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Review article

Examining the links between air quality, climate change and respiratory health in Qatar

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ABSTRACT

Little information exists concerning (i) source contributions to airborne particulate pollution in Qatar, (ii) the potential impact that deteriorating air quality may have on the respiratory health of residents, and (iii) how climate change may affect respiratory health through its impact on air quality. Air quality in Qatar may be negatively affected by naturally occurring contributions including dust/sand originating from adjacent desert regions, microbial communities that may be associated with these particulates, and volatile organic compounds (VOCs) released by blooms of phytoplankton in coastal waters. Of increasing concern are anthropogenic contributions, including emissions from the rapidly growing number of vehicles, from ships travelling in the Persian Gulf, and from industrial and construction activities. We examine the relative importance of these contributions and discuss some of the expected impacts on respiratory health. We conclude by speculating on the impact that climate change may have on air quality and respiratory health around Qatar.

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BACKGROUND

The deterioration of air quality in many regions of the world has generated increasing concern with growing evidence of its impact on human health. While anthropogenic sources of air pollution originating largely from industrial and vehicular emissions have received the most attention, exposure to natural sources of airborne particulate matter, including those generated from fires, volcanic eruptions, and sand/dust storms also impact health. Many areas around the Middle East, including Qatar, have experienced substantial development over the past few decades, funded largely by gas and oil industries, raising concerns about air quality. Compounding problems generated by anthropogenic air pollutants are natural sources of airborne particulates, mainly dust and sand, originating from surrounding arid regions [¹ and references therein].

In this article, we first examine some of the sources that may impact air quality in Qatar and review general effects they may have on human health. We then look more specifically at the impact of air quality on respiratory heath. This is not meant to be an exhaustive review of the health issues that may be incurred by exposure to various air pollutants, but rather an initial assessment of the potentially important sources and effects of airborne particulates in the region.

CONTRIBUTING SOURCES TO POOR AIR QUALITY

Natural sources

Air quality is affected by a diverse array of substances including respirable suspended particulates, carbon monoxide, sulphur and nitrous oxides, acid gases, metals, volatile organics, solvents, pesticides, and bioaerosols.² In the absence of anthropogenic sources of pollutants, air quality can be negatively affected by airborne particulates and chemicals derived from a variety of natural sources. Some natural air pollutants originating from forest fires and sand storms are considered to be as harmful as fossil combustion-related air pollutants.^{3.4} Volcanic emissions, for example, can contain large amounts of particulates as well as sulphur dioxide, fluorides, hydrogen chloride, and toxic metals.²

Of particular concern in Qatar and other regions of the Middle East are suspended particles of dust/sand. High concentrations of suspended particles are common in desert regions when moisture-laden cooler air drops to the surface and is subsequently pushed back up causing wind and eddies, carrying with it particles picked up from the ground. These particles are carried by wind over varying distances, depending largely on the size of the granules and the wind velocity. The concentration of airborne particulates generated in this way can be classified by its impact on visibility where blowing dust, dust storm and severe dust storm refer to times when horizontal visibility is less than 11 km, 1000 m, and 200 m, respectively. Akbari⁵ noted that in some regions of the Middle East, and for about 30% of the time, dust conditions fall into one of these three categories.

Natural mineral and chemical constituents of dust

Airborne mineral dust originates from the weathering of surface rocks and soils and subsequent transport via strong surface winds. In the absence of other inputs, the initial mineral and chemical properties of the dust are therefore determined by the substrate from which they originated. Dust origination from soil and the evaporation of seawater are the primary sources of airborne particles worldwide. Low precipitation in much of the Middle East favours longer-term suspension of these particles in this region. Engelbrecht et al. Provided a comprehensive overview of aerosol dust throughout the Middle East noting that all samples contained silicate minerals, carbonates oxides, sulfates and salts in various proportions. Mineralogical analysis around Qatar suggests that dust in this area contain high amount of calcite, quartz and feldspar.

Substantial evidence exists concerning the impact of sand/dust storms on human health. Recent studies have shown that hospital admission rates for various respiratory illnesses, including asthma, bronchitis, no pneumonia, and general respiratory problems, increase shortly after exposure to wind-generated dust. In addition, non-respiratory problems such as stroke, acardiovascular morbidity and congestive heart failure, as well as general emergency admissions, falso increase following such events. It has been suggested that high levels of quartz found in dust in Kuwait City may be associated with a number of health problems, including silicosis. While the health costs of these events have not, to our knowledge, been determined, clearly they are substantial. This is expected to be particularly important for countries such as Qatar where dust storms occur on a relatively frequent basis.

Physical, chemical and biological properties of the dust may all play a role in determining the type, frequency and seriousness of illnesses. Particles with diameters of less than 4 μ m can penetrate into the bronchioles and alveoli of the lungs¹⁷ and it is generally agreed that particles less than 2.5 μ m (PM_{2.5}) pose the most serious threat to respiratory function.¹⁸ It has also been established that improvements in air quality through a lowering of PM_{2.5} concentrations can decrease mortality associated with respiratory and cardiovascular problems.¹⁹ Larger particles, classified as PM₁₀ and defined as between 2.5–10 μ m, are more likely to become trapped along the respiratory tract and subsequently expelled. However, even exposure to these coarse particles is known to increase the rates of hospital admissions for chronic obstructive pulmonary disorder (COPD) and asthma.^{20,21} In general, chronic exposure to airborne particulate matter can result in an increase in lower respiratory symptoms, COPD, reduction in lung function and reduction in life expectancy.²²

Microbial communities

Airborne particulates may contain bacteria, viruses, and fungi, as well as a number of allergens including pollens and organic debris. Since desert soils are the source of most of the airborne particulates in arid regions, a number of investigations have attempted to provide information on their biological communities. Griffin [²³ and references therein] estimated that one gram of desert topsoil contains approximately 109 bacteria and 108 viruses. Gonzalez-Martin et al.²⁴ found substantial variability in both bacterial and viral estimates in soils taken from different desert environments around the world. Importantly, the harsh ecological conditions of these environments is thought to select for characteristics that increase the effectiveness of long distance atmospheric dispersal by these organisms.^{23,25}

Griffin²³ reviewed research that detected bacteria and fungi in dust storms.

Sixteen different genera of bacteria and 17 genera of fungi were detected in three studies in which dust had originated in the Middle East.^{26–28} More recently, 11 types of bacteria and two species of fungus were detected in airborne dust samples from various regions around Iraq.²⁹ *Bacillus* species were the most common type of bacteria, making up just over 40% of all microorganisms identified, while the fungi *Aspergillus* and *Candida* made up 14.5% and 7.7% of the microbial community, respectively.

Although direct links between human illness and microorganisms identified in dust storms have been difficult to establish, samples typically contain species known to be associated with known health problems. Isolates found in dust samples from Kuwait that are known to be pathogenic included *Neisseria, Staphylococcus, Bacillus, Pantoea, Ralstonia,* and *Cryptococcus*. ²⁶ Leski et al. ³⁰ identified at least five different human pathogens in desert dust samples taken from Kuwait and Iraq. Earlier studies had suggested links between sand-dust storms and pneumonitis, ³¹ bacterial and atypical pneumonia, ³² and anaphylactic and non-anaphylactic respiratory problems. ²⁷ One of the clearest links between dust-borne pathogens and human illness is that between the bacterium *Neisseria* and seasonal outbreaks of meningitis observed in regions of North Africa. ³³ One microbial community that has attracted recent attention in the deserts of Qatar is cyanobacteria. These organisms help bind desert sands and remain dormant until they are activated after rainfalls. The dried crusts and mats in which these communities occur can contribute to airborne dust, particularly if disturbed as a result of traffic. It has been suggested that cyanotoxins released by these organisms might be a risk factor in the development of certain neurological diseases. ^{34,35}

Phytoplankton

Phytoplankton blooms in the Persian and Arabian Gulf and wider Arabian Sea are a normal ecological phenomenon. However, in recent years, the characteristics of these blooms have changed dramatically, both in terms of phytoplankton abundance and the organisms present.^{36–38} The factors controlling these blooms are numerous and complex, but primarily include natural ocean circulation and seasonal weather patterns,³⁷ anthropogenic stress on marine ecosystems [³⁹ and references therein], and fertilisation of the water column by trace element rich Aeolian dust from surrounding deserts.⁴⁰ While not comprising a substantial component of airborne particulate matter, these marine phytoplankton are known to emit a large suite of volatile organic compounds (VOCs) including terpenes and organohalogens.^{41–46} Phytoplankton can be grouped into species or size classes that fulfil different ecological functions – commonly referred to as phytoplankton functional types (PFTs) – and PFTs have been shown to emit VOCs variably, both in terms of compound type and emission rate.^{42,46,47}

These phytoplankton-derived compounds can play an important role in air quality: for example, they may be involved in the formation and loss of tropospheric ozone, alter the lifetime of important atmospheric gases (e.g., stratospheric ozone) and, in the cases of dimethyl sulphide and isoprene, act as precursors to secondary organic aerosol (SOA) formation. Biogenic fluxes from the ocean can, therefore, potentially contribute to the total atmospheric loading of $PM_{2.5}$ and VOCs around Qatar.

Anthropogenic sources

Anthropogenic additions to windborne dust are largely dependent on industrial and other pollutant-generating activity in a region. Fine particles, because they provide more surface area per unit weight, may carry greater concentrations of toxic air pollutants, diffuse to surfaces faster and are far more reactive than larger particles. ⁴⁸ Such pollutants may include metals, ⁴⁹ heavy metals, ⁵⁰ pesticides, ⁵¹ and a suite of chemicals associated with vehicular emissions. ⁵² In a survey of Middle Eastern countries, Lelieveld ⁵³ found that the main nitrous oxide NOx source category is transport (59%), being dominated by road traffic, except in the United Arab Emirates (UAE) where emissions from international shipping are more prominent. The second and third most important NOx emission categories are power generation and industry, respectively. In Qatar, three important anthropogenic sources of air pollutants are vehicular emissions, industry (particularly gas and oil refineries), and construction activities.

Vehicular emissions

Although few studies have examined the impact of vehicular traffic on air quality in Middle Eastern countries, Waked and Afif⁵⁴ suggested that road transport is a major contributor to air pollutants in the region. For example, El Raey⁵⁵ estimated that the transport sector is responsible for about 70% of urban air pollution in Syria. In Doha, rapid population growth, lack of a well-developed transit system, low fuel prices, and high personal incomes combine to influence the high number of personal vehicles on the road; the number of cars more than doubled from 287,500 vehicles in 2000 to 656,686 in 2010.⁵⁶ In addition, traffic congestion, common in many regions of Doha, adds significantly to vehicular emissions.

Sixty air samples collected over a one year period (2006-2007) in Qatar revealed average concentrations of total suspended particulates of $282 \,\mu g/m^3$, with PM_{10} and $PM_{2.5}$ concentrations of $165 \,\text{and} \, 67 \,\mu g/m^3$, respectively. The observed concentration of $PM_{2.5}$ in Qatar is more than double the recommended target across Canada⁵⁷ and Europe⁵⁸ and four times higher than recommended by the U.S. Environmental Protection Agency. Indeed, due to the increasing body of evidence linking fine particles to serious human health issues, the EPA is recommending lowering the exposure level standard to $12 \,\mu g/m^3$ from its current $15 \,\mu g/m^3$. There was a 5.4% annual increase of minute particles between 2007 and 2010, as well as a 9.3% and 2.6% increases in nitrogen oxides and sulphur dioxide levels, respectively; all are at least partially attributed to increasing vehicular use in the area. The same partially attributed to increasing vehicular use in the area.

Health problems associated with vehicular emissions are expected to be more pronounced in pedestrians and outdoor labourers as compared to vehicle drivers as the latter are partially shielded from pollutants. However, as outdoor air quality is closely associated with indoor air quality, even people in buildings near heavy traffic areas may be impacted. Emissions that may be of particular concern include sulphur, nitrogen oxides, ozone, carbon monoxide and benzene. Although substantial evidence exists concerning the harmful effects of total emissions, specific causal agents are difficult to identify. The effects of sulphur and nitrogen dioxide on human health, for example, are not well understood. Exposure to ozone and carbon monoxide, on the other hand, is known to affect lung and cardiovascular function and result in increased hospital admissions. Benzene exposure has been associated with an increased incidence of childhood leukemia.

In addition to emissions from road traffic, ships are known to be an important source of $PM_{2.5}$ in coastal cities such as Doha. ^{65,66} There have been a number of studies demonstrating that ship emissions significantly impact air quality in port cities. ^{67,68} Corbett et al. ⁶⁶ estimated 60,000 cardiopulmonary and lung cancer deaths annually can be attributed to ship emissions in Europe, East Asia, and South Asia alone. The main ship emissions of health concern are $PM_{2.5}$ oxides of nitrogen and sulphur dioxide (SO₂). Other major air pollutants of health concern found in ship emission plumes include black carbon/elemental carbon (soot), heavy metals, polynuclear aromatic hydrocarbons (PAHs), ⁶⁹ volatile organic compounds (VOCs), ultrafine particles ⁷⁰ and carbon monoxide (CO). ⁶⁶ The VOCs and NO2 generated by ships are precursors to ground-level ozone (O₃), which is known to be

harmful to health and a powerful greenhouse gas.⁷¹ Furthermore, because ship pollution travels great distances, many inland populations are also susceptible to marine emissions.⁷²

Industrial emissions

Total greenhouse gas emissions (including carbon dioxide, methane, and nitrous oxide) increased by 47% in Qatar over the period between 2001 and 2006.⁷³ This increase was due primarily to increased oil and gas operations (70%) although increased vehicle use accounted for 10% of this increase. Only one study in Qatar has examined suspended particulates originating from the oil industry. Abou-Leila et al.⁷⁴ examined possible differences in air particulates before and during the burning of oil fields in Kuwait during the Gulf War. They detected aluminium, silicon, sulphur, chlorine, potassium, calcium, iron and zinc of which only zinc and sulphur increased during the war. Clearly, this does not reflect emissions from normal industrial activity. In addition, emissions from gas and oil industries may be less of a concern for human health since they are released in areas away from major urban centers. Of growing concern, however, are emissions of aerial plankton and dust from the cement industry, which has grown substantially in the past decade in response to urban development and increased construction.⁵⁶

Construction activity

Construction-caused environmental pollution has increasingly become a significant cause of poor air quality⁷⁵ and is of particular concern to human health as it generally occurs in heavily populated regions. Construction activities generate dust from concrete, cement, wood, stone and silica, all of which can contribute to health problems. In addition, they contribute to increased vehicular use that are associated with problems discussed above, as well as noxious vapours arising from glues, paints, plastics, cleaners, etc.. Thus, areas around construction sites are typically exposed to an intense, and often unpredictable, array of hazardous air pollutants. Sand and dust created by the manufacturing industry and the soaring number of construction projects here have all contributed to the deterioration of air quality around Doha.⁵⁶ Unfortunately, little quantitative data exists concerning the air quality deterioration resulting from construction activities.

Air quality and respiratory health

Although exposure to various air pollutants can have wide-ranging impacts on human health, of primary concern is respiratory health. Illnesses associated with the respiratory system are important reasons for clinic visitation, hospital admission and drug use in Qatar and in neighbouring countries. The incidence of respiratory illnesses varies across the Middle East and, in most cases, detailed analyses have not yet been done. Asthma is the most common respiratory problem, particularly in children, and often results in hospital admission. The prevalence of asthma in children has been found to be 13% in the UAE, 76 16.8% in Kuwait, 77 19.6% in Saudi Arabia, 78 and just over 20% in Oman. 79 Rates are similar for Qatar; Janahi et al. 80 found that 19.8% of 6–14 year old schoolchildren were asthmatic and AlMarri 78 reported a hospital admission rate for asthma of 42 per 100,000, of which 35% were less than 15 years of age. While some of these differences may be due to different age cohorts of children studied, they suggest the incidence of asthma in the Middle East is relatively high and likely increasing. 78,81

While several studies have focused on the prevalence of asthma, other respiratory problems contribute significantly to hospital admissions in Qatar. Dr. Hussain al Awadhi, a senior consultant at Hamad Medical Corporation (HMC), noted that "While statistics continue to show a steady decrease in reported cases of health conditions such as stroke, hypertension and even cancer, the reverse is the case for COPD diseases commonly referred to as chronic bronchitis and emphysema, as they continued to be on the increase" (Qatar Tribune, 27/10/10). Janahi et al.⁸⁰ reported high prevalence of diagnosed allergic rhinitis (30.5%), and chest infection (11.9%) among schoolchildren in Qatar, with the prevalence of each illness being similar in parents. Two other major respiratory problems that may be related directly or indirectly to air quality include tuberculosis (TB) and pneumonia. Unfortunately, there are few published studies concerning the incidence of either in the Middle East. Memish et al.⁸² reported that TB is a serious illness throughout the region and that its incidence in Saudi Arabia is 17 per 100, 000 people. Tuberculosis has been particularly problematic in Qatar, which has not only the highest incidence of the disease, but is one of the only countries in the region that showed no decline in its incidence between 1990 and 2006.⁸³ Waness et al.⁸⁴ described the recent increase in community

acquired pneumonia in the Middle East and prevalence of other types of bacteria responsible for this illness throughout the region.

Particulate-induced inflammation is regarded as the main mechanism underlying respiratory health effects. Fine and ultrafine particles are more strongly associated with this response due to their ability to deposit deep into the lungs, access the alveolar tissue, and interact with both macrophages and epithelial cells, the principal cells that process airborne particles in the lung. A6,87 In fact, there is a link between high levels of inflammatory markers in blood and cardio-respiratory effects in populations exposed to airborne particulates. The formation of reactive oxygen species (ROS) has been suggested as an important initiating factor of particle-induced inflammation as well as being associated with oxidative stress leading to cytotoxicity and DNA damage.

As previously stated, particulate matter is a complex mixture of compounds of different origin and chemical composition that contribute to its toxicological potential. Several toxicological studies have established an association between some metals in particulate matter and the particulate-induced inflammation in the lungs. Exposure to particulate matter collected near a steel plant in the United Kingdom caused inflammation in the rat lung correlated with the concentration of metals in particulate mass.⁹¹ Metals associated with particles in welding fumes induced an inflammatory response in an alveolar cell line.⁹² Present in almost all combustion-related missions, polycyclic aromatic hydrocarbons (PAHs) are also a significant constituent of particulate matter and may induce inflammatory, cytotoxic, and genotoxic effects. A number of studies^{93,94} have reported DNA damage in lung epithelial cells exposed to particulate matter sampled in different cities. In fact, levels of vehicular emissions have been correlated with levels of DNA damage with samples from highly urban sites inducing greater DNA damage compared to sites with lower traffic emissions.⁹⁵

To date, no studies have examined the inflammatory potential and toxicological properties of particulate matter from the Middle Eastern region, despite the high concentration of airborne dust throughout the regions and high level of air pollution in urban centres. Differences in air quality and frequency of dust storm events during certain periods of the year are likely associated with effects on respiratory health but the epidemiological data and experimental studies to this effect are lacking. In terms of mitigating harmful emissions, identifying compounds with the great toxicological activity (i.e. metals, PAHs, microbes) may help to define more efficient strategies to reduce air pollution by focusing on those sources that emit the most harmful particles.

Weather and the potential impact of climate change on air quality in Qatar

A variety of climatic factors are known to influence respiratory health, usually through their impact on air quality. The region around Qatar is one of the driest on earth with maximum daily average temperatures in August reaching 45°C.⁹⁶ Wind, particularly during the winter months, can carry significant amounts of dust/sand. This results in the dust loading in Qatar and neighbouring countries (200 mg/m²) ranking as the second highest in the world (after Saharan Africa).⁹⁷ While a relationship between weather patterns and respiratory problems are commonly noted in newspaper articles and websites (e.g., "Weather flux triggers respiratory diseases" – Qatar Tribune; "Residents advised to take health precautions during dust storms" – Qatar is Booming), detailed investigations concerning such links are lacking. Interestingly, Dr. Osama al Dulaimi reported that the number of asthma cases at the Qatar Medical Centre (QMC) increased by as much as 30% during and shortly after very windy conditions (Qatar Tribune, 27/03/11).

As weather patterns play an important role in determining air quality, it is important to understand the potential impact of climate change if we are to better evaluate stresses that may be placed on the health care system in the coming decades. The impacts of climate change are most often discussed in light of how changes in temperature, patterns of precipitation, and sea level rise will likely affect a particular region. Differences in topography, vegetation, proximity to water, and natural variability in weather make predictions for specific regions in the Middle East difficult 98 although it is widely accepted that climate change will result in even hotter, drier conditions over the next few decades. 99,100 Predicted temperature increases range from $1.5-4^{\circ}\text{C}^{98}$ to $3.5-7^{\circ}\text{C}^{101}$ by the end of the century. Changes in precipitation are more difficult to predict, given the extreme inter-annual variability in rainfall throughout much of the region. In general, more northern areas are expected to receive significantly less rainfall, with impacts diminishing as one moves further south. Although the region around Qatar may in fact experience a slight increase in rainfall by the end of the century, this will likely be offset by more extensive evaporation due to higher temperatures. Expected changes due

to climate change that may have implications for human health in Qatar are 1) higher temperatures, 2) more frequent extreme weather events, 3) heavy rains leading to local flooding, and 4) more frequent sandstorms.⁷³ While changes in humidity are often not presented in climate change predictions, they may also have important implications for human health as described below. At least one model suggests that, on a global scale, specific humidity will increase but relative humidity is unlikely to change significantly.¹⁰²

There is already some evidence of the possible effects of climate change in the region. Zhang et al.¹⁰³ examined data from 75 weather stations in 15 Middle Eastern countries, including Qatar, to determine climate trends that occurred between 1950 and 2003. They found a significant warming trend across the region with an increase in average daily maximum and minimum temperatures as well as in the number of warm days. Rainfall patterns, as expected, were less conclusive and not significant in general. AlSarmi and Washington¹⁰⁴ followed up this study by examining climate trends over the last two to three decades. Although they used fewer stations and a shorter time period, the results were similar to those of Zhang et al.¹⁰³ Fourteen of the 21 stations showed significant warming trends with the greatest responses observed in Oman and the UAE. Doha experienced the second highest monthly temperature increase with a 1.54°C increase per decade for February. While the amount of precipitation at most sites declined, the only significant decreases were observed in Saik (Oman) and Tabuk (Saudi Arabia). The few studies that have examined current trends in humidity levels were critically evaluated by Willett.¹⁰⁵ The data, while not of the same quality as those for temperature and precipitation, suggest that surface level atmospheric moisture has increased over the latter part of the last century.

Climate change is expected to have a direct impact on air quality. The Intergovernmental Panel on Climate Change (IPCC)¹⁰⁶ has suggested that air quality in cities is almost certain to decline in response to climate change if remedial actions are not taken. Rising temperatures are associated with reduced air quality, placing people at risk for skin, eye, and respiratory irritation. Most importantly, increased temperatures are positively associated with ozone levels in areas with heavy vehicular traffic, even where the normal temperatures are typically high. ^{107,108} Humidity can affect air quality and subsequently human health in two ways. First, increased humidity may result in heat stress at higher temperatures as it interferes with the body's ability to cool effectively through perspiring. Secondly, more humid air can hold greater concentrations of particulates that may be damaging to respiratory health and related illnesses. ¹⁰⁹ Increased wind speed can have both positive and negative effects on air quality. Good airflow can disperse ground level pollutants in regions where air quality is poor, thus providing a healthier environment. In Qatar, however, increased wind speeds, particularly of those coming from the north and northwest, can result in dusty conditions. Climate change is expected to increase the frequency of extreme weather events; Qatar can expect more sandstorms and the accompanying health problems with which they are associated.

SUMMARY

Qatar faces a growing risk of health-related problems due to poor air quality originating from both natural and anthropogenic sources. Dust from adjacent deserts can carry both living and nonliving constituents that may be harmful to health while populations of phytoplankton in the surrounding waters can release volatile organic chemicals that have been linked to human illness. Anthropogenic contributions to poor air quality are linked to the rapid development of the country and can originate from vehicular and ship emissions, as well as emissions from industrial and construction activities. While there is a substantial body of evidence linking poor air quality to human health, a number of important questions remain. For example, what are the relative contributions of the various sources in the region? What microorganisms are normally present in airborne dust and do they pose a risk to human health? What are the specific toxicological properties of airborne particulates around Qatar? What are the expected health costs if, as predicted, climate change intensifies the deterioration in air quality in the region? Answers to these and related questions are required to assist in the development of remediation strategies to improve air quality as well as health care strategies to prepare for expected increases in respiratory-related illnesses.

COMPETING INTERESTS

None of the authors have competing interests or conflicts of interest with respect to the material presented in this paper.

AUTHOR CONTRIBUTIONS

KT organized and wrote a substantial part of the paper.

NH contributed to the writing and revising of the manuscript.

KC contributed to the writing and revising of the manuscript

MG, SC and JH all wrote sections of the paper.

All authors have read and approved the final manuscript.

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