
Windspeed	1.1	0.8	1.2	0.0	4.2
Rainfall	1.4	6.9	0.0	0.0	96.8
Br	17	23	8.6	0.2	254
Ca	156	160	106	0	997
Cl	53	129	11.8	0.0	1238
Fe	297	216	261	1.7	1454
K	251	327	115.9	1.5	1917
S	1175	1752	496	0.4	11841
Si	646	687	507	4.1	5532
Ti	34	29	27.7	0.5	212
Zn	57	91	20.5	0.1	809

Units: $PM_{2.5}$ ($\mu g.m^{-3}$), soot ($m^{-1} \times 10^{-5}$), BC ($\mu g.m^{-3}$), UV-PM ($\mu g.m^{-3}$), temperature (^{o}C), relative humidity (%), windspeed (ms^{-1}), rainfall (mm), trace elements ($ng.m^{-3}$)

No missing values, except for four soot values

Table 2: Descriptive statistics of the daily number of respiratory disease hospital admissions at three private hospitals in Pretoria, South Africa during 18 April 2017 to 28 February 2020 on the 350 days that $PM_{2.5}$ was sampled at the School of Health Systems and Public Health, University of Pretoria

Group	Mean	Min	Median	Max
All ages and both sexes (n=15155)	43.3	4.0	44.0	114.0
Females (n=8060)	23.0	0.0	23.0	61.0
Males (n=7095)	20.3	0.0	20.0	66.0
0-14 year olds (n=8225)	23.5	0.0	23.0	71.0
15-64 year olds (n=4932)	14.1	0.0	14.0	37.0
≥65 year olds (n=1998)	5.7	0.0	5.0	25.0

Abbreviations: Max: maximum value; Min: minimum value

Table 3: Descriptive statistics of the daily number of specific respiratory disease hospital admissions at three private hospitals in Pretoria, South Africa during 18 April 2017 to 28 February 2020 on the 350 days that $PM_{2.5}$ was sampled at the School of Health Systems and Public Health, University of Pretoria: By age group and sex

		Female			Male		
Age group	**Variable**	**Mean**	**Std. Dev.**	**Range**	**Mean**	**Std. Dev.**	**Range**
>14	All respiratory disease (J00–J99)	11.00	6.80	1 - 38	13	8.1	1 - 49
	Pneumonia (J12–J18)	7.00	5.00	0 - 33	8.5	6.6	0 - 41
	Bronchitis (J40–J42)	0.10	0.23	0 - 5	0.006	0.11	0 - 2
	Chronic obstructive pulmonary disease (J44)	0.00	0.00	0.00	0.004	0.1	0 - 3
	Emphysema (J43)	0.00	0.00	0.00	0.00	0.00	0.00
	Asthma (J45–J46)	1.60	2.30	0 - 14	2.4	2.8	0 - 16
	Respiratory distress syndrome (J80)	0.50	0.40	0 - 6	0.075	0.48	0 - 7
	Other diseases of the respiratory system (J95, J97–J99)	0.20	0.79	0 - 6	0.12	0.78	0 - 8
	Respiratory failure (J96)	0.05		0 - 4	0.076	0.48	0 - 6
15-64	All respiratory disease (J00–J99)	9.80	5.70	1 - 29	5.4	3.7	1 - 27
	Pneumonia (J12–J18)	2.50	2.70	0 - 15	1.6	2.1	0 - 20
	Bronchitis (J40–J42)	0.05	0.31	0 - 4	0.016	0.18	0 - 3
	Chronic obstructive pulmonary disease (J44)	0.25	0.88	0 - 11	0.29	0.86	0 - 8
	Emphysema (J43)	0.06	0.40	0 - 6	0.12	0.72	0 - 11
	Asthma (J45–J46)	4.20	3.40	0 - 22	1.6	1.7	0 - 11
	Respiratory distress syndrome (J80)	0.63	1.40	0 - 11	0.56	1.4	0 - 13
	Other diseases of the respiratory system (J95, J97–J99)	0.73	1.40	0 - 11	0.58	1.5	0 - 19
	Respiratory failure (J96)	0.41	1.20	0 - 10	0.47	1.5	0 - 19
64<	All respiratory disease (J00–J99)	3.90	2.70	1 - 15	3.5	2.7	1 - 15
	Pneumonia (J12–J18)	1.70	2.10	0 - 14	1.6	2.2	0 - 12
	Bronchitis (J40–J42)	0.10	0.56	0 - 8	0.037	0.28	0 - 4
	Chronic obstructive pulmonary disease (J44)	0.72	1.40	0 - 9	1	1.7	0 - 10
	Emphysema (J43)	0.29	0.97	0 - 8	0.48	1.2	0 - 9
	Asthma (J45–J46)	1.40	1.50	0 - 12	0.96	1.7	0 - 13
	Respiratory distress syndrome (J80)	0.49	1.30	0 - 10	0.61	1.5	0 - 10
	Other diseases of the respiratory system (J95, J97–J99)	0.77	1.50	0 - 9	0.86	1.8	0 - 13
	Respiratory failure (J96)	0.37	1.10	0 - 8	0.5	1.5	0 - 13

Table 4: Apparent temperature for all year and the seasons for 16 April 2017 to 28 February 2020 as a function of relative humidity, wind speed and average temperature as reported by the South African Weather Services (SAWS).

		Seasons			
Pretoria Tapp	**All (350)**	**Autumn (78)**	**Winter (90)**	**Spring (92)**	**Summer (90)**
Mean and SD	18.8 ± 5.31	18.4 ± 4.3	12. ± 8 3	20 ± 3.5	23.8 ± 2.9
Range	6.27 - 30.6	10.2 - 30	6.3 - 20.9	10.9 - 27.9	15.2 - 30.6
Percentiles					
25th 95%CI	14.2 (13.3, 15.4)	15 (13.7, 16.4)	10.9 (10, 11.4)	18.2 (17.3, 19.4)	22.2 (21.3, 23.4)
50th 95%CI	19.1 (18.4, 20.1)	18 (17.3, 19)	12.3 (11.7, 13.3)	20.2 (19.3, 21.4)	24.2 (23.8, 25.4)
75th 95%CI	23.4 (24.4, 25.9)	22 (19.8, 22.2)	14.7 (13.6, 16.1)	23 (22.3, 24.4)	25.8 (25.3, 26.3)
Average Temperature					
Mean and SD	19 ± 4.1	18.4 ± 3.0	14 ± 2.6	21 ± 2.9	23 ± 2.2
Range	8.9 - 26.9	11.7 - 26	8.9 - 21	13.7 - 26	8.9 - 21
Percentiles					
25th 95%CI	15.9 (15, 16.8)	16.6 (15.5, 17.2)	12.8 (12.3, 13.5)	19.3 (18.3, 20.2)	21.7 (21.3, 22.3)
50th 95%CI	19.6 (18.8, 20.5)	18 (17.73, 18.8)	14.3 (14, 14.8)	21.3 (20.6, 21.7)	23.3 (22.5, 23.8)
75th 95%CI	22.7 (22, 23.4)	20 (19.1, 21.6)	16.5 (15.2, 17.9)	22.9 (22.4, 24.1)	24.2 (24, 24.8)
Relative Humidity					
Mean and SD	59.3 ± 17.4	68.8 ± 14.4	59 ± 17	47 ± 17	64 ± 13
Range	13 - 99	29 - 97	19 - 94	13 - 97	19 - 94
Percentiles					
25th 95%CI	49(46,52)	59.5 (54, 63.7)	47 (44.4, 53)	32.3 (29.6, 38.9)	56(53.2, 61)
50th 95%CI	61 (58.6,63)	67.5 (65, 71.2)	58 (54, 63)	47 (44, 52.9)	64 (62, 66)
75th 95%CI	70 (68.6,72)	79.3 (73.5, 84.3)	73 (65.8, 76)	60.4(56, 94.9)	70 (67.7, 72)
Wind speed					
Mean and SD	1.3 ± 0.54	1.0 ± 0.48	0.99 ± 0.44	1.6 ± 0.47	1.5 ± 0.44
Range	0 - 3	0 - 2.4	0.2 - 2.2	0.8 - 2.9	0.2 - 2.2
Percentiles					
25th 95%CI	0.9 (0.8, 1.0)	0.7 (0.6, 0.8)	0.6 (0.6, 0.7)	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)
50th 95%CI	1.3 (1.2, 1.3)	1 (0.9, 1.1)	0.9 (0.8, 1)	1.5 (1.4, 1.7)	1.5 (1.3,1.6)
75th 95%CI	1.6(1.6, 1.7)	1.3 (1.2, 1.4)	1.3 (1.1, 1.4)	1.9(1.8, 2.1)	1.8 (1.7, 2)

Table 5: Model 1: Percentage change (95% CI) in daily respiratory disease hospital admissions per increment increase in an air pollutant level (lag0) measured at the School of Health Systems and Public Health, University of Pretoria during 18 April 2017 to 28 February 2020 (350 days).

Air pollutant	All	0-14 year old	15-64 year old	≥65 year old	Females	Males
$PM_{2.5}$	**2.7 (0.6, 4.9)**	**3.6 (0.8, 6.5)**	2.5 (-0.7, 5.8)	-0.3 (1.0, 1.1)	2.6 (-0.1, 5.4)	**2.9 (0.1, 5.7)**
BC	1.1(-0.7, 2.8)	0.6(-1.7, 2.9)	1.7 9-0.9, 4.2)	1.7(-2.1, 5.6)	1.8(-0.4, 4.0)	0.3(-2.0, 2.6)
UV-PM	1.8(-1.0, 4.6)	0.9(-2.7, 4.6 0	2.4(-1.6, 6.6)	3.9(-2.2, $_{10}$.3)	2.7(-0.8, 6.2)	0.7(-2.8, 4.4)
Soot	1.6(-0.4, 3.7)	2.1(-0.7, 4.9)	0.4(-2.6, 3.6)	2.7(-1.9, 7.50	**5.8 (0.6, 11.3)**	0.5(-7.6, 9.2)
Br	1.6 (-0.4, 3.7)	1.5(-1.1, 4.2)	2.0(-1.0, 5.0)	1.5(-3.1, 6.4)	**2.6 (0.2, 5.2)**	0.4(-2.3, 3.2)
Ca	**4.0 (1.4, 6.8)**	**6.2 (2.7, 9.8)**	1.6(-2.3, 5.7)	-0.1(-6.1, 6.2)	**3.8 (0.5, 7.3)**	**4.3 (0.8, 7.9)**
Cl	**0.7 (0.0, 1.4)**	1.0(0.0, 1.9)	0.5(-0.5, 1.5)	0.2(-1.5, 1.8)	**0.9 (0.1, 1.8)**	0.4(-0.5, 1.4)
Fe	**3.3 (0.5, 6.1)**	**5.2 (1.6, 9.0)**	1.4(-2.7, 5.6)	-0.3(-6.3, 6.1)	**3.6(0.1, 7.2)**	2.9(-0.7, 6.6)
K	**1.8 (0.2, 3.5)**	**2.9 (0.7, 5.1)**	0.5(-2.0, 3.1)	0.1(-3.7, 4.1)	1.6(-0.5, 3.7)	2.2(0.0, 4.4)
S	1.5 (-0.3, 3.4)	2.1(-0.3, 3.6)	1.0(-1.7, 3.7)	0.7(-3.5, 5.1)	0.8(-1.4, 3.2)	2.3(0.0, 4.7)
Si	**1.3 (0.1, 2.5)**	**2.1 (0.6, 3.6)**	0.3(-1.6, 2.1)	-0.1(-2.9, 2.8)	1.2(-0.3, 2.7)	1.5(-0.1, 3.0)
Ti	1.7 (-0.4, 3.9)	**3.2 (0.4, 6.1)**	-0.2(-3.3, 3.0)	0.1(-4.8, 5.2)	2.3(-0.3, 5.1)	1.0(-1.7, 3.9)
Zn	-0.7 (-0.7, 3.1)	2.0(-0.5, 4.4)	0.0(-2.8, 2.8)	6.0(-3.5, 4.9)	0.8(-1.5, 3.2)	1.6(-0.8, 4.1)

All the models included only one air pollutant or one trace element. Models adjusted for apparent temperature (lag0), day of the week, public holidays and monthyear
The IQR is used as the increment for the trace elements (in $ng.m^{-3}$): Br (11.6), Ca (124.4), Cl (29.2), Fe, (150.8), K (162.2), S (1017.2), Si (256.1), Ti (19.2), Zn (48.2)
10 $\mu g.m^{-3}$ is used as the increment for $PM_{2.5}$ and 1 $\mu g.m^{-3}$ for BC and UV-PM. The increment for soot is per 1 m^{-1} x 10^{-5} increase.

Table 6: Model 2: Percentage change (95% CI) in daily respiratory disease hospital admissions per inter-quartile range increase in trace element levels (lag0) measured at the School of Health Systems and Public Health, University of Pretoria during 18 April 2017 to 28 February 2020 (350 days).

Air pollutant	All	0-14 year old	15-64 year old	≥65 year old	Females	Males
Br	0.6 (-1.7, 2.9)	0.0 (-2.9, 3.1)	1.1 (-2.3, 4.6)	2.2 (-3.1, 7.7)	2.0 (-0.8, 4.8)	-1.0 (-4.1, 2.1)
Ca	**3.2 (0.3, 6.1)**	**5.2 (1.5, 9.1)**	0.6 (-3.7, 5.0)	**0.1 (-6.4, 7.1)**	3.0 (-0.6, 6.8)	3.3 (-0.4, 7.3)
Cl	0.5 (-0.3, 1.2)	0.7 (-0.3, 1.7)	0.3 (-0.8, 1.4)	0.2 (-1.5, 2.0)	0.7 (-0.2, 1.6)	0.2 (-0.8, 1.2)
Fe	1.9 (-1.5, 5.3)	3.8 (-0.7, 8.4)	-0.6 (-5.5, 4.5)	0.0 (-7.5, 8.0)	2.6 (-1.7, 7.0)	1.1 (-3.2, 5.6)
K	1.2 (-0.5, 3.1)	2.2 (-0.1, 4.5)	-0.2 (-2.9, 2.5)	0.2 (-3.8, 5.8)	1.0 (-1.2, 2.4)	1.6 (-0.8, 3.9)
S	0.7 (-1.3, 2.7)	1.0 (-1.6, 3.6)	0.1 (-2.8, 3.1)	1.0 (-3.6, 5.8)	-0.1 (-2.6, 2.4)	1.6 (-1.0, 4.2)
Si	0.9 (-0.4, 2.1)	1.6 (0.0, 3.2)	-0.3 (-2.2, 1.7)	0.0 (-3.0, 3.0)	0.7 (-0.9, 2.3)	1.0 (-0.6, 2.7)
Ti	0.7 (-1.7, 3.1)	2.0 (-1.0, 5.2)	-0.5 (-4.8, 2.0)	0.3 (-5.1, 6.1)	1.5 (-1.4, 4.5)	-0.3 (-3.3, 2.9)
Zn	0.3 (-1.7, 2.4)	0.9 (-1.7, 3.6)	-1.0 (-4.0, 2.0)	0.9 (-3.6, 5.6)	0.0 (-2.5, 2.5)	-1.8 (-1.8, 3.4)

All the models included only one trace element air pollutant. Models adjusted for $PM_{2.5}$, apparent temperature (lag0), day of the week, public holidays and monthyear
The IQR is used as the increment for the trace elements (in $ng.m^{-3}$): Br (11.6), Ca (124.4), Cl (29.2), Fe, (150.8), K (162.2), S (1017.2), Si (256.1), Ti (19.2), Zn (48.2)
10 $\mu g.m^{-3}$ is used as the increment for $PM_{2.5}$ and 1 $\mu g.m^{-3}$ for BC and UV-PM
The increment for soot is per 1 m^{-1} x 10^{-5} increase

Supplementary table S1: Descriptive statistics for covariate data (PM_{10}, NO_2 and SO_2) as reported by SAAQIS City of Tshwane

		Seasons			
Pretoria	All	Autumn	Winter	Spring	Summer
PM_{10}					
Mean and SD	71.9 ± 72.8	50.6 ± 25 8	108 ± 95.6	84.3 ± 79.8	35 ± 14
Range	11.0 - 707	17.8 - 139	21.8 - 375	11 - 706	11.8 - 83
Percentiles					
25th 95%CI	34(32,36)	32.5(29,37.7)	56(49,58.8)	40.7(36.7,46.8)	25(23.7,27.3)
50th 95%CI	51(48, 54)	46.7(40.5,49.7)	72(67,78.5)	61.6(56.3,66)	32.5(29.6,35)
75th 95%CI	79(71, 82)	57.2(53.1,64.9)	101(95.3,112)	93(80.1,117)	40.6(37,45)
NO_2					
Mean and SD	16.4 ± 9.6	16 ± 6.6	26 ± 12.4	15 ± 7.5	11 ± 3.6
Range	4.0 - 78.8	4.2 - 41.5	7.0 - 78.8	4.0 - 38	4.1 - 22
Percentiles					
25th 95%CI	9.8(9.5,10)	11.3(13.7,12.5)	17.5(16.7,19)	9.79(9.22,10.4)	8(7.8,8.4)
50th 95%CI	14(13, 14)	15.2(13.9,16.2)	23(21.3,25)	12.7(12.2,13.7)	10.2(9.5,10.7)
75th 95%CI	20(19,21)	19.2(17.9,20.9)	31.7(29.2,35.1)	19.6(17,22)	13.1(12.2,13.7)
SO_2					
Mean and SD	6.15 ± 9.6	6.5 ± 11.5	7.11 ± 4.32	4.7 ± 2.4	6.5 ± 5.8
Range	0.95 - 117	1 - 117	1.8 - 43	1.3 - 13	0.95 - 34
Percentiles					
25th 95%CI	3(2.9,3.3)	3.2(2.7,3.5)	4.8(4.3,5.1)	2.9(2.6,3.2)	2.7(2.5,2.9)
50th 95%CI	4.9(4.6,5.1)	4.4(4,5.1)	6.1(5.8,6.5)	4.4(4.0,4.7)	4.2(3.6,4.7)
75th 95%CI	7.4(7,8)	6.6(6.0,7.6)	8.3(7.8,8.9)	6.15(5.6,6.8)	8.6(8.0,10)

Supplementary table S2: Descriptive statistics of 24-hour $PM_{2.5}$, PM_{10}, NO_2 and SO_2 levels (in $\mu g.m^{-3}$) measured at the nine ambient air pollution monitoring stations of the City of Tshwane municipality (Pretoria), South Africa on 350 days during 18 April 2017 to 28 February 2020 when $PM_{2.5}$ was sampled at the School of Health Systems and Public Health, University of Pretoria

Variable	% missing	Min	Mean	Median	Max	Std Dev
$PM_{2.5}$						
Bodibeng	37	6.5	28.8	24.4	127.5	20.0
Booysens (not monitored)	NA	NA	NA	NA	NA	NA
Ekandustria	19	0.1	15.7	18.0	39.5	$_{10}$.7
Hammanskraal	67	2.4	25.3	20.0	78.1	16.2
Mamelodi (not monitored)	NA	NA	NA	NA	NA	NA
Olievenhoutbosch	33	0.0	36.7	26.8	120.0	27.3
Pretoria West (not monitored)	NA	NA	NA	NA	NA	NA
Rosslyn	21	6.1	24.2	21.2	78.8	12.9
Tshwane Market	3	45.7	60.2	60.5	79.6	9.9
Citywide average	55*	6.4	27.8	24.9	97.8	14.9
PM_{10}						
Bodibeng	33	18.2	73.5	$6_{2.5}$	212.1	37.8
Booysens	23	15.8	59.9	52.7	184.0	35.2
Ekandustria	15	1.9	6.9	6.3	19.8	3.4
Hammanskraal	52	6.4	68.4	43.6	877.1	89.7
Mamelodi	17	4.8	65.9	58.0	276.5	45.5
Olievenhoutbosch	40	0.0	61.5	45.3	259.4	56.5
Pretoria West	2	12.2	19.6	17.2	37.4	8.2
Rosslyn	24	11.8	$_{10}$9.6	46.6	500.6	154.0
Tshwane Market	3	22.1	24.3	24.3	26.1	1.4
Citywide average	60*	11.9	71.7	51.6	371.7	69.9
NO_2						
Bodibeng	62	4.5	21.6	17.7	83.8	13.3
Booysens	62	8.1	28.9	25.7	75.5	13.2
Ekandustria	23	5.8	25.3	22.0	48.9	11.8
Hammanskraal	71	0.0	19.9	17.9	57.5	13.3
Mamelodi	64	9.0	43.0	33.6	162.6	29.6
Olievenhoutbosch	26	0.0	27.0	26.0	79.6	12.7
Pretoria West	39	0.0	61.3	30.0	568.3	85.8
Rosslyn	36	5.4	23.5	19.7	59.3	12.8
Tshwane Market	31	$_{10}$.8	33.6	31.6	66.1	12.4

Variable	% missing	Min	Mean	Median	Max	Std Dev
Citywide average	88*	9.1	30.8	25.8	148.2	18.0
SO_2						
Bodibeng	54	1.0	7.5	5.7	34.7	5.8
Booysens	69	0.0	32.0	13.5	819.1	68.7
Ekandustria	83	2.3	12.8	$_{10}$.0	87.5	$_{10}$.2
Hammanskraal	76	0.0	11.0	8.7	49.6	9.0
Mamelodi	65	0.2	15.6	13.6	56.5	11.7
Olievenhoutbosch	35	0.1	15.8	9.4	75.2	17.2
Pretoria West	44	0.0	17.9	16.5	68.1	11.4
Rosslyn	84	2.4	1$_{2.5}$	$_{10}$.4	45.1	7.8
Tshwane Market	23	0.0	12.4	6.8	115.3	24.2
Citywide average	90*	$_{2.5}$	15.9	13.2	213.5	15.2

*Daily 24-hour averages of each pollutant were calculated from the hourly data and were based on at least 18 hourly values. If more than six hourly values were missing during the 24-hour period then the daily average was set as missing. Subsequently, a citywide 24-hour average for each of the pollutants was calculated and was based on the data of at least two monitoring stations. The nine AAQM stations are within a 50 km radius of the $PM_{2.5}$ sampling site at the SHSPH.

Supplementary table S3: Correlation between 24-hour $PM_{2.5}$ and the trace elements on 350 days at the School of Health Systems and Public Health, University of Pretoria during 18 April 2017 and 28 February 2020

	$PM_{2.5}$	Soot	BC	UV-PM	Br	Ca	Cl	Cu	Fe	K	S	Si	Ti	U	Zn
$PM_{2.5}$	1														
Soot	0.45	1													
BC	0.74	0.47*	1												
UV-PM	0.71	0.47*	0.95*	1											
Br	0.81	0.45*	0.80*	0.79*	1										
Ca	0.58	0.34*	0.52*	0.51*	0.64*	1									
Cl	0.55	0.40*	0.60*	0.57	0.64*	0.58*	1								
Cu	0.38	0.14*	0.32*	0.24*	0.33*	0.26*	0.39*	1							
Fe	0.67	0.50*	0.64*	0.68*	0.78*	0.69*	0.57*	0.14*	1						
K	0.55	0.38*	0.49*	0.51*	0.65*	0.67*	0.72*	0.19*	0.68*	1					
S	0.21	0.2096*	0.07	0.11*	0.21*	0.38*	0.27*	-0.07	0.37*	0.53*	1				
Si	0.39	0.19*	0.22*	0.22*	0.39*	0.58*	0.36*	0.17*	0.51*	0.49*	0.48*	1			
Ti	0.54	0.28*	0.3-*	0.38*	0.56*	0.70*	0.50*	0.25*	0.68*	0.55*	0.37*	0.60*	1		
U	-0.81	0.12*	-0.19*	-0.24*	-0.18*	-0.16*	$-0._{10}$	0.12*	-0.27*	-0.13*	-0.20*	0.08	-0.08	1	
Zn	0.68	0.45*	0.69*	0.66*	0.75*	0.60*	0.54*	0.31*	0.69*	0.47*	0.29*	0.37*	0.56*	-0.22*	1

Correlations were significant; mostly $p<0.001$

*Not significant; $p\geq0.001$

No missing values

Supplementary table S4: Spearman's Rank correlation coefficients between air pollution, Tapp and weather variables as reported by the South African Weather Services (SAWS) for the 34-month study period.

	PM_{10}	**NO_2**	**SO_2**	**Temp**	**RH**	**windspeed**	**Tapp**
PM_{10}	1						
NO_2	0.31	1					
SO_2	0.15	0.83	1				
Temp	-0.13	-0.32	-0.17	1			
RH	-0.15	0.023	0.13	-0.11	1		
windspeed	-0.10	-0.16	-0.14	0.35	-0.12	1	
Tapp	-0.18	-0.31	-0.14	0.96	0.33	0.33	1

Abbreviations: PM_{10}: particulate matter with an aerodynamic diameter of less than 10 μm; NO_2: nitrogen dioxide; Tapp: apparent temperature; RH: relative humidity. All correlations were significant ($p<0.001$)