Environmental factors contribute to 12.6 million deaths globally, accounting for 23% of global burden of disease. Majority of these deaths occur in low- and middle-income countries (LMICs) of Asia and Africa. Incidentally, 8.2 million of these deaths are due to non-communicable diseases (NCDs).1

Every year, globally, a total of 15 million individuals develop stroke leading to 6 million deaths and 5 million permanent disabilities. About 90% of strokes are preventable. Unhealthy diet, harmful use of alcohol, physical inactivity and smoking has been the focus of attention for stroke prevention. However, an estimated 2.5 million (about a third) of stroke are attributed to air pollution.2 Air pollution is a pervasive, ubiquitous concern where every nine out of ten individuals (91%) on earth are breathing unhealthy air. The World Health Assembly has declared air pollution as the single largest environmental risk causing over 7 million deaths globally. Fossil fuel that burns in vehicles, industries and emission from energy required in residential and commercial buildings and infrastructure are major contributors for air pollution. While several thousand pollutants, particles and gases, are emitted which may be harmful for human health, six pollutants are called criteria pollutants: particulate matter (PM), sulphur oxides (SOx), nitrous oxides (NOx), carbon monoxide (CO), ozone (O3) and lead (Pb). PM – suspended solid or liquid particles in air – of size <10µm (PM10) are considered inhalable. Furthermore, smaller particles of <2.5 µm (PM2.5) or <0.1 µm (PM1) can be absorbed into the blood and travel to every organ and systems of the body. The PM2.5 and PM1 are particularly important for effects on brain and composed of both organic and inorganic compounds.3

A recent meta-analysis of short-term exposure studies suggest that air pollution is a strong risk factor for stroke.4 Overall, every 10µg/m3 increase in PM2.5 leads to 1.1% (95% CI: 1.1-1.2) increase in incidence of admission or mortality from stroke. While PM10 (considerable proportion of larger particles) are less strongly associated with admission or mortality from stroke (0.3%, 95% CI: 0.2-0.4). Overall, one part per million (ppm) increase in CO leads to 1.5% (95% CI: 0.4-2.6) increase in incidence of admission or mortality from stroke. While every 10 ppb increase in sulphur oxide (SO2) lead to 1.9% (95% CI: 1.1-2.7) increase in admission or mortality from stroke. Every 10ppb increase in nitrogen oxide (NO2) lead to 1.4% (95% CI: 0.9-1.9) increase in admission or mortality from stroke. Similarly, every 10ppb increase in O3 lead to 0.1% (95% CI: 0.0-0.2) increase in admission or mortality from stroke. When stratified by income, the strength of association for all measures were stronger for LMICs than high-income countries (HICs).4

Evidence for long-term exposure based on meta-analysis which included 16 cohort studies (>2.2 million people and above 49 149 endpoint events – incident stroke and death from stroke) reported pooled hazard ratio (HR) of 11% (95% CI: 5-17) increased incidence of stroke and mortality for each 5 µg/m3 increment in PM2.5. These pollutants are 8-10 times higher in LMICs than the guideline values considered safe for health. The World Federation of Neurology has also reiterated to readdress the burden of air pollution.6,7

Air pollution components cause chronic neuro-inflammation, as these cross the blood-brain barrier. Furthermore, systemic effects (inflammation and oxidative stress) known to impact lung and cardiovascular disease also impinge upon brain health. Air pollution appears activates microglia and brain capillaries and lead to changes in blood-brain barrier which may be the key factor causing neuro-inflammation.8

In Pakistan, an estimated 350,000 strokes occur every year (~1000 per day) and among them 40% die within 30 days (~400 per day).9 The level of air pollution in Pakistan is alarming. A study in Karachi city reported annual mean PM2.5 levels of 76.5±SD38.4 µg/m3 and 101±SD45.6 at two locations,10 levels 8 to 10 times higher than the World Health Organization’s guidelines. Over the last several years, the air quality of Lahore city has been a big concern. Poor air quality limiting even visibility has caused travel delays, disrupted businesses and led to school closures. Although there are no direct studies for association of stroke and air pollution in Pakistan, the concern for attributable burden of stroke and air pollution has been voiced vehemently.11 Nonetheless, a time-series study in Karachi found that black carbon (BC) is associated with cardiovascular diseases. The study did not distinguish between those suffering from stroke and those who had cardiac disease.12,13 Interestingly, the long-term exposure

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studies based on longitudinal cohorts showed no significant results for Asia (HR=2.31, 95% CI: 0.49, 10.95) when the data was stratified according to regions. However, significant association between PM$_{2.5}$ and incidence of stroke was found in North America (HR=1.09, 95% CI: 1.05, 1.14) and Europe (HR=1.07, 95% CI:1.05, 1.10). This apparent disparity across regions raises questions and invites further region specific studies.

**Risk Mitigation efforts**

In September 2018, the United Nations General Assembly held a meeting on the prevention and control of non-communicable diseases (NCDs), and moving from ‘4 by 4’ to ‘5 by 5’ agenda, including air pollution as a risk factor and mental health as a disease. Five diseases include: cardiovascular disease (including stroke); chronic respiratory diseases; cancer; diabetes; mental and neurological conditions. While five modifiable risk factors include: unhealthy diet; tobacco use; harmful use of alcohol; physical inactivity; and air pollution. The prevention of air pollution requires improvement in fuel quality; industrial and vehicular technologies; traffic and industrial management; and lifestyle changes. The behavioural interventions for efficient energy use is one of the major factor for improvement of air quality, particularly for South Asia and Africa. The contribution of air pollution through household energy use (and emission of PM$_{2.5}$) in South Asia and Africa is estimated 64% and 78%. Secondly, the improvement in fuel quality such as halving the Sulphur content in fuel may decrease the toxic emissions of SOx to half. Thirdly, improvement in the technology for vehicles and industries reduces the emission to a greater extent. The import of spent vehicles and industrial technologies in LMICs in one of the major causes of increased emission. This requires conducive policies to address these issues. Enforcing and ensuring compliance with standards and regulations for industries as well as management of traffic is another viable option for reduction of pollution. Reducing the number of vehicles on the road and traffic management is needed to reduce air pollution in mega cities. These include mass transit services, carpooling and street environmental management. Thus, provision and use of public transport not only increases opportunity for physical activity, reduces road traffic accidents, reduces cost to society but also reduces air pollution.

Pakistan needs to develop robust monitoring of pollution. Monitoring should be used for risk communication for protection from exposure to pollution during high pollution periods. Specific guidelines are available for vulnerable population including elderly and those suffering from cardiovascular and respiratory ailments regarding avoiding exposure during high pollution periods. In the immediate and longer run it is imperative that we address fuel quality, traffic and industrial standards, as stated above, for improvement in environmental pollution. The National Environmental Quality Standards have been established in Pakistan and need to be updated, however, the major problem is in their uniform enforcement and implementation.

Furthermore, addressing the problem of exposure to environmental pollution and protection of health requires multi-stakeholder alliance. At the very least, the ministries of climate change and health must collaborate. Several public and private sector research and interventions are being undertaken in silos - environmental science institutions have carried out assessments on environment but have failed to relate these to the impact on human health. For interventions to gain public buy in and long term sustainability, synergy between environmental and health agendas is required in Pakistan. Addressing NCDs in our country, where the major contribution to risk is made by the environmental factors, requires focus on environmental pollution. The Aga Khan University has recently organized a think tank comprised of multi-sectoral, nationally representative group of experts to address NCDs, called the Aga Khan University Pakistan Initiative for NCDs (AKUPI-NCDs) The focus of this body is to address NCDs in the most comprehensive way and consider the five risk factors, including, importantly, air pollution.

**Dilemma and the unknowns**

Addressing air pollution through person personal protection is inconclusive. For example, use of N-95 face masks during heavy pollution may prevent exposure and protect health. However, there are variable results regarding its regular use, fit of the mask on the face and its effectiveness. Secondly, avoiding heavy air pollution days (avoiding work or schools) and spending time indoors using early warning systems have shown some promise. Also, dilemma surrounds regarding avoiding physical activity during heavy air pollution days and there is no consensus regarding this strategy. Thus, the above strategies are not fully effective, cost-effective or even sustainable.

Furthermore, the impact of air pollution on stroke is still unfolding. The indirect influence of air pollution on stroke through affecting diabetes and hypertension control, negative influence on physical activity and synergistic effects of smoking and air pollution has not been well studied.
Conclusions
Air pollution is the single largest environmental risk factor and considered the ‘new tobacco,’ where every 9 out of 10 individuals globally are exposed to unhealthy air. Stroke is the number one disease associated with environmental pollution and about a third of stroke can be prevented by addressing air pollution exposure alone. Concerted, multi-sectoral, local and national efforts and a systematic approach is needed to address air pollution through lifestyle changes, quality of fuel, addressing emissions from industry, vehicles and international standards enforcement.

References