

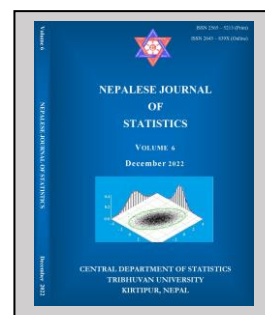
## Burden of Respiratory Diseases Attributable to Household Air Pollution in Nepal: National and Provincial Estimates

Srijan Lal Shrestha

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### ABSTRACT

**Background:** Household air pollution (HAP) is widespread in Nepal particularly in rural poor households where use of unprocessed biomass fuels (wood, animal dung and crop residues) for cooking is abundant. Studies have shown that health effects associated with HAP are primarily respiratory and cardiovascular diseases which are amongst the top burden of diseases in Nepal.

**Objective:** The study is conducted to estimate Attributable Fraction (AF) and corresponding Attributable Burden (AB) of diseases such as childhood pneumonia, acute respiratory infection/pneumonia and COPD/asthma which can be associated with HAP in Nepal, nationally and sub-nationally.

**Materials and Methods:** Estimates on fuel use in Nepal disaggregated by rural and urban areas and provinces are obtained from Nepal Multiple Indicator Cluster Survey (NMICS), 2019 published by Central Bureau of Statistics (CBS). The corresponding total disease burdens of Nepal related to respiratory diseases are obtained from the Department of Health Services (DoHS) for 2019/20. Estimates of model coefficients of the targeted respiratory diseases that can be attributed to HAP are obtained from several studies conducted previously in Nepal. Methodology adopted by World Health Organization (WHO) for estimation of AF and AB is applied in the present analysis.

**Results:** The estimated AF and AB of childhood pneumonia, ARI/pneumonia and COPD/asthma are obtained as 34.6% (95% CI = 7.4%-56.4%) and 7.3 (96% CI = 1.5-11.8) per 1000 under five children, 42.5% and 63.6 per 1000 population and 54.8% and 10.3 per 1000 population, respectively. AFs are found substantially higher (1.3-1.5 times) in rural Nepal compared to urban Nepal. Provincially, Karnali is found worst affected with highest attributions (45.3% - 65.6%) for the accounted burden of diseases and Bagmati found least affected with lowest attributions (18.7% - 34.6%) for the year 2019/20.

**Conclusion:** HAP is found to be a potential risk factor with high attributions for the occurrence of respiratory ailments in Nepal.

**Keywords:** Biomass fuel, burden of diseases, clean fuel and technologies, indoor air pollution, respiratory diseases.

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**Address correspondence to the author:** Central Department of Statistics, Tribhuvan University, Kirtipur, Kathmandu, Nepal. Email: srijan.shrestha@cds.tu.edu.np

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## INTRODUCTION

Household air pollution (HAP) or Indoor air pollution (IAP) is widespread in Nepal mainly in rural poor households where people do not have easy access to cleaner fuels like kerosene, biogas and LPG for domestic cooking and heating homes. People using mainly solid biomass fuels such as wood, animal dung or crop residue are found to be exposed to high air pollutants like particulate matter, carbon monoxide and other air pollutants. In Nepal, solid biomass fuel is the principal source of energy used for domestic purposes. According to Population Census of Nepal, 2011, 74.4% of the total households used biomass fuels like wood/firewood and animal dung in Nepal for cooking. Among the biomass fuel user households, 93% were rural households (Central Bureau of Statistics [CBS], 2012). According to a study conducted in Illam in 2015, 59% of the households used wood for cooking, 38% used mixed fuels, and remaining 3% used clean fuels (LPG, electricity, Biogas) (Dhimal, et al., 2016).

The latest available data of fuel use is from Nepal Multiple Indicator Cluster Survey (NMICS) conducted in 2019. According to the survey report, the percent of population (household members) in Nepal with primary reliance on clean fuels and technologies for cooking is found to be 43.2% and for cooking, space heating and lighting is found to be still 26.9%. This implies that the percent population relying on biomass and other unprocessed fuels for cooking is around 56.8% and for cooking, space heating and lighting is still 73.1% which is an overwhelmingly high figure (Central Bureau of Statistics [CBS] & United Nations Children's Fund [UNICEF], 2020). According to the report, the percent population with primary reliance on clean fuels and technologies for cooking is found to be 56.0% and 16.8% in urban and rural Nepal, respectively which implies that rural areas of Nepal is still predominantly relying in unprocessed fuels (83.2%) which is 1.89 times higher compared to urban areas of Nepal (Central Bureau of Statistics [CBS] & United Nations Children's Fund [UNICEF], 2020). Similarly, the comparison between percent of unprocessed fuel use (solid fuel) in urban and rural areas of Nepal based upon 2016 NDHS report shows that the percent was 88% in rural areas and 52% in urban areas which is equivalent to about 1.7 times higher in rural areas (Ministry of Health [MoH], New ERA & ICF, 2017). Province-wise comparison shows that Karnali has the highest reliance in biomass fuel (89.5%) followed by Sudoorpschim (79.6%), Province I (67.1%), Madhesh (64.9%), Lumbini (61.7%), Gandaki (49.9%) and least reliance in Bagmati province (24.8%). Kathmandu valley urban areas has only about 4.9% reliance in biomass fuel for cooking as per NMICS Report, 2019 (Table 1).

**Table 1.** Percent of population with primary reliance on clean fuels and technologies in Nepal, NMICS, 2019.

Area	Percent of population with primary reliance on clean fuels and technologies		Percent of population with primary reliance on biomass / unprocessed fuels	
	Cooking	Cooking, space heating and lighting	Cooking	Cooking, space heating and lighting
Nepal	43.2	26.9	56.8	73.1
Urban	56.0	36.8	44.0	63.2
Rural	16.8	6.4	83.2	93.6
Province I	32.9	17.5	67.1	82.5
Urban	43.0	23.7	57.0	76.3
Rural	16.1	7.2	83.9	92.8
Madhesh	35.1	18.3	64.9	81.7
Urban	41.7	22.0	58.3	78.0
Rural	18.5	9.0	81.5	91.0
Bagmati	75.2	59.2	24.8	40.8
Kathmandu valley urban	95.1	84.3	4.9	15.7
Other urban	71.1	44.6	28.9	55.4
Rural	22.6	6.7	77.4	93.3
Gandaki	50.1	28.2	49.9	71.8
Urban	64.0	37.3	36.0	62.7
Rural	24.0	11.0	76.0	89.0
Lumbini	38.3	15.8	61.7	84.2
Urban	51.3	23.3	48.7	76.7
Rural	19.0	4.7	81.0	95.3
Karnali	10.5	5.8	89.5	94.2
Urban	17.5	10.6	82.5	89.4
Rural	2.9	0.6	97.1	99.4
Sudoorpaschim	20.4	13.3	79.6	86.7
Urban	28.9	19.2	71.1	80.8
Rural	8.7	5.3	91.3	94.7

According to the World Bank database (2022), the percent population with access to clean fuels and technologies is found to have increased slowly over the past 20 years with around 5.7% in 2000, increased to 21.6% in 2010 and reached to 34.8% in 2020 (Fig. 1). Regarding the nature of the growth curve of clean fuel use, a parametric quadratic curve fits very well to the curve with  $R^2=0.999$  and estimated model equation as:  $3.1.07+1.817t - 0.014t^2$  considering  $t$  as the year. Percent access to clean fuels and technologies is an important indicator as it is also mentioned as a Sustainable Development Goal (SDG) indicator (SDG Indicator 7.1.2: Proportion of population with

primary reliance on clean fuels and technologies for the sustainable energy goal) (The World Bank, 2022). Respiratory and cardiovascular diseases have been closely associated exposure to air pollutants generated from biomass fuel combustion. Examination of respiratory burden of diseases of Nepal for the year 2019/20 shows high acute respiratory infection (ARI) outpatient department (OPD) visits (142 per 1000) with significantly higher OPD visits per 1000 in rural Nepal (169 per 1000) compared to urban Nepal (127 per 1000), province-wise the ARI OPD visits were highest in Karnali (203 per 1000) followed by Karnali (198 per 1000), and so on with least in Madhesh province (96 per 1000). Similarly, pneumonia, bronchitis, asthma and chronic obstructive pulmonary disease (COPD) OPD morbidities were 6-10 per 1000 population for 2019/20 (Department of Health Services [DoHS], 2021) (Table 2).

Evidently, pneumonia and COPD OPD visits per 1000 were relatively higher for urban areas compared to rural areas in Nepal which may be due to other factors apart from HAP such as high urban outdoor air pollution situation in Nepal. All these respiratory diseases are associated with HAP as shown by many studies around the world specifically the developing nations. If the reliance on clean fuels and technology is compared between the South Asian countries, it is found that the percent reliance is highest in Maldives (99%) followed by Bhutan (80%), India (68%), Pakistan (49%), Nepal (35%), and so on with the least in Bangladesh (25%) (The World Bank, 2022).

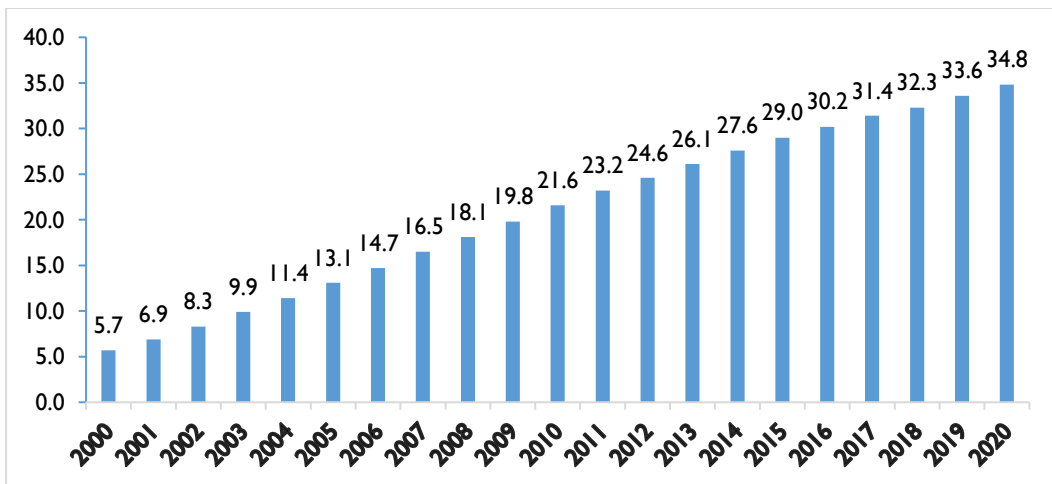


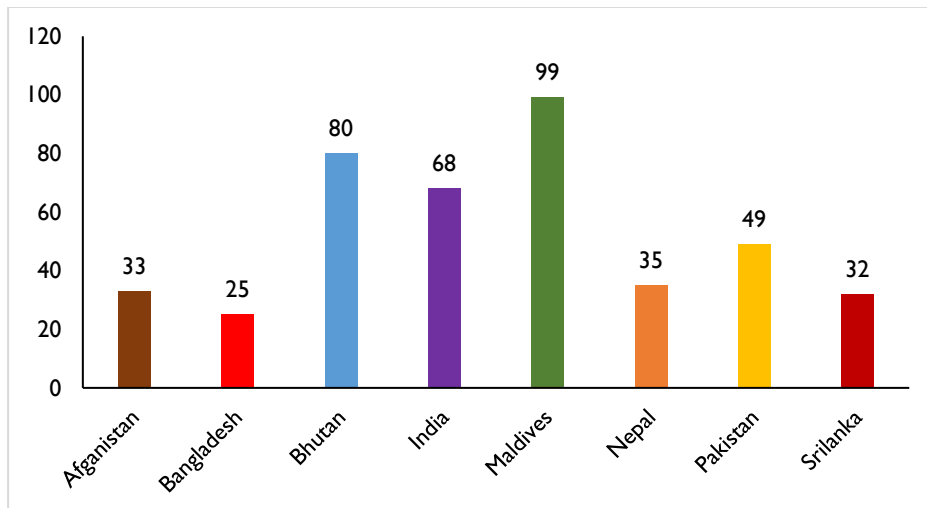
Fig. 1. Percent of population with access to clean fuels and technologies in Nepal.

**Table 2.** Morbidity (OPD visits) per 1000 population for the year 2019/20 in Nepal.

Region	ARI	Pneumonia	Bronchitis	Asthma	COPD
Nepal	142	8	6	10	9
Rural	169	6	5	11	6
Urban	127	8	6	9	10
Province I	156	10	6	7	7
Rural	174	8	5	7	5
Urban	145	12	8	7	8
Madhesh	96	4	6	9	3
Rural	108	3	6	10	3
Urban	91	5	6	9	4
Bagmati	128	7	5	8	12
Rural	191	7	5	11	7
Urban	107	7	5	7	14
Gandaki	198	9	6	11	12
Rural	219	4	5	10	9
Urban	186	12	7	12	15
Lumbini	156	7	7	11	10
Rural	175	6	7	11	6
Urban	139	8	7	10	12
Karnali	203	11	7	17	13
Rural	211	11	7	18	10
Urban	194	11	8	16	17
Sudoorpaschim	140	7	4	14	9
Rural	141	6	3	14	8
Urban	139	9	4	14	10

The recent burden of disease study in Nepal (2019) by Nepal Health Research Council (NHRC), Ministry of Health and Population (MoHP), Institute of Health Metrics and Evaluation (IHME) and UKaid Nepal Health Sector Programme 3, Monitoring Evaluation and Operational Research (MEOR) reported on the Nepal disease burden situation for the year 2019. According to the report, CVD, chronic respiratory diseases and respiratory infections (including TB) were amongst the top 5 burden of diseases regarding mortality assessed by years of life lost (YLL) and these diseases have been linked to HAP by many studies. Considering years of healthy life lost due to disability (YLD), chronic respiratory diseases were amongst the top ten burden of diseases (8<sup>th</sup>) in Nepal for 2019. CVD was placed in 14<sup>th</sup> top burden of diseases considering YLD. The overall situation of burden of diseases accounted by disability-adjusted life years (DALYs) again showed that CVD, chronic respiratory diseases and respiratory infections (including TB) were amongst the

top 5 burden of diseases. HAP from solid fuels was found to be amongst leading risk factors (3<sup>rd</sup>) of burden of diseases (mortality) in Nepal after smoking and high systolic BP (Nepal Health Research Council [NHRC], Ministry of Health and Population [MoHP], Institute of Health Metrics and Evaluation [IHME] & Monitoring Evaluation and Operational Research [MEOR], 2021).



**Fig. 2.** Percent of population with primary reliance on clean fuels and technologies for cooking in South Asian countries, 2020.

### *Air pollution monitoring studies*

There have been few HAP related studies in Nepal. Among them, some of the studies have been based upon air pollution measurements (Shrestha & Shrestha, 2005; Kurmi, Semple, Steiner, Henderson & Ayres, 2008; Kurmi et al., 2014; Chen, Breyse, Katz, Checkley, Curriero & Tielsch, 2016) and rest of them were based upon surrogate measures like fuel types and stove types (Ranabhat, Kim, Kim, Jha, Deepak & Connel, 2015; Ghimire, Mishra, Sharma, Siweya, Shrestha & Adhikari, 2019; Budhathoki et al., 2020; Pokharel, Smith, Khalakdina, Deuja & Bates, 2005; Dhimal et al., 2016; Nepal Health Research Council [NHRC], 2016). The studies showed that the levels of particulate air pollution ( $PM_{10}$ ,  $PM_{2.5}$ , SPM) were much higher (3-7 times) in houses using biomass fuels (wood, dung, etc.) compared to houses that used cleaner fuels (LPG, biogas, kerosene, etc.) with 24-hour averaging time and at cooking time. Particulate levels ( $PM_{10}$ ) were as high as  $2400 \mu\text{g}/\text{m}^3$  during cooking time and  $450 - 1380 \mu\text{g}/\text{m}^3$  ( $PM_{2.5}$ ) for 24-hr daily average. Similarly, mean CO concentration was 6.8 times higher (biomass:  $15.6 \text{ mg}/\text{m}^3$  and clean fuel:  $2.3 \text{ mg}/\text{m}^3$ ) during biomass fuel cooking time compared to clean fuel cooking time considering 15 minutes averaging time. The ratio is found to be similar (6.7 times) considering 24-hr averaging time for CO. The studies have made associations and risk analysis for different respiratory symptoms (Cough, phlegm, wheezing and breathlessness) and diseases (Asthma, COPD, ARI, etc.) and showed significant associations characterized by high prevalence, odds ratios (ORs) and other categorical data analysis measures for biomass fuel use. Some confounding variables like age, smoking habit, etc. were addressed in the studies (Table 3).

**Table 3.** Monitoring results of HAP related studies.

Area of study	PM level ( $\mu\text{g}/\text{m}^3$ )		CO level		Remarks	Reference
	Biomass fuel	Cleaner fuel	Biomass fuel	Cleaner fuel		
Some rural and urban areas of Nepal, 2003 (including Kathmandu valley)	PM <sub>10</sub> : 2418	793	15.6 mg/m <sup>3</sup>	2.3 mg/m <sup>3</sup>	15 min averaging cooking time for CO, 98 HHs	Shrestha & Shrestha, 2005
Rural and urban areas of Kathmandu valley 2006/2007	Rural (SP*: 893; DT*: 3580)	Urban: SP: 121 DT: 231	-	-	24-hr average 490 HHs	Kurmi et al., 2008
Rural and urban areas of Kathmandu valley 2006/2007	PM <sub>2.5</sub> : 455±2.4 1790 peak	101±2 141 peak	13.4 ± 2.2 ppm	2.0 ± 2.0 ppm	24-hr average 846 HHs	Kurmi et al., 2014
Rural southern Nepal, 2010-12	PM <sub>2.5</sub> : 1,376 (95% CI, 1,331–1,423)		10.9 (10.5–11.3) ppm		24-hr average, 2980 HHs for PM and 2013 HHs for CO	Chen et al, 2016

SP = SidePak; DT = DustTrak; ppm = part per million; HHs = Households;  
CO = carbon monoxide

HAP is a major environmental risk factor to exposed population regarding many diseases particularly respiratory and cardiovascular diseases and mortality associated with these diseases including all cause mortality. Few studies have been conducted to assess HAP and its health effects in Nepal and some in Kathmandu valley also. Some of the studies have estimated health risks in terms of relative risks (RRs) which are useful in calculation and assessment of health burdens that can be attributed to HAP mainly caused by burning unprocessed biomass fuels like wood, dung and crop residues for cooking and heating homes. Table 4 summarizes RRs obtained from different studies conducted in Nepal, and particularly in Kathmandu valley. These estimates are used for calculation of Attributable Fractions (AFs) and Attributable Burdens (ABs) associated with HAP.

**Table 4.** Health effect estimates from HAP obtained from studies in Nepal.

Health effect	RR	95% CI	Year	Name of study / Reference
Respiratory (COPD, Asthma)	3.13	0.83-11.76	2004	Situation analysis of indoor air pollution and development of guidelines for indoor air quality assessment and house building for health. Nepal Health Research Council [NHRC], 2004; Shrestha & Shrestha, 2005
Respiratory symptoms	2.78	0.57-11.76	2004	Situation analysis of indoor air pollution and development of guidelines for indoor air quality assessment and house building for health. Nepal Health Research Council [NHRC], 2004; Shrestha & Shrestha, 2005
ARI/Pneumonia	2.3 (PAF = 0.496)	-	2010	Environmental burden of acute respiratory infection and pneumonia due to indoor smoke in Dhading. Dhimal, Dhakal, Shrestha & Maskey, 2010
Respiratory symptom, Cough	2.00	0.55-7.31	2016	Indoor air quality and ventilation assessment of rural mountainous households of Nepal. Parajuli, Lee & Shrestha, 2016
Under five Mortality	13.4* (PAF=0.498)	4.84-29.48* (0.2350–0.6950)	2016	Attributable risk and potential impact of interventions to reduce household air pollution associated with under-five mortality in South Asia. Naz, Page & Agho, 2018
Childhood Pneumonia	1.93	1.14-3.28	2016	The association of childhood pneumonia with household air pollution in Nepal: Evidence from Nepal Demographic Health Surveys. Budhathoki et al., 2020

The purpose of the present study is to estimate AFs and ABs associated with HAP in Nepal based upon estimates of health effects associated with HAP from studies undertaken in Nepal, data on household fuel use in the recent years (2020) in Nepal and the total morbidity burden data assessed by OPD visits for respiratory ailments as mentioned in the Annual Report of DoHS.

## METHODOLOGY

### Study area

The study area covers the whole Nepal with disaggregation of urban and rural areas of federal states of Nepal and Kathmandu valley for comparative analysis and assessment.



## Data

Data for percent of population having access to clean fuels and technologies was compiled from published reports by CBS and United Nations Children's Fund (UNICEF) on Population Census, NMICS reports and World Bank website. Data for burden of diseases was taken from DoHS Annual Reports and its website. Model estimates of different health effects associated with HAP were extrapolated from different studies conducted earlier.

## Analysis

Assessment of health effects based upon coefficients obtained from previous studies were used to estimate AFs with percent of population relying on clean fuels and technologies for Nepal and different federal states of Nepal. Attributable health burdens are calculated with total burden of disease obtained from DoHS Annual Reports. Population Attributable Fraction (PAF) for each accounted health effect is calculated by the following expression (used by WHO for environmental burden of disease (EBD) assessment).

$$PAF = \frac{(P_{\text{exposed}} \times RR_{\text{exposed}} + P_{\text{unexposed}} \times 1) - 1}{P_{\text{exposed}} \times RR_{\text{exposed}} + P_{\text{unexposed}} \times 1}$$

where  $P_{\text{exposed}}$  = Proportion of exposed population by biomass fuel;  $P_{\text{unexposed}} = 1 - P_{\text{exposed}}$ ;  $RR_e$  = Relative risk of the exposed population obtained from exposure-response analysis.

Attributable burden is calculated as: PAF X Total burden

## RESULTS AND DISCUSSION

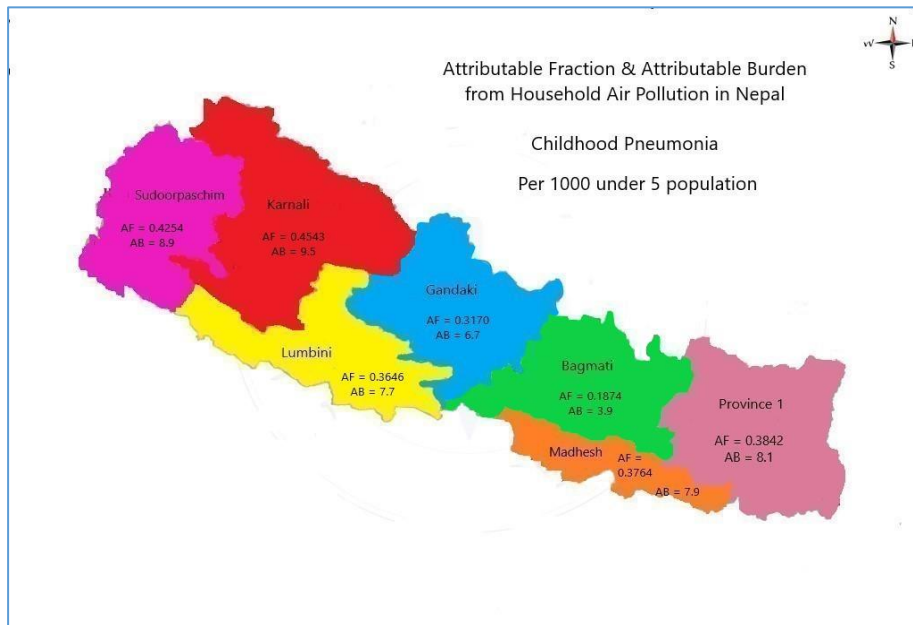
### Attributable burden due to HAP

Computation and assessment of attributable fractions and corresponding attributable burdens due to HAP are performed for childhood pneumonia ARI/pneumonia and COPD /asthma separately in the following sub-sections.

### Childhood pneumonia

The overall AF of childhood pneumonia for Nepal is found high (0.3457; 95% CI = 0.0737-0.5643) which means that around 34.6% of reported childhood pneumonia through OPD visits can be attributed to HAP in Nepal for the year 2019/20. The corresponding estimate of AB per 1000 under five population (3 Million) is found to be around 7.3 (96% CI = 1.5-11.8). Understandably, the rural estimate of AF is substantially higher (0.4362; 95% CI = 0.1043-0.6548) compared to urban estimate of AF (0.2904; 95% CI = 0.0580-0.5008), which amounts to around 1.5 times higher in rural Nepal compared to urban Nepal. If fuel consumption pattern is compared, the domestic fuel use of unprocessed fuels for cooking is also much higher in rural Nepal (83.2%) compared to urban (44.0%), which amounts to around 1.9 times higher in rural Nepal. Provincial-wise comparison revealed that the highest attributable statistics of childhood pneumonia due to HAP is detected in Karnali with AF = 0.4543 and AB = 9.5 per 1000 under five children in 2019/20, followed by Sudoorpaschim (AF = 0.4254 and AB = 8.9 per 1000 under five children), Province I (AF = 0.3842

and AB = 8.1 per 1000 under five children), Madhesh (0.3864 and AB = 7.9 per 1000 under five children), Lumbini (AF = 0.3646 and AB = 7.7 per 1000 under five children), Gandaki (AF = 0.3170 and AB = 6.7 per 1000 under five children) and the least in Bagmati (AF = 0.1874 and AB = 3.9 per 1000 under five children) (Fig. 3 & Annex).

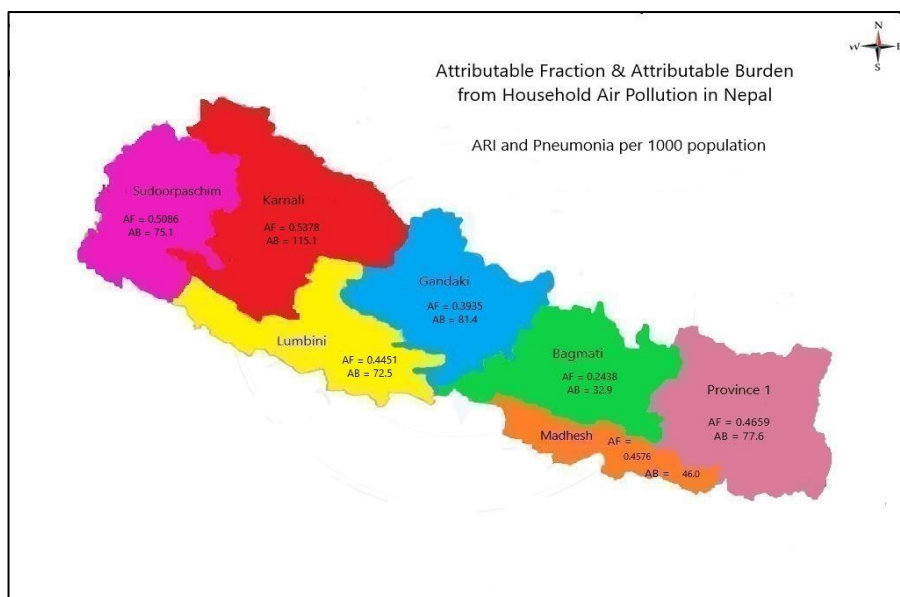


**Fig. 3.** AF and AB of childhood pneumonia in Nepal.

### ARI and pneumonia

The overall AF of ARI and pneumonia is found even higher (0.4248) than childhood pneumonia in Nepal. The figure reveals that around 42.5% of the reported ARI and pneumonia (OPD visits) can be attributed to HAP in Nepal for the year 2019/20. The corresponding estimate of AB per 1000 population is found to be around 63.6<sup>1</sup>. As in childhood pneumonia, the rural estimate of AF is substantially higher (0.5196) compared to urban estimate of AF (0.3639), which amounts to around 1.4 times higher in rural Nepal compared to urban Nepal. Provincial-wise quantitative comparison revealed that the highest attributable statistics of ARI / pneumonia due to HAP is detected in Karnali with AF = 0.5378 and AB = 115.1 per 1000 population in 2019/20, followed by Sudoorpaschim (AF = 0.5086 and AB = 75.1 per 1000), Province I (AF = 0.5883 and AB = 77.6 per 1000), Madhesh (0.4576 and AB = 46.0 per 1000), Lumbini (AF = 0.4451 and AB = 72.5 per 1000), Gandaki (AF = 0.3935 and AB = 81.4 per 1000) and the least in Bagmati (AF = 0.2438 and AB = 32.9 per 1000). Moreover, in all provinces of Nepal, the AFs of ARI and pneumonia attributable to HAP are found significantly higher in rural areas within the provinces compared to the urban areas (Fig. 4 & Annex).

<sup>1</sup> 95% CI is unavailable for ARI / pneumonia.

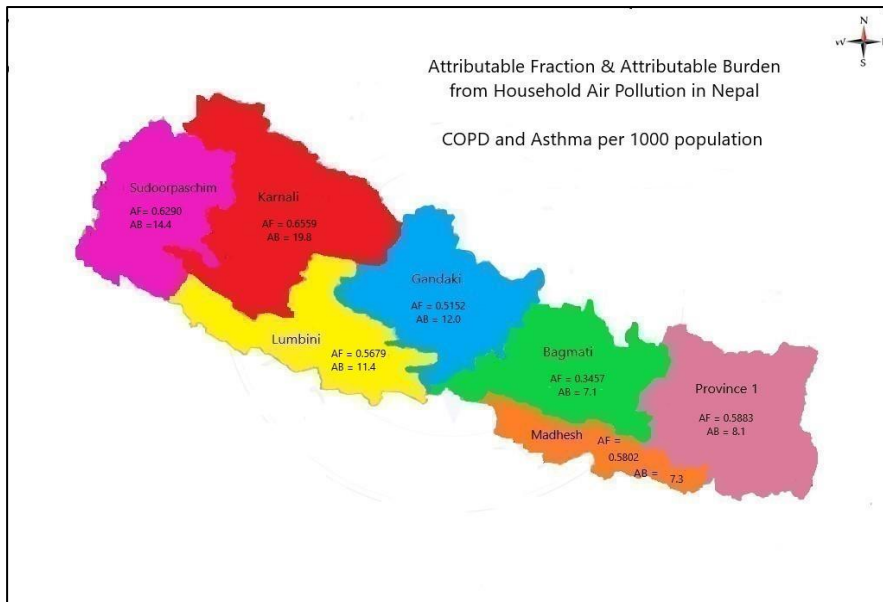


**Fig. 4.** AF and AB of ARI and pneumonia in Nepal.

### *COPD and asthma*

The overall AF of COPD and asthma is found highest (0.5475) compared to childhood pneumonia and ARI and pneumonia in Nepal. It reveals that around 54.8% of the reported COPD and asthma (OPD visits) can be attributed to HAP in Nepal for the year 2019/20 which can be regarded as very high attribution to HAP. The corresponding estimate of AB per 1000 population is found to be around 10.3<sup>2</sup>. As in childhood pneumonia and ARI / pneumonia, the rural estimate of AF is substantially higher (0.6393) compared to urban estimate of AF (0.4838), which amounts to around 1.3 times higher in rural Nepal compared to urban Nepal. Provincial-wise quantitative comparison revealed that the highest attributable statistics of ARI / pneumonia due to HAP is detected in Karnali with AF = 0.6559 and AB = 19.8 per 1000 population in 2019/20, followed by Sudoorpaschim (AF = 0.6290 and AB = 14.4 per 1000), Province I (AF = 0.5883 and AB = 8.1 per 1000), Madhesh (0.5802 and AB = 7.2 per 1000), Lumbini (AF = 0.5679 and AB = 11.4 per 1000), Gandaki (AF = 0.5152 and AB = 12.0 per 1000) and the least in Bagmati (AF = 0.3457 and AB = 7.1 per 1000). It is also to be noted that in all provinces of Nepal, the AFs are found significantly higher in rural areas within the provinces compared to the urban areas (Fig. 5 & Annex).

<sup>2</sup> 95% CI is considered not acceptable for COPD / asthma.



**Fig. 5.** AF and AB of COPD and asthma in Nepal.

### Limitations

Estimates of model coefficient of association between HAP and health effects are based upon only few studies that have been conducted in Nepal. More such studies are desirable for health effect attribution in studies similar to the present. However, due to lack of substantial number of studies based upon local data, more studies could not be incorporated in the present analysis. Moreover, confidence interval estimates for ARI/pneumonia and COPD / asthma could not be incorporated due to absence of its reliable estimates. Also, other health effects that can be associated with HAP such as cardiovascular diseases could not be included due to lack of estimates based upon local data incorporated studies. Moreover, only OPD visits data could be accounted since inpatient data disaggregated for provinces and rural / urban areas was unavailable for the present analysis. Additionally, comparisons have been made based upon provincial estimates and could not be analyzed based upon lower level boundaries such as at municipality/ward level which would be more appropriate especially for adjacent locations but lying in different provinces primarily due to data unavailability of local level fuel use pattern in recent years. Also, it needs to be noted that the provincial estimates put forward are based upon data and estimates available for present analysis. Upon availability of more recent and representative data, and estimates, further analysis can be performed.

### CONCLUSION

The study findings reveal that HAP in Nepal is a serious public health concern to Nepalese people, particularly the rural poor with substantially high proportion of attribution to respiratory diseases that can be attributed HAP. Rural people are found to be significantly more affected with respiratory ailments such as ARI, pneumonia, COPD and asthma that can be associated with HAP

compared to urban residents in Nepal. Provincial estimates depicted that Karnali and Sudoorpaschim provinces are relatively more affected by HAP than other provinces with least effects found in Bagmati province.

## CONFLICT OF INTEREST

The author declared absence of conflict of interest.

## ACKNOWLEDGEMENTS

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