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Original Article

Macrolevel association of COVID-19 with non-communicable disease risk factors in India

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ABSTRACT

Background & aims: Greater COVID-19 related mortality has been reported among persons with various non-communicable diseases (NCDs). We performed an ecological study to determine the association of state-level cases and deaths with NCD risk factors and healthcare and social indices.

Methods: We obtained cumulative national and state-level data on COVID-19 cases and deaths from publicly available database www.covid19india.org from February to end November 2020. To identify association with major NCD risk factors, NCDs, healthcare related and social variables we obtained data from public sources. Association was determined using univariate and multivariate statistics.

Results: More than 9.5 million COVID-19 cases and 135,000 deaths have been reported in India towards end of November 2020. There is significant positive correlation (Pearson r) of state-level COVID-19 cases and deaths per million, respectively, with NCD risk factors- obesity (0.64, 0.52), hypertension (0.28, 0.16), diabetes (0.66, 0.46), NCD epidemiological transition index (0.58, 0.54) and ischemic heart disease mortality (0.22, 0.33). Correlation is also observed with indices of healthcare access and quality (0.71, 0.61), urbanization (0.75, 0.73) and human (0.61, 0.56) and sociodemographic (0.70, 0.69) development. Multivariate adjusted analyses shows strong correlation of COVID-19 burden and deaths with NCD risk factors ($r^2 = 0.51, 0.43$), NCDs ($r^2 = 0.32, 0.16$) and healthcare ($r^2 = 0.52, 0.38$).

Conclusions: COVID-19 disease burden and mortality in India is ecologically associated with greater state-level burden of NCDs and risk factors, especially obesity and diabetes.

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1. Introduction

There is strong association of COVID-19 with non-communicable diseases (NCDs) and their risk factors [1]. Multiple studies from across the globe have reported that individuals with established coronary heart disease, heart failure, chronic respiratory, renal or liver disease and cancers or their risk factors such as diabetes, hypertension, obesity, and other vascular risk factors are at greater risk of acquiring infection and developing complications and deaths from COVID-19 [2–10]. Environmental factors such as

urbanization, crowding, ambient and indoor air pollution, poor sanitation and low socioeconomic status are also important in increasing the risk of disease incidence and deaths [5,11–13].

India has one of the highest absolute burden of COVID-19 infection with more than 9.5 million cases and 135,000 deaths reported by November 2020 [14]. However, the rates of infection related cases and deaths per million population are lower than many developed countries [15]. Mortality rate (case-fatality rates) from the infection are also lower than many developed countries [15]. There is significant state-level variation in incidence of cases and deaths with more developed and urbanized states of the country reporting greater disease burden [16,17]. Small case-series from India have reported greater mortality from COVID-19 among hospitalized patients with diabetes, heart failure, chronic respiratory and chronic liver and kidney diseases [18–20]. It is likely that

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state-level variation in incidence of COVID-19 and mortality is influenced by presence of NCDs and their risk factors in these states, as hypothesized in a previous study [21]. We performed a macrolevel ecological analysis using publicly available data to identify association of regional (state-level) burden of COVID-19 cases and deaths with non-communicable diseases, NCD risk factors and selected social determinants.

2. Methods

The study has been conducted using publicly available data on COVID-19, NCD risk factors and social factors [14,22]. The project proposal was approved by the institutional ethics committee as part of COVID-19 database at our centre. Daily data on COVID-19 in various states and regions of India are being regularly updated at a non-commercial public website, www.covid19india.org [14]. This website updates daily data on COVID-19 related cases, deaths, recovery and testing at the state level of India. We obtained data for all the states in the country and clubbed daily data into weekly and monthly numbers beginning February 2020 to end of November 2020. The data were collated on spreadsheets. We then calculated number of cases and deaths per million population, using 2020 estimates, for each state (Table 1).

We obtained data on state-level burden of related NCD risk factors (obesity, hypertension, diabetes, smoking, literacy), NCDs (epidemiological transition index, ETI, proportion of disability adjusted life years due to NCDs vs. communicable, maternal, neonatal and nutritional diseases) [25], and diseases (ischemic heart disease deaths and disability adjusted life years, DALYs) from national data sources as shown in Table 2 [22–29]. Data on healthcare related factors (healthcare availability index (HAI), healthcare access and quality in index (HAQI) and

sociodemographic indices of each state were also obtained from public websites [25,26]. The following indices were used: urbanization index (UI, proportion of urban to rural population) [27], human development index (HDI) [28], sociodemographic index (SDI) [25], social development index [29], and vulnerability index [30]. Details of estimation of each of these indices have been reported earlier [22].

Statistical analyses: We determined burden of COVID-19 cases and deaths per million population at end of November 2020 for each state of the country. Descriptive statistics for each state is reported. To determine association of COVID-19 cases and death with state-level NCD and risk factors, healthcare indices and sociodemographic variables we calculated Pearson’s correlation coefficient (r value) using SPSS Statistical Package. MS Office Powerpoint-2007 was used to plot scatter-graphs for estimation of correlation of various NCD risk factors, NCD and sociodemographic indices with total cases/million and deaths/million. Linear correlation was calculated and R² values are reported. To identify factors of importance we also calculated multivariate regression statistics. P value < 0.05 was considered significant.

3. Results

More than 9.5 million COVID-19 cases and 135,000 deaths have been reported in India towards the end of November 2020 [14]. The national burden of cases and deaths is 6900/million and 100.4/million respectively. There are wide disparities in rates of cases and deaths in different states of India (Table 1) with reported cases more than 20,000/million in states of Delhi and Goa and 10,000–20,000/million in a number of states. Similarly deaths rates of more than 300/million are observed in Delhi (490), Goa (434) and Maharashtra (383). There is significant association of state-

Table 1
COVID-19 cases, deaths and rates/million population in various states in India at 30th November 2020.

States	Population 2020	Cases		Deaths		Case:Fatality ratio
		Number	Per million	Number	Per million	
India	1371360650	9463254	6900.63	137659	100.38	1.45
Andhra Pradesh	53903393	868064	16104.07	6992	129.71	0.81
Arunachal Pradesh	1570458	16282	10367.68	54	34.38	0.33
Assam	35607039	212776	5975.67	981	27.55	0.46
Bihar	124799926	235616	1887.95	1264	10.13	0.54
Chhattisgarh	29436231	237322	8062.24	2861	97.19	1.21
Delhi	18710922	570374	30483.48	9174	490.30	1.61
Goa	1586250	47963	30236.72	688	433.73	1.43
Gujarat	63872399	209780	3284.36	3989	62.45	1.90
Haryana	28204692	234126	8300.96	2428	86.08	1.04
Himachal Pradesh	7451955	40518	5437.23	635	85.21	1.57
Jammu Kashmir	13606320	110224	8100.94	1694	124.50	1.54
Jharkhand	38593948	109151	2828.19	964	24.98	0.88
Karnataka	67562686	884897	13097.42	11778	174.33	1.33
Kerala	35699443	602983	16890.54	2245	62.89	0.37
Madhya Pradesh	85358965	206128	2414.84	3260	38.19	1.58
Maharashtra	123144223	1823896	14811.06	47151	382.89	2.59
Manipur	3091545	25045	8101.13	281	90.89	1.12
Meghalaya	3366710	11810	3507.88	111	32.97	0.94
Mizoram	1239244	3825	3086.56	5	4.03	0.13
Nagaland	2249695	11186	4972.23	64	28.45	0.57
Odisha	46356334	318725	6875.54	1792	38.66	0.56
Punjab	30141373	152091	5045.92	4807	159.48	3.16
Rajasthan	81032689	268063	3308.08	2312	28.53	0.86
Sikkim	690251	4990	7229.25	109	157.91	2.18
Tamilnadu	77841267	781915	10044.99	11712	150.46	1.50
Telangana	39362732	269816	6854.61	1458	37.04	0.54
Tripura	4169794	32692	7840.20	367	88.01	1.12
Uttar Pradesh	237882725	543888	2286.37	7761	32.63	1.43
Uttarakhand	11250858	74795	6647.94	1231	109.41	1.65
West Bengal	99609303	483484	4853.80	8424	84.57	1.74

Table 2
State level non-communicable disease risk factors and burden, healthcare indices and social factors.

	Smoking/ Tobacco (%)	Obesity (%)	Hypertension (%)	Diabetes (%)	Literacy (%)	Epidemiological Transition index	IHD DALYs	IHD death rate/ 100,000	Healthcare availability index	Healthcare access and quality index	Urbanization index	Human development index	Socio Demographic Index	Social Development Index	Vulnerability Index
Data sources	NFHS	NFHS	DLHS	DLHS	Census	GBD	GBD	GBD	NITI	GBD	Census	Niti	GBD	IEG	IIPS
Andhra Pradesh	26.8	33.1	24.3	9.1	67.02	2.70	2099143	163.43	65.13	46.50	33.49	0.64	0.59	0.652	0.71
Arunachal Pradesh	60.0	18.5	23.0	4.1	65.39	1.82	14399	37.27	46.07	44.30	22.67	0.66	0.59		0.03
Assam	63.9	12.5	18.2	3.5	72.19	1.61	573640	66.41	48.85	34.00	14.08	0.61	0.56	0.632	0.26
Bihar	50.1	11.2	18.9	2.5	61.8	1.35	2666743	103.02	32.11	37.00	11.30	0.58	0.44	0.226	0.97
Chhattisgarh	55.2	11.0	15.2	4.4	70.28	1.67	649384	93.15	53.36	37.40	23.24	0.61	0.56	0.543	0.31
Delhi	30.4	25.8	21.9	8.2	86.21	2.63	516942	107.62	49.42	56.20	97.50	0.75	0.75		0.51
Goa	20.8	32.2	28.8	16.7	88.7	4.76	45319	136.28	51.90	64.80	62.17	0.76	0.74		0.31
Gujarat	51.4	19.9	0.0	0.0	78.03	2.17	2508489	159.59	63.52	45.00	42.58	0.67	0.62	0.635	0.77
Haryana	35.8	18.0	21.3	4.9	75.55	2.50	1213832	174.92	53.51	45.00	34.79	0.71	0.66		0.40
Himachal Pradesh	40.5	24.6	33.7	3.2	82.8	3.33	179914	113.7	62.41	51.70	10.04	0.72	0.67	0.499	0.06
Jammu Kashmir	38.2	22.1	0.0	0.0	67.16	2.94	401570	143.21	62.37	46.70	27.21	0.69	0.60	0.640	0.71
Jharkhand	48.6	10.1	20.6	3.3	66.41	1.45	790885	95.69	51.33	37.40	24.05	0.60	0.52	0.921	0.91
Karnataka	34.3	22.1	22.6	9.5	75.37	2.94	2577991	169.35	61.14	46.60	38.57	0.68	0.61	0.468	0.57
Kerala	25.7	33.0	40.3	14.2	94	6.25	1227249	170.36	74.01	63.90	47.72	0.78	0.68	0.730	0.31
Madhya Pradesh	59.5	11.4	17.0	2.4	69.32	1.67	2283586	122.41	38.39	39.50	27.63	0.61	0.53		1.00
Maharashtra	36.5	21.9	23.2	5.0	82.34	3.03	4469799	163.78	63.99	49.80	45.23	0.70	0.67		0.83
Manipur	70.6	22.6	21.3	7.6	76.9	2.38	50620	68.98	60.60	44.20	30.21	0.69	0.61		0.54
Meghalaya	72.2	11.0	20.4	2.9	74.43	1.56	29460	39.41	55.95	39.60	20.08	0.66	0.59		0.29
Mizoram	80.4	20.5	19.2	3.4	91.33	1.89	8193	27.37	74.97	48.90	51.51	0.71	0.63		0.14
Nagaland	69.4	14.1	33.2	5.6	79.6	2.13	28504	50.92	38.51	46.10	28.97	0.68	0.66	0.467	0.66
Odisha	55.9	16.5	16.1	3.2	72.89	1.72	808170	71.55	35.97	36.30	16.68	0.61	0.55	0.766	0.80
Punjab	19.2	26.5	31.7	6.3	75.84	3.45	1725787	261.05	63.01	49.50	37.49	0.72	0.65		0.43
Rajasthan	46.9	12.7	18.6	2.7	66.11	1.52	1762007	94.96	43.10	40.70	24.89	0.63	0.53	0.732	0.69
Sikkim	40.3	27.4	29.7	4.5	81.42	2.22	10289	65.07	50.51	50.50	24.97	0.72	0.63	0.732	0.00
Tamilnadu	31.7	29.4	23.2	15.3	80.09	3.85	3629123	207.5	60.41	51.20	48.45	0.71	0.65		0.57
Telangana	28.3	26.0	22.9	8.0		2.63	1213030	134.51	59.00	48.50	48.45	0.67	0.61	0.340	0.94
Tripura	67.8	15.3	19.8	9.1	87.22	2.22	112459	106.59	46.38	42.30	26.18	0.66	0.57		0.63
Uttar Pradesh	53.0	13.2	17.7	3.2	67.68	1.47	5008099	99.47	28.61	34.90	22.28	0.60	0.51	0.709	0.89
Uttarakhand	43.7	18.4	26.3	3.8	78.82	2.17	297063	119.58	40.20	43.20	30.55	0.68	0.64		0.43
West Bengal	58.8	16.2	20.7	9.2	76.26	3.03	3284771	146.32	57.17	47.10	31.87	0.64	0.58		0.83

DLHS District level health survey; GBD Global burden of diseases study; IEG Institute for economic growth; IIPS Indian institute of population sciences; NFHS National family health survey-4; NITI National institute for transforming India.

level cases/million and deaths/million ($r = 0.86$). The case-fatality rate also shows significant differences with less than 0.5% in Mizoram, Arunachal Pradesh, Kerala and Assam to more than 2% in Punjab, Maharashtra and Sikkim. Data on various state-level NCD risk factors (obesity, hypertension, diabetes, smoking, and literacy), NCDs (NCD epidemiological transition index, ischemic heart disease), healthcare indices and various sociodemographic indices are in Table 2 and also shows wide variability.

Univariate correlation analysis (Pearson’s r value) (Table 3) shows significant correlation of state-level COVID-19 cases/million with obesity (0.642), hypertension (0.283), diabetes (0.656) and literacy (0.460) and inverse association with tobacco use (−0.555). Significant correlation is also observed with ETI (0.585), HAQI (0.710), urbanization (0.745), HDI (0.608), sociodemographic index (0.698) and social development index (0.608). COVID-19 death rates show significant correlation with obesity (0.520), diabetes (0.458) and literacy (0.458) and inverse association with tobacco use (−0.554). Significant correlation is also observed with ETI (0.437), IHD death rate (0.332), HAQI (0.614), urbanization (0.726), HDI (0.563) and sociodemographic index (0.686). Correlation of NCD risk factors (obesity, hypertension, diabetes and tobacco with COVID-19 cases (Fig. 1) and deaths (Fig. 2) show that the strongest association is with state-level diabetes prevalence.

Multivariate analyses shows significant association of COVID-19 cases as well as deaths with NCD risk factors (unadjusted r^2 , cases 0.73, deaths 0.51; multivariate adjusted r^2 , cases 0.65, deaths 0.36) (Table 4). NCD burden as estimated by epidemiological transition index shows significant association with COVID-19 cases (unadjusted r^2 0.34, adjusted r^2 0.32) and not with deaths. This association disappears after adjustment for NCD risk factors. Association of COVID-19 cases and deaths was also observed with healthcare related factors (unadjusted r^2 , cases 0.55, deaths 0.42; multivariate adjusted r^2 , cases 0.52, deaths 0.38), however, this association was no longer observed with various social factors after adjusting for NCD risk factors, NCDs and healthcare related factors (Table 4).

4. Discussion

Indian states with greater burden of non-communicable disease risk factors (obesity, diabetes) and in advanced stage of

epidemiological transition with greater NCD burden, better healthcare access and quality, greater urbanization and higher human and sociodemographic development have greater COVID-19 case burden and mortality. This finding has important implications for implementation of population and individual level preventive measures and equitable vaccine deployment.

That NCD risk factors as well as the disease conditions increase risk of adverse outcomes in COVID-19 is well reported. Large registries as well as population based databases in UK, USA, Europe and elsewhere have reported such association. OpenSafely and QRESEARCH patient-level cohorts in UK [5,31], and multiple cohorts in USA have reported that presence of diabetes, hypertension and obesity is associated with greater disease incidence and mortality [3,4]. In OpenSafely population-based cohort of more than 17 million adults in UK, NCD risk factors were associated with significantly greater age-adjusted hazard ratios and 95% confidence intervals (CI) for COVID-19 related deaths: hypertension 1.22 (CI 1.15–1.30), respiratory disease 2.35 (CI 2.21–2.50), chronic heart disease 2.01 (CI 1.90–2.13), controlled diabetes 2.02 (CI 1.89–2.16) and uncontrolled diabetes 3.61 (CI 3.34–3.90) while current smoking was associated with reduced risk [5]. All the hazard ratios attenuated after adjusting for multiple lifestyle variables [5], similar to the present study, highlighting underlying importance of lifestyle and anthropometric factors in NCD risk factors. Similar findings have been reported in studies from China [3], USA [4,5], other low and middle income countries including India [16–10,18–20].

Little is, however, known regarding macrolevel association of NCD risk factors and diseases on COVID-19 burden and mortality. A significant association of aging with adverse outcomes in COVID-19 has been reported in China, Europe and USA [1]. In India a study reported heightened adverse events among the elderly using a modeling algorithm [32]. It is well known that NCD risk factors such as hypertension and diabetes as well as NCDs increase with age [24,33], and this could be a reason of greater COVID-19 related deaths in better developed states as observed in the present study (Table 3). Inverse association with smoking is an outlier and could be due to greater smoking in lesser developed states in India where COVID-19 burden is lower [23]. Average life expectancy of all these states is significantly greater than those states where the disease

Table 3
Association of various non-communicable diseases, healthcare and social indices with COVID-19 cases and deaths (Pearson’s r).

Variables	Cases/million	Deaths/million
Non-communicable disease risk factors		
Obesity (NFHS)	0.642**	0.520**
Hypertension (DLHS/AHS)	0.283	0.164
Diabetes (DLHS/AHS)	0.656**	0.458*
Literacy rates (Census)	0.460*	0.458*
Smoking/Tobacco (NFHS)	−0.555**	−0.554**
Non-communicable diseases		
NCD Epidemiological transition index (GBD)	0.585**	0.437*
Ischemic heart disease DALYs (GBD)	−0.120	0.067
Ischemic heart disease death rate (GBD)	0.224	0.332*
Healthcare Related Factors		
Healthcare availability index (NITI)	0.226	0.177
Healthcare accessibility and quality index (GBD)	0.710**	0.614**
Macrolevel Social Factors		
Urbanization index (Census)	0.745**	0.726**
Human development index (MOSPI)	0.608**	0.563**
Sociodemographic index (GBD)	0.698**	0.686**
Vulnerability index (IIPH)	−0.207	−0.095
Social development index (IEG)	0.608*	0.035

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

DLHS/AHS District level health survey/Annual health survey; GBD Global burden of diseases study; IEG Institute for Economic Growth; IIPH Indian institute of population health; MOSPI Ministry of Statistics and Program Implementation; NCD non-communicable diseases; NFHS National family health survey-4; NITI National institute for transforming India.

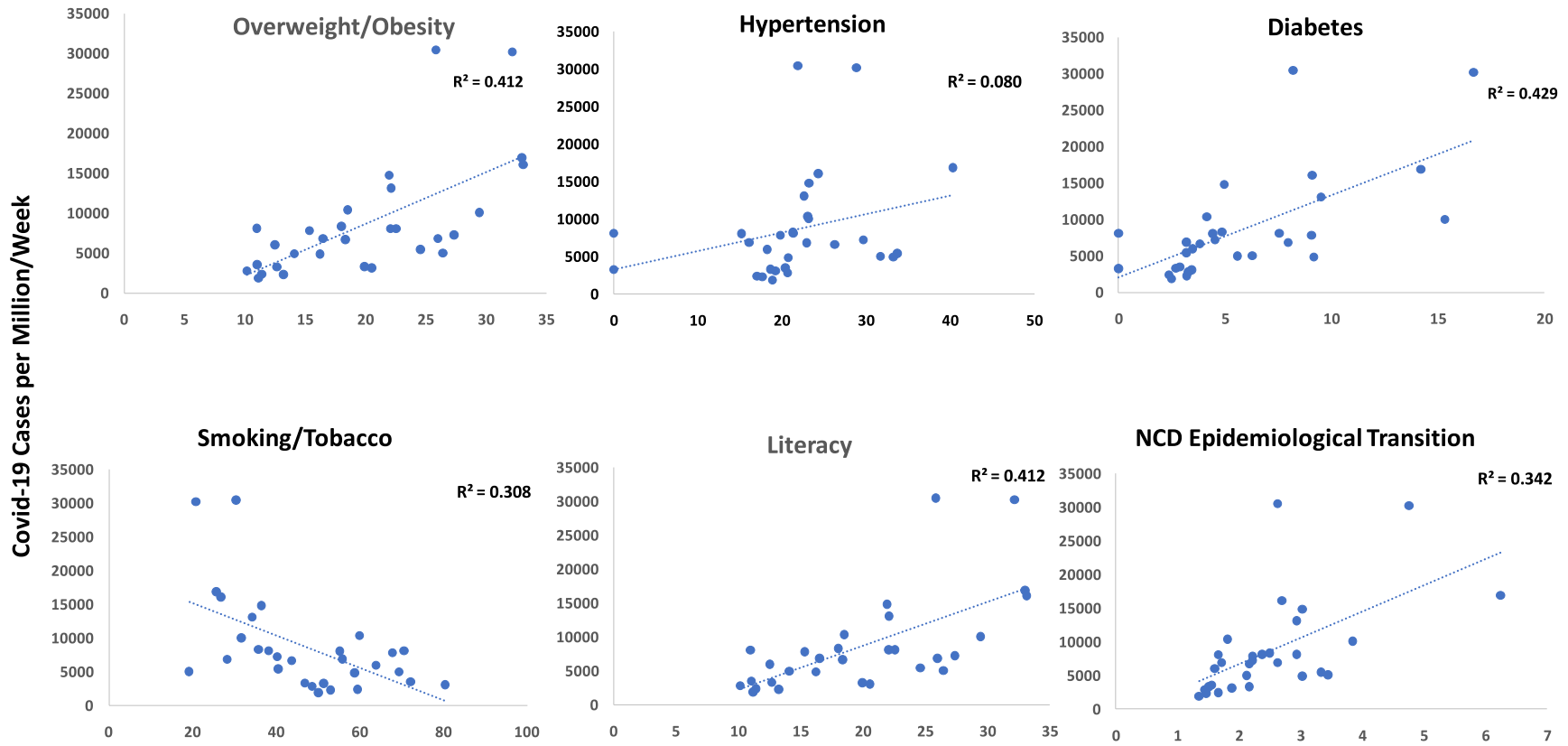


Fig. 1. Association of multiple non-communicable disease (NCD) risk factors with cumulative COVID-19 cases/million.

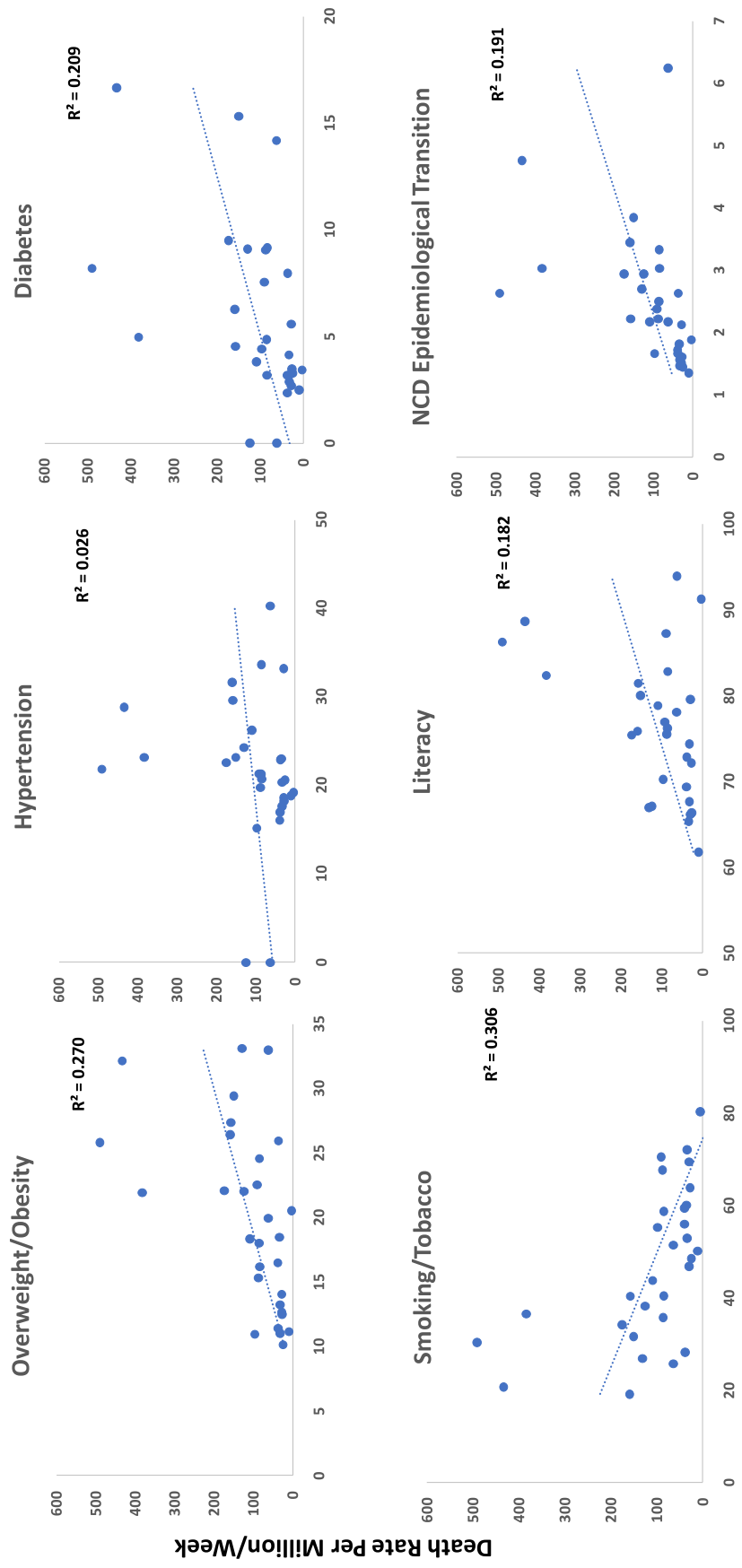


Fig. 2. Association of non-communicable disease (NCD) risk factors with cumulative COVID-19 deaths/million.

Table 4
Multiple regression analysis of COVID-19 cases and deaths with various risk factors.

Variables	COVID-19 Cases/million			COVID-19 Deaths/million		
	B value	Standardized beta	P value	B value	Standardized beta	P value
Non-communicable disease risk factors						
Overweight or Obesity	109.90	0.11	0.66	-2.29	-0.13	0.62
Hypertension	-172.84	-0.20	0.23	-3.94	-0.27	0.14
Diabetes	747.18	0.43	0.04	5.51	0.19	0.37
Smoking/Tobacco	-150.87	-0.34	0.11	-4.66	-0.63	0.01
Literacy rate	191.32	0.22	0.25	6.48	0.44	0.04
Multivariate correlation	$r^2 = 0.601$; Adjusted $r^2 = 0.514$			$r^2 = 0.533$, Adjusted $r^2 = 0.433$		
Non-communicable diseases burden						
NCD epidemiological transition index	3907.961	0.58	<0.01	49.56	0.44	0.02
Univariate correlation	$r^2 = 0.343$; Adjusted $r^2 = 0.319$			$r^2 = 0.192$; Adjusted $r^2 = 0.163$		
Multivariate correlation	Model not significant			Model not significant		
Healthcare related factors						
Healthcare availability index	-157.77	-0.26	0.111	-2.60	-0.25	0.169
Healthcare accessibility and quality index	814.88	0.86	<0.001	12.21	0.76	<0.001
Multivariate correlation	$r^2 = 0.549$; Adjusted $r^2 = 0.516$			$r^2 = 0.420$; Adjusted $r^2 = 0.377$		
Macrolevel social factors						
Model Not Significant			Model Not Significant			

burden is lower [26,27]. A macrolevel analysis from India previously reported greater case-fatality in states with greater population of the aged [21]. In USA, a study reported macrolevel association of COVID-19 burden and case-fatality with air pollution, gross domestic product (GDP) per capita and urbanization [34]. An international macroecological study reported association of COVID-19 burden and mortality with national GDP, urbanization, population density, number of tourists in a country and geographic longitude [35]. Influence of demographic and socioeconomic factors in the COVID-19 case-fatality rate globally was examined among 10.5 million cases in 209 countries. Doubling in size of population, proportion of female smokers, higher stringency index and active testing policies were associated with higher case-fatality rate while inverse association was found between cardiovascular disease death rate and diabetes prevalence [36]. In the present study we did not find any association of case-fatality rates in different Indian states with NCD risk factors and other indices (data not shown) and therefore we have not commented on this issue.

No sub-national studies, similar to the present study, have been reported from developed countries although recent surge of COVID-19 in rural locations in USA, where the NCDs as well as risk factors are significantly greater [37], suggest such an association [38]. A prospective study using UK Biobank participants reported significantly greater disease in Blacks and South Asians [39]. Greater COVID-19 disease and mortality among Blacks, South Asians and Minority ethnic groups in UK have been attributed to multiple factors including harmful social behaviors, health behaviors and comorbidity-burden, especially diabetes [40]. Greater COVID-19 burden and mortality among socioeconomically deprived African Americans and Hispanics in USA has also been attributed to comorbidities [3,4,41]. In the present study NCD risk factors are greater in states with greater HDI, SDI, urbanization and epidemiological transition index (Table 2), in contrast to studies in developed countries. Positive association of NCDs and risk factors with urbanization and human development has been reported in India [33]. This could be the reason that while importance of NCD risk factors is present with univariate and risk factor-specific multivariate analysis it is eliminated on multivariate analyses with addition of healthcare related and social factors (Table 4). Further studies are needed to validate our findings.

In the present study, association of COVID-19 with sociodemographic factors such as urbanization and other indices of development and better healthcare access and quality indices could indicate better diagnosis of the condition in these locations [1]. In

lesser developed states of the country as well as rural areas of India it is likely that the condition is not diagnosed due to lack of access to quality healthcare [42]. Undiagnosed COVID-19 related deaths in the rural hinterlands of the country are also possible [43]. Possible gaps in COVID-19 data from India has been highlighted [44]. Other limitations of our analyses are absence of detailed readily available cause-specific morbidity and mortality data, lack of population based registries of COVID-19 cases and deaths, absence of concurrent mortality data to evaluate excess deaths from COVID-19 and absence of other collinear data [1].

Our study shows that COVID-19 burden is significantly greater in more developed and urbanized states of the country where there is a greater prevalence of NCD risk factors. These findings have important implications for prioritization in deployment of preventive strategies and vaccinations. Large scale government-led non-pharmaceutical prevention strategies that have proven effective in COVID-19 control [45], and include mandatory mask-wearing in public spaces, limited public gatherings, closure of non-essential businesses, schools and universities, and stay at home orders with appropriate exemptions are important. So are individual level non-pharmacological interventions include proper masking, physical distancing and avoiding crowded spaces [1,45]. Vaccines have now become available and need scientifically appropriate strategies to achieve maximum impact and development of population-level immunity [46,47]. Equitable vaccine distribution is essential [48]. It has been identified that there are regional differences in target groups for vaccination and each country has been advised to allocate strategies based on local epidemiology, underlying population health and preference for vaccination strategies that favor direct or indirect benefits [49]. Although equitable population level distribution is justified [50], in the macrolevel scenario highlighted in this report, we posit that better developed states of India, are at forefront of the COVID-19 epidemic, and need various interventions including vaccination earlier than the lesser developed states.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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