The Impact of Baseline Incidence Rates on Burden of Disease Assessment of Air Pollution and Onset Childhood Asthma: Analysis of Data from the Contiguous United States

Haneen Khreis[1, 2, 3, 4 *], Raed Alotaibi[1,5,6] and Jennifer Horney[7]

[1] Center for Advancing Research in Transportation, Emissions, Energy, and Health (CARTEEH), Texas A&M Transportation Institute (TTI), Texas, USA

[2] ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

[3] Universitat Pompeu Fabra (UPF), Barcelona, Spain

[4] CIBER Epidemiologia y Salud Publica (CIBERESP), Madrid, Spain

[5] Department of Family and Community Medicine, Imam Abdulrahman Bin Faisal University, Saudi Arabia

[6] Texas A&M Health Science Center School of Public Health, Texas, USA

[7] University of Delaware

*** Corresponding author at Center for Advancing Research in Transportation Emissions, Energy, and Health (CARTEEH), Texas A&M Transportation Institute (TTI), 1111 RELLIS Parkway, Room 3412, Bryan, Texas 77807, USA.**

Abbreviations

AC: Attributable number of cases

ACBS: Asthma Call Back Survey

AF: Attributable fraction of cases

BRFSS: Behavioral Risk factor Surveillance System

CDC: Center for Disease Control and Prevention

CRF: Concentration-Response Function

D.C.: District of Columbia

EPA: United States Environmental Protection Agency

U.S.: United States

LUR: Land use regression

NHGIS: National Historical Geographic Information System

PAF: Population attributable fraction

IR: Incidence rate

PR: Prevalence rate

TRAP: Traffic-related air pollution

Introduction

Burden of disease assessment (BoD) is a powerful and relatively practical method to estimate the number/percentage of premature mortality and morbidity cases which may be attributable to environmental exposures. Such estimates can indicate how many cases of premature deaths and/or disease may be prevented by eliminating or reducing the exposure of interest. In the context of air pollution exposure, BoD methods have become increasingly popular and have been predominantly used to assess the burden of premature mortality which may be attributable to air pollution at the global, national, regional and local scales (Cohen et al., 2017, Cohen et al., 2005, Ostro and Organization, 2004, Lelieveld et al., 2015, Bhalla et al., 2014, Tainio, 2015, Mueller et al., 2017). The previous focus on mortality may reflect availability of well-established epidemiological data which associate air pollution with premature death but may also reflect the level of advancement in BoD, which is a relatively new practice still concerned with the most extreme outcome (death). Yet, to truly map, grasp and communicate to the true public health impact of air pollution exposures, extending BoD beyond premature mortality is required, especially to chronic health outcomes. Chronic outcomes are important as they have significant impacts on the quality of life of individuals and families, affect productivity at work and school, can result in death and imply significant health care costs which may be preventable. Further, given the ubiquity of air pollution exposure, especially in urban areas where it occurs near many people, the relatively modest-sized risk estimates from epidemiology translate into a large, yet modifiable, burden of disease.

One chronic health outcome which recently received more attention in the context of air pollution is the onset of childhood asthma. Asthma is a burdensome disease which is often cited as the most chronic illness of childhood (Gasana et al., 2012, National Survey of Children's Health, 2012), and is the third leading cause of hospitalization in children under the age of 15 and the leading cause of school absenteeism due to a chronic disease (American Lung Association, 2019, Hsu et al., 2016). In the United States (U.S.) alone, 6 million children had ongoing asthma in 2016 (Zahran et al., 2018). The economic burden of asthma on the U.S., including costs incurred by absenteeism and mortality, was $81.9 billion in 2013 (Nurmagambetov et al., 2018). The CDC estimated that the number of missed schooled days in a single year, 2008, had reached 10.4 million for children with asthma, with it a large number of missed work days among the children's caregivers (CDC, 2010).

There is emerging evidence that the exposure to air pollution, primarily when traffic-related, is associated with the onset of children’s asthma (Khreis et al., 2017), and more recent studies reconfirm these associations (Rancière et al., 2016, Rice et al., 2018, Lee et al., 2018, Pennington et al., 2018). A limited number of studies investigated the burden of childhood asthma onset which may be attributable to air pollution, building on this emerging evidence base which established positive and statistically significant associations between the risk of childhood asthma onset and increased exposures to traffic-related air pollution (TRAP). All previous BoD studies investigating this issue (Achakulwisut et al., 2019, Khreis et al., 2018b, Perez et al., 2009, Perez et al., 2013, Khreis et al., 2018a, Alotaibi et al., 2019) agreeably highlighted several data gaps which might impact the final BoD estimates and introduce uncertainty and error. These gaps are in fact applicable to BoD studies of air pollution and *any* health outcome. In summary, the accuracy of the BoD estimate are dependent on accuracy if the input data, namely: 1) the air pollution exposure levels and distribution, 2) the exposure-response functions, and 3) the baseline asthma incidence rates that are used. Some of the studies cited above have investigated the impacts of different input datasets on final BoD estimates and found that different exposure assessment methods (dispersion versus land use regression modeling) may result in up to % different BoD estimates. Similarly, we recently explored the impact of the exposure-response functions on the final burden of disease estimate and found that using the most conservative ERF (the lower 95% CI) can reduce the estimated burden by up to % when compared to the central estimate. On the other hand, using the most extreme ERF (the upper 95% CI) can increase the estimated burden by up to % when compared to the central estimate. The impact of asthma baseline incidence rates, however, has not been studied yet, despite being cited as a potential key source of error in BoD studies, and despite childhood asthma being a very challenging disease to ascertain and diagnose. All previous literature has relied on country-based asthma incidence rates, which is indeed in line with practice by prominent institutions and studies such as the Global Burden of Disease analysis. We, however, wanted to explore the potential impact of using state-specific varying asthma incidence rates on the final burden of childhood asthma due to NO_2 exposure and compare the change in burden estimates from those produced by Alotaibi et al. (2019) which used a country level asthma incidence rate, as is typically done in BoD studies (Achakulwisut et al., 2019, Khreis et al., 2018b, Perez et al., 2009, Perez et al., 2013, Khreis et al., 2018a). We also explored the trends in the BoD by socioeconomic status and urban versus rural status using this more granular incidence rate data to confirm (or otherwise) previous trends we observed in our past analysis. We selected NO_2 as the exposure of interest, as more studies underline this pollutant's EFR and as it has been commonly used in previous BoD studies. Furthermore, the selection of the pollutant in this instance is less relevant as our aim is to compare previous estimates with present ones, only by altering the baseline childhood asthma incidence rates.

Methods

Study area and time point

We analyzed data for the 49 states within the contiguous U.S. and the District of Columbia (D.C.) for the year 2010 at the census block level: the smallest geographical unit available. Population counts, urban or rural living location and annual NO_2 concentrations were all available at the census block level. However, median household income was available at the census block group level, which is one level higher than the census block (US Census Bureau, 2010). Childhood asthma incidence rates were calculated at the state level. NO_2 concentrations were not available for states outside the contiguous U.S. (Alaska, Hawaii and Puerto Rico), and hence these states were excluded from the analysis.

Census data

We included populated census blocks of the contiguous U.S. for the year 2010, as obtained from the National Historical Geographic Information System (NHGIS) website (Manson et al., 2018, US Census Bureau, 2010). Each block included information on the total population of children <18 years old, and whether the census block was designated as an urban or a rural block. Census-designated urban areas were defined by the census bureau using multiple criteria including total population thresholds, density, nonresidential urban land use (e.g. paved areas and airports), and distance to other urban developed areas (US Census Bureau, 2016). Census blocks are the basic geographical units of urban areas. Further, census-designated urban areas are classified into two subtypes; urban clusters or urbanized areas. Urban clusters have a population threshold of ≥2,500 and <50,000, while urbanized areas have a population threshold of ≥50,000 people. The median household income in the past 12 months using 2010 inflation adjusted dollars was divided into five categories consistent with two previous relevant publications: <\$20,000, \$20,000 to <\$35,000, \$35,000 to <\$50,000, \$50,000 to <\$75,000 and ≥\$75,000 (Clark et al., 2017, Alotaibi et al., 2019). Census blocks were assigned the same median household income of the census block group they resided within.

There were 2,686 (0.04%) census blocks with missing median household income data in 2010. These census blocks were assigned a "Not defined" status in the analysis of median household income. Table 1 summarizes the geographical and demographic data across all census blocks included in this analysis.

Table 1: Census data description, year 2010

Geographic characteristics	**Total populated census blocks**	6,182,882
	Total census-designated urban areas	3,590,278 (58%)
Demographic characteristics	**Total population**	306,675,006
	Total population of children (birth – 18)	73,690,271 (24%)
	Mean (range) number of children in census blocks	12 (0-2214)
Population of children by living location	**Rural**	13,763,183 (19%)
	Urban clusters (≥2,500 and <50,000 people)	6,994,464 (9%)
	Urbanized area (≥50,000 people)	52,932,624 (72%)
Population of children by median household income	**<\$20,000**	2,614,804 (4%)
	\$20,000 to <\$35,000	12,770,843 (17%)
	\$35,000 to <\$50,000	18,573,954 (25%)
	\$50,000 to <\$75,000	21,953,876 (30%)
	≥\$75,000	17,763,239 (24%)

NO_2 exposure assessment

Annual average NO_2 concentrations for each populated census block were available at the centroid location for the year 2010. Concentrations were derived from a land use regression model (LUR) developed by Bechle et al. (2015). The model incorporates spatial and temporal air pollutant data. The spatial data is derived from the U.S. Environmental Protection Agency (EPA) air quality monitoring data, satellite data and several GIS covariates including impervious surfaces, elevation, major, minor and residential roads, and distance to coast. The temporal data of the LUR model is incorporated by scaling the spatial data with the average monthly readings for 11 consecutive years. The model achieves a relatively high predictive power using hold-out cross validation when compared to similar NO_2 LUR models (Vienneau et al., 2013, Beelen et al., 2009, Hystad et al., 2011, Novotny et al., 2011) with an R^2 reaching 82%. The LUR model has been used in multiple studies including Clark et al. (2017) and Alotaibi et al. (2019). A detailed description of the model can be found at Bechle et al. (2015). NO_2 concentrations were converted from ppb to ug/m^3 through multiplying by 1.88 (WHO, 2005). Exposure data was matched with census blocks using a unique identifier for each census block as provided from the NHGIS dataset.

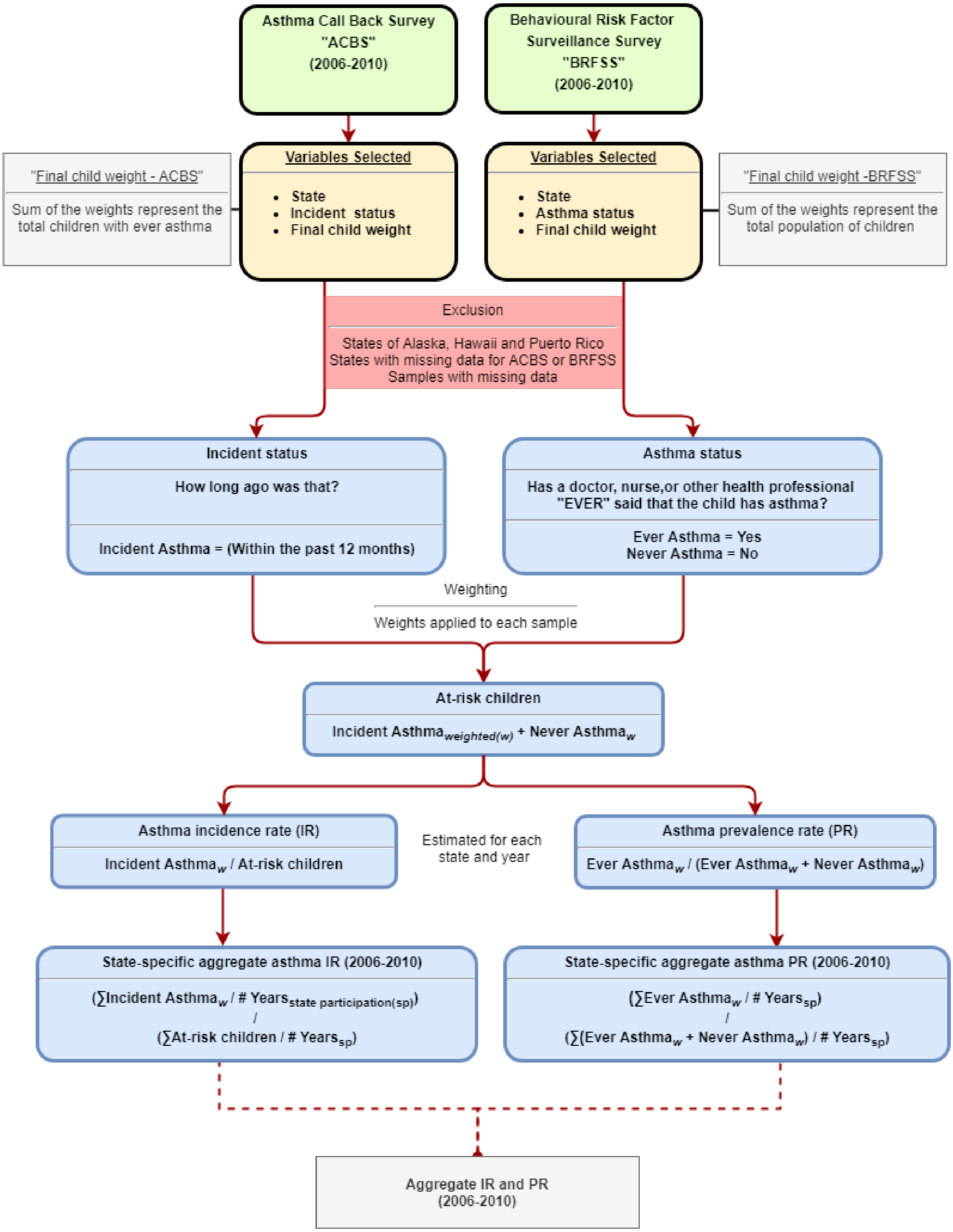
Concentration-response functions

We used an asthma development concentration-response function (CRF) of 1.05 (95% CI = 1.02-1.07) per 4 ug/m^3 of NO_2. The CRF was obtained from a meta-analysis of 20 studies examining the association between exposure to TRAP and the risk of developing asthma among children from birth to 18 years of age (Khreis et al., 2017). These CRF represent data from the most up-to-date and widest analysis on traffic-related air pollution and the onset of childhood asthma, and has been used in several published peer-reviewed BoD assessments (Khreis et al., 2018b, Khreis et al., 2018a, Achakulwisut et al., 2019, Alotaibi et al., 2019, Khreis, In press).

Asthma incidence and prevalence rate

An incidence rate (IR) is defined as the number of new cases of a disease within a specified time period among an at-risk population (Mausner and Kramer, 1985). To estimate the childhood asthma IR aggregated for the years 2006 through 2010 among U.S. states, we obtained the Behavioral Risk Factor Surveillance System (BRFSS) and Asthma Call Back Survey (ACBS) child data sets (CDC, 2011, CDC, 2009), which can be found in the Center for Disease Control and Prevention (CDC) website https://www.cdc.gov/brfss/. We followed methods described by Winer et al. (2012) to estimate the asthma incidence rates, and present our steps in Figure 1. The ACBS and BRFSS define children as birth to 18 years of age. The following variables were extracted: the state, asthma status question (from the BRFSS), incident status question (from the ACBS), and children sample weights from both surveys. All analysis was conducted using R statistical software (R Core Team, 2018). States and territories not within the contiguous U.S. were excluded from the analysis, namely Alaska, Hawaii and Puerto Rico.

Figure 1: Childhood asthma incidence rate estimation flow chart



To determine the “Asthma status” of children, respondents to the BRFSS were asked “Has a doctor, nurse, or other health professional EVER said that the child has asthma?”, If the answer was “Yes”, the respondent was designated as “Ever asthma”. If the answer was “No”, the respondent was designated as “Never asthma”. Respondents with children designated as “Ever asthma” were requested to participate in the ACBS follow up. To determine the “Incident status” of children, respondents to the ACBS were asked: “How old was the [name of child] when a doctor or other health professional first said [he/she] had asthma? How long ago was that?” If the answer to the latter part of this question was “within the past 12 months”, the respondent was designated as an “Incident asthma”, while other responses were not relevant to the analysis described next.

Each respondent (sample) from the BRFSS and ACBS was assigned a weight to adjust for the disproportionate population sample selection as compared to the state’s overall population distribution, the variation in probability of selection, the actual response of each respondent, or nonresponse (Garbe et al., 2011, Korn and Graubard, 2011). To simplify this, the weight of each sample represents the number of children within each state, with similar characteristics (age, sex and race) to the sample. Weights were used to convert samples to population estimates of children. For example, if respondent (X) had a weight of 150, her/his response to survey questions represented answers of 150 children within their state. The sum of childhood weights for the BRFSS represent the total population of children within each state, while the sum of weights for the ACBS represent the total population of children with “Ever asthma” within each state.

“At-risk children” were then estimated by taking the weighted sum of respondents designated as “Incident asthma” and “Never asthma”, as shown in Equation 1.

$$At-risk\ children\ =\ Incident\ asthma_{weighted(w)} +\ Never\ asthma_{w}$$

Equation 1

The asthma incidence rate (IR) was the weighted “Incident asthma” divided by “At-risk children”, as shown in Equation 2.

$$Asthma\ incdence\ rate\ (IR) = Incident\ asthma_{w}\ /\ At-risk\ children$$

Equation 2

The asthma prevalence rate (PR) was the weighted “Ever asthma” divided by the sum of weighted “Ever asthma” and weighted “Never asthma”, as shown in Equation 3.

$$Asthma\ prevalence\ rate\ (PR) = Ever\ asthma_{w}\ /\ (Ever\ asthma_{w} + Never\ asthma_{w})$$

Equation 3

To estimate the aggregate asthma IR across all available years for each state, we re-weighted the samples to adjust for the number of available years of data. For example, the state of Arizona had two years of available data (2006 and 2007), to estimate the aggregate IR across all available years, we summed the weighted “Incident asthma” across all the years and divided it by two (since there were only two years of available data for the state of Arizona), we divided the results by the sum of “At-risk children” across all the years divided it by two, as shown in Equation 4.

$$Aggregate\ IR_{State-specific\ (s)} = \left(\frac{\sum Incident\ asthma_w}{\#\ Years}\right) / \left(\frac{\sum At-risk\ children}{\#\ Years}\right)$$

Equation 4

The aggregate asthma PR across all available years for each state was estimated as shown in Equation 5.

$$Aggregate\ PR_s = \left(\frac{\sum Ever\ asthma_w}{\#\ Years}\right) / \left(\frac{\sum(Ever\ asthma_w + Never\ asthma_w)}{\#\ Years}\right)$$

Equation 5

To estimate the overall "Aggregate" asthma incidence rate and prevalence rate, we simply took the sum of the numerators and denominators across all states after re-weighting. States that did not participate and/or states that did not have available data in the ACBS during the period 2006 through 2010 (n = 19 states) were assigned the aggregate asthma incidence rate (11.6 per 1,000 at-risk children) and prevalence rates (13.1 per 100 children).

Burden of disease estimation

To estimate the burden of disease, we followed the methods described in Alotaibi et al. (2019) with the following steps:

The total number of at-risk children residing in a census block was estimated for each state by subtracting the total number of children within the census block multiplied by the state-specific aggregate PR (from Equation 5) from the total number of children within the same census block, as shown in Equation 6.

$$At-risk\ children_{census\ block(c)} = Total\ children_c - (Total\ children_c * Aggregate\ PR_s)$$

Equation 6

We then estimated the number of childhood asthma incident cases within each census block by multiplying the state-specific aggregate asthma IR (from Equation 4) by the at-risk children at each census block, as shown in Equation 7.

$$Asthma\ incident\ cases_c = At-risk\ children\ _c * Aggregaget\ IR_s$$

Equation 7

We then calculated the relative risk (RR_{diff}) for asthma onset due to the exposure difference between the estimated exposure levels from the LUR model (NO_2 concentration at the census block level) and no exposure (zero concentration for NO_2) at each census block, as shown in Equation 8.

$$RR_{diff} = e^{((\ln(RR)\ /\ RR_{unit} * Exposure_c)}$$

Equation 8

Where RR is the CRF and RR_{unit} is the exposure unit (4 ug/m^3) for the CRF as extracted from Khreis et al. (2017). The population attributable fraction (PAF) was then estimated at each census block using Equation 9:

$$PAF_c = (RR_{diff} - 1)/\ RR_{diff}$$

Equation 9

The attributable number of asthma incident cases (AC) was estimated by multiplying the PAF with the total number of asthma incident cases at each census block (from Equation 7), as shown in Equation 10.

$$AC_c = PAF_c * Asthma\ incident\ cases_c$$

Equation 10

The attributable number of asthma incident cases for each census block was then summed across the state to obtain state total AC estimates, and the entire country to obtain the national estimates, as shown in Equation 11.

$$Total\ AC = \sum AC_{c,s}$$

Equation 11

Results

NO_2 concentrations and trends

The mean (min-max) NO_2 concentrations were 13.2 (1.5-58.3) ug/m^3 (Table 2). By living location, the mean NO_2 concentration was highest in urbanized areas (18.4 ug/m^3) (Figure S1), while the mean NO_2 concentration was highest among the highest median household income group of ≥$75,000 (16.5 ug/m^3) followed by the lowest median household income group of <$20,000 (16.1 ug/m^3) (Figure S2). When stratifying NO_2 concentrations by median household income groups but separately for each living location, rural areas had an increasing average concentration as income increased, urban clusters has a decreasing average concentration as income increased, and urbanized areas showed a U-shaped trend (Figure S3 and Figure S4). South Dakota had the lowest mean NO_2 concentration (5.2 ug/m^3), while the District of Columbia had the highest (26.3 ug/m^3) (*Table S1* and Figure S5). Figure S6 and Figure S7 demonstrate NO_2 concentrations across median household income and living location, separately for each state.

Table 2: NO_2 concentrations (ug/m^3) by strata

		Mean	Min	25%	Median	75%	Max
Total		13.2	1.5	7.9	11.4	16.6	58.3
By living location	**Rural**	8.0	1.5	6.0	7.8	9.8	37.7
	Urban cluster	12.0	1.6	9.6	11.9	14.2	35.6
	Urbanized area	18.4	2.6	13.0	17.0	22.1	58.3
By median household income	**<$20,000**	16.1	2.0	10.4	14.9	20.1	56.8
	$20,000 to <$35,000	13.2	1.6	8.1	11.7	16.7	58.3
	$35,000 to <$50,000	11.8	1.5	7.0	10.0	14.5	58.0
	$50,000 to <$75,000	12.8	1.6	7.6	10.8	15.7	55.7
	≥$75,000	16.5	2.1	10.9	14.9	20.6	55.5

ACBS and BRFSS results

Overall, there were 32 states we were able to extract childhood asthma incidence rates and 41 states for childhood asthma prevalence rates (*Table S2*-S4). The total childhood samples included for the period 2006-2010 were 293,464 samples from the BRFSS and 16,156 samples from the ACBS (Table 3). The BRFSS samples ranged between 55,094 samples (2006) and 61,862 (2008). The ACBS samples ranged between 2,017 samples (2006) and 4,095 (2009). The weighted estimates represent the childhood population counts of available states from the BRFSS and the ACBS, for the years when the survey was conducted.

Across all available states, the overall aggregate asthma incidence rate for the years 2006-2010 was 11.6 per 1,000 at-risk children (Table 3). The state of Montana had the lowest aggregate childhood asthma incidence rate (IR = 4.3 per 1,000 at-risk children), while the District of Columbia had the highest aggregate childhood asthma incidence rate (IR = 17.7 per 1,000 at-risk children) (*Table S2*). States that did not have an incidence rate available (n = 19 states) were assigned the overall aggregate asthma incidence rate of 11.6 per 1,000 at-risk children (*Table S2*-S4).

The overall aggregate asthma prevalence rate for the years 2006-2010 was 13.1 per 100 children (Table 3). The state of Iowa had the lowest aggregate childhood asthma prevalence rate (PR = 8.4 per 100 children), while the District of Columbia had the highest aggregate childhood asthma prevalence rate (PR = 19.9 per 100 children) (*Table S2*). States that did not have a prevalence rate available (n = 8 states) were assigned the overall aggregate asthma prevalence rate of 13.1 per 100 children.

Table 3: Childhood asthma survey summaries

	2006	**2007**	**2008**	**2009**	**2010**	**Total**
BRFSS sample (weighted)	55,094 (50,674,742)	59,487 (43,661,381)	61,862 (53,327,550)	59,821 (47,747,373)	57,200 (39,975,264)	293,464
Ever asthma sample (weighted)	7,168 (6,493,224)	7,971 (5,763,409)	8,255 (7,218,400)	8,126 (6,279,938)	7,483 (5,158,455)	39,003
ACBS Sample (weighted)	2,017 (4,580,870)	2,797 (5,459,638)	3,924 (4,343,245)	4,095 (4,154,076)	2,196 (3,116,669)	16,156
Incident case sample (weighted)	154 (404,276)	173 (312,917)	169 (385,818)	153 (297,546)	160 (319,743)	809
At-risk sample (weighted)	48,080 (30,825,589)	51,689 (36,050,557)	53,776 (26,491,259)	51,848 (25,942,087)	49,877 (22,900,850)	255,270
Incidence rate	13.1	8.7	14.6	11.5	14.0	11.6*
Prevalence rate	12.8	13.2	13.5	13.2	12.9	13.1**
Number of states included	18	26	20	17	17	32***

**Aggregate asthma incidence rate per 1,000 at-risk children*

***Aggregate asthma prevalence rate per 100 children*

***Total number of states included in the aggregate asthma incidence rate estimation*

Asthma incident cases

Using state-specific asthma incidence rates, the estimated number of childhood asthma incident cases were 747,437 in 2010 (Table 4). By living location, 19% lived in a rural area, while 9% and 72%

lived in an urban cluster and urbanized area, respectively. The largest percentage of childhood asthma cases (30%) lived in an income block group of $50,000 to <$75,000, while the lowest percentage (4%) lived in the lowest income block group of <$20,000. The state with the lowest number of estimated childhood asthma incident cases was Montana with 900 cases, while the state with the largest number was Texas with 99,100 cases (Table S5).

Attributable number of cases and fraction

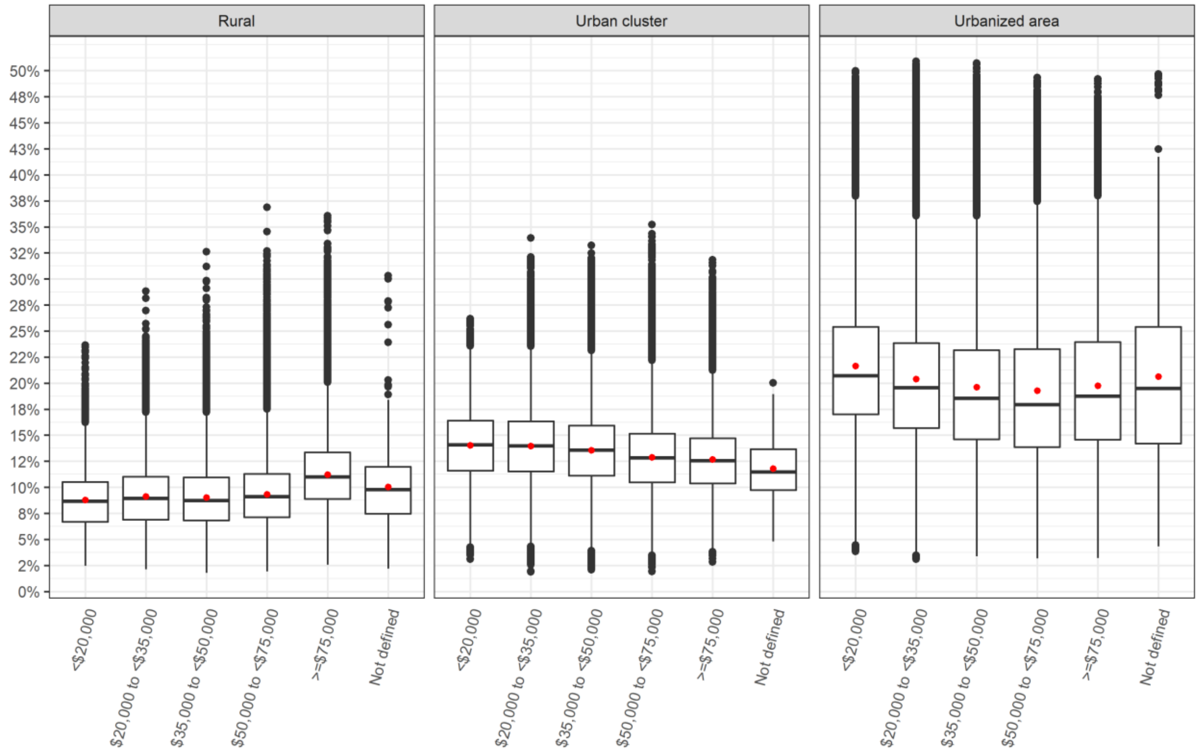
We estimated a total of 131,739 childhood asthma incident cases attributable to NO_2 exposure which accounted for 17.6% of all childhood asthma incident cases (Table 4). By living location, urbanized areas had the largest number of attributable cases totaling 108,745 cases and the highest percentage of all asthma incident cases at 20.3%. Rural areas had total of 13,788 cases and accounted for the least percentage of all asthma cases at 9.8%, while urban clusters had only 9,206 cases representing 13.1% of all asthma incident cases (Table 4 and Figure S8). By income, $50,000 to <$75,000 had the largest number of cases attributable to NO_2; 37,253 cases accounting for 16.8% of all asthma incident cases. However, the income group with the largest percentage of asthma cases attributable to NO_2 exposure was the lowest income group <$20,000, accounting for 20.8% of all asthma incident cases (Figure S9). The mean value of the attributable fraction increased by income group in rural areas, decreased by income group in urban clusters and presented as a U shape in urbanized areas (Figure 2 and Figure S10). [Note: The attributable fraction presented in the table is estimated by dividing the AC by Incident cases, while the red dot in the figures represent the average AF value across the census blocks for the strata. In other words, the red dot in the figures are not the AF values in the tables, since they measure the mean value across all census blocks]

The state with the lowest number of estimated attributable cases was Montana with 100 cases, while the state with the largest number of estimated attributable cases was California with 19,200 cases (Figure 3 and Table S5). The state with the lowest attributable fraction was North Dakota (6.3%), while the state with the highest attributable fraction was District of Columbia (28.6%)

Table 4: Comparing results of the burden of disease using state-specific estimates vs original estimates

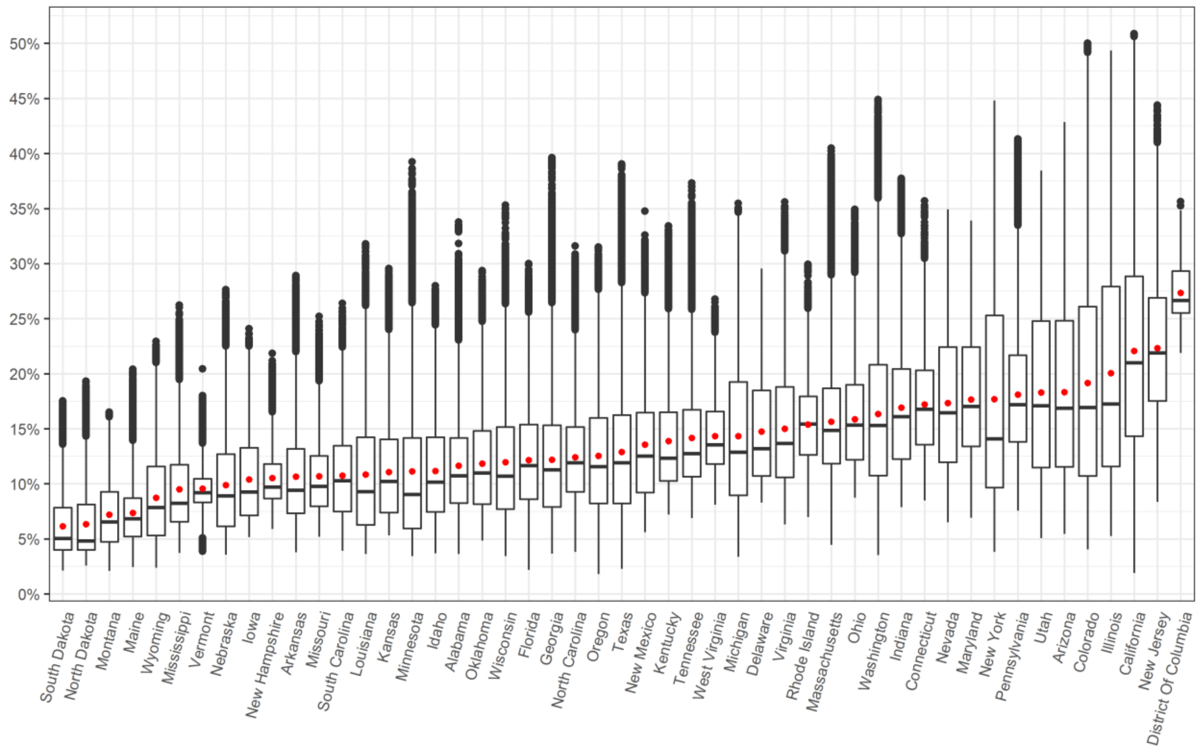
		Results using flat national-level IR			Results using state-specific IR			Difference			Difference (%)		
		Incident cases	**AC**	**AF**	**Incident cases**	**AC**	**AF**	**Incident cases**	**AC**	**AF**	**Incident cases**	**AC**	**AF**
	Total	794,934	141,931	17.9%	747,437	131,739	17.6%	-47,497	-10,192	-0.3%	-6.0%	-7.2%	-1.7%
By living location (% of Total)	**Rural**	148,470 (19%)	14,466 (10%)	9.7%	140,799 (19%)	13,788 (10%)	9.8%	-7,671	-678	0.1%	-5.2%	-4.7%	1.0%
	Urban cluster	75,453 (9%)	9,844 (7%)	13.0%	70,524 (9%)	9,206 (7%)	13.1%	-4,929	-638	0.1%	-6.5%	-6.5%	0.8%
	Urbanized area	571,011 (72%)	117,621 (83%)	20.6%	536,113 (72%)	108,745 (83%)	20.3%	-34,898	-8,876	-0.3%	-6.1%	-7.5%	-1.5%
By median household income (% of Total)	**<$20,000**	28,207 (4%)	5,892 (4%)	20.9%	27,770 (4%)	5,786 (4%)	20.8%	-437	-106	-0.1%	-1.5%	-1.8%	-0.5%
	$20,000 to <$35,000	137,765 (17%)	25,794 (18%)	18.7%	132,843 (18%)	24,699 (19%)	18.6%	-4,922	-1,095	-0.1%	-3.6%	-4.2%	-0.5%
	$35,000 to <$50,000	200,367 (25%)	34,549 (24%)	17.2%	188,466 (25%)	32,088 (24%)	17.0%	-11,901	-2,461	-0.2%	-5.9%	-7.1%	-1.2%
	$50,000 to <$75,000	236,827 (30%)	40,540 (29%)	17.1%	221,334 (30%)	37,253 (28%)	16.8%	-15,493	-3,287	-0.3%	-6.5%	-8.1%	-1.8%
	≥$75,000	191,621 (24%)	35,128 (25%)	18.3%	176,880 (24%)	31,885 (24%)	18.0%	-14,741	-3,243	-0.3%	-7.7%	-9.2%	-1.6%

Figure 2: Attributable fraction by median household income group stratified into living location



**Red dot represents the mean value while the midline represents the median value*

Figure 3: Attributable fraction by state



Error! Not a valid bookmark self-reference. and Figure 5 present the distribution of attributable fraction by living location and median household income group for each state. The majority of states broadly follow a distribution similar to the national level as shown in Figure S8 and Figure S9, with a few exceptions (By living location see; Delaware, Maryland, Mississippi, Vermont. By median household income see; Arizona, Connecticut, District of Columbia, Florida, Maine, Massachusetts, Montana, Nevada, New Hampshire, New Jersey, New Mexico, Vermont, West Virginia, Rhode Island & Wyoming).

Figure 4: Attributable fraction by state and living location

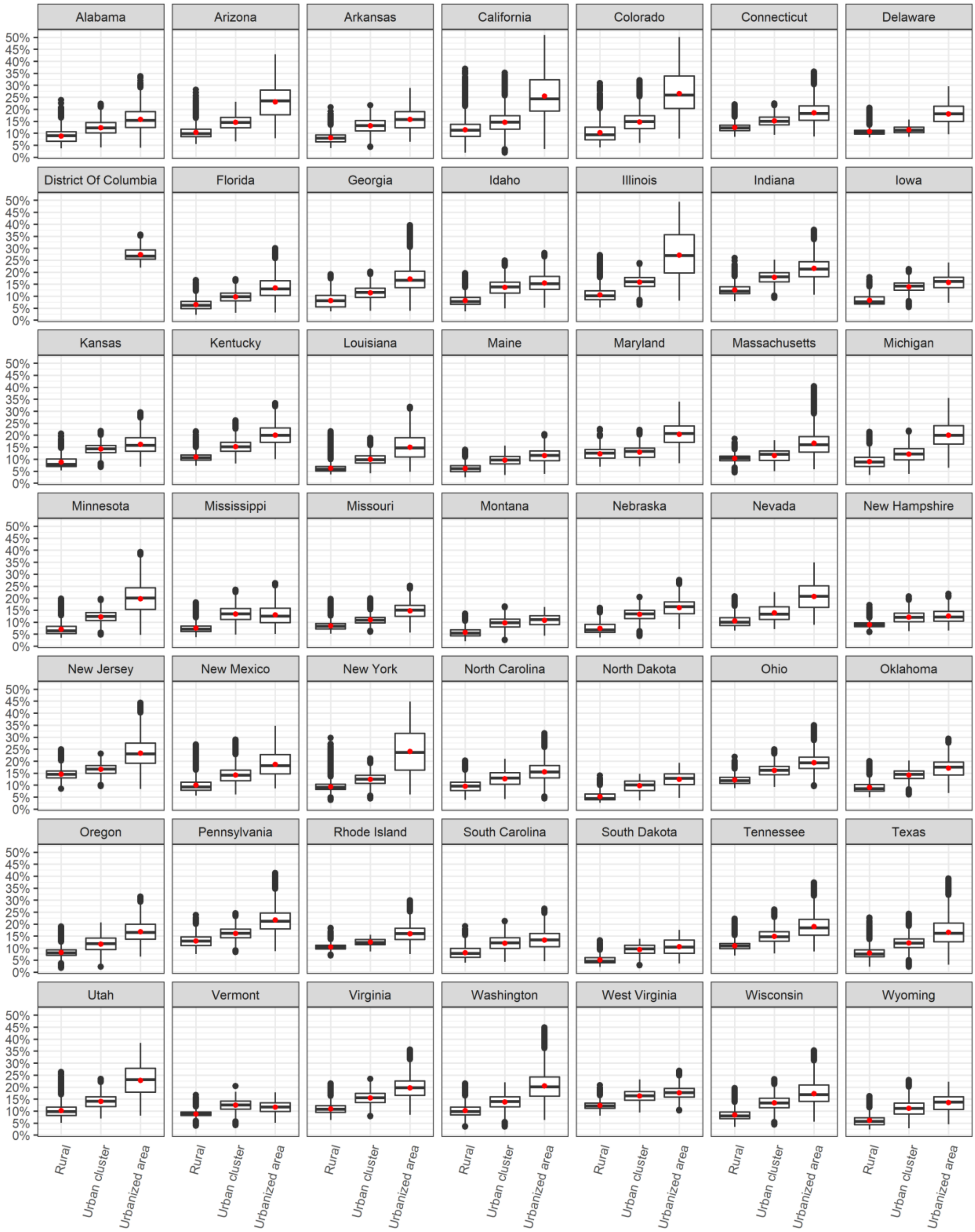
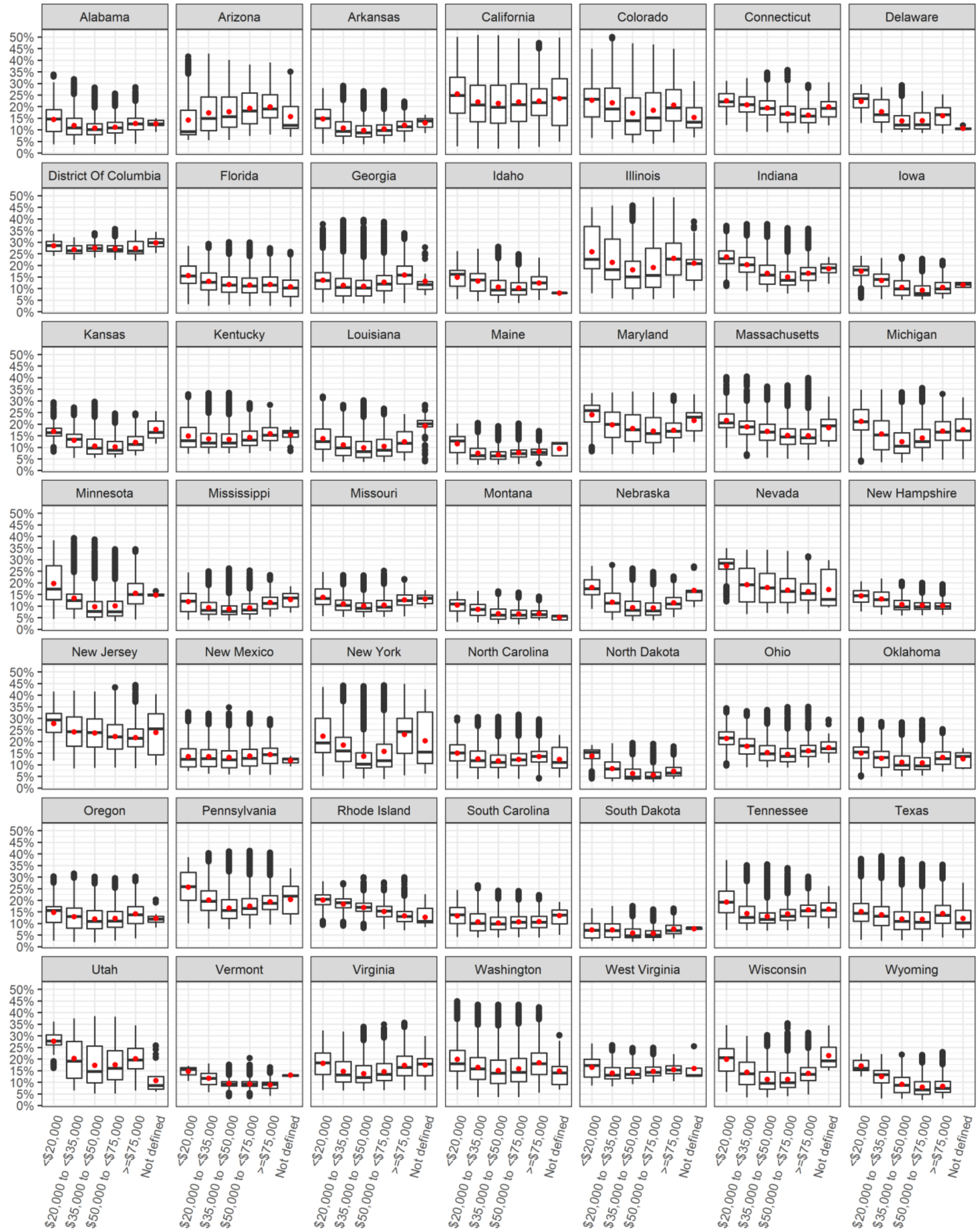


Figure 5: Attributable fraction by state and median household income group



Comparison with the original paper

Comparing total asthma incident cases

Using state-specific asthma incidence rates, the overall number of incident asthma cases was reduced by 47,497 (6%) cases compared to estimates presented in the original paper which used a flat national asthma incidence rate of 12.5 per 1,000 at-risk children (Table 4) (Alotaibi et al., 2019).

By living location, the largest relative change was among urban clusters with a decrease of 4,929 (6.5%) cases followed by urbanized areas which reduced by 34,898 (6.1%) cases. By income group, the largest relative change in the number of cases was among the highest income groups by a decrease of 14,741 (7.7%) cases, while the least relative change was among the lowest income group by a decrease of 437 (1.5%) cases. The state of California had the largest decrease in numbers of total childhood asthma incident cases by 24,500 cases while the state of Texas had the largest increase in numbers of total childhood asthma incident cases by 25,000 cases (*Table S5*). The state of Montana had the largest relative reduction in total childhood asthma incident cases by 62.5% while the state of Texas had the largest relative increase by 33.7% (*Table S5*).

Comparing attributable asthma incident cases due to NO_2

The total attributable cases reduced by 10,192 (7.2%) cases when compared to the original paper which used a flat national asthma incidence rate (Table 4). By living location, urbanized areas had the largest relative change by a decrease of 8,876 (7.5%) cases, while rural areas had the least relative change by a decrease of 678 (4.7%) cases attributable to NO_2 exposure. By income group, the highest income group had the largest relative change by a decrease in attributable cases by 3,243 (9.2%) while the lowest income group had the least relative change by a decrease of 106 (1.8%) cases. The state of California had the largest decrease in attributable cases by 6,200 cases while the state of Texas had the largest increase by 3,600 cases (Table S5).

Comparing attributable asthma incident fractions due to NO_2

The overall attributable fraction reduced by 0.3% (a 1.7% reduction). In terms of living location, urbanized areas had the largest relative reduction by 1.5%, while rural areas had a relative increase in AF by 1%. In terms of income group, the largest relative reduction was 1.8% for \$50,000 to <\$75,000 (Table 4). The attributable fraction across states did not differ when using state-specific asthma incidence rates, the difference observed in (*Table S5*) is due to rounding errors.

Discussion

- The results in this paper re-affirm our finding in the main paper, more specifically the sensitivity analysis. In our main paper we argued that changing or testing ranges of asthma IR in the analysis did not alter the end results compared to a change in the CRF function (Check the sensitivity matrix).
- We can derive from this finding, that using national level incidence rates to estimate asthma burden due to TRAP is acceptable even if asthma incidence rates is not available at a finer level.
- The state-specific attributable fractions did not change. The reason is that the incident rate is applied uniformly across the state (spatially), thus the total asthma cases and total attributable cases will change with equal proportion when applying the new asthma incidence rate. The attributable fraction is a function of CRF and exposure estimate regardless of the IR. Had we applied an incidence rate based on other factors like age, gender, race, income group, then the attributable fraction across the state would differ since the change in incidence rate won't be uniform within the state.
- The percentage of all asthma cases has a U shaped distribution when examining income groups. The lowest income group had the highest % then drops and rises again with the highest income group (we need to explore why).
- The AF of states across strata (living location and income) generally followed the national average except for a few states (we need to explore why).

Conclusions

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Disclaimer

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Supplementary Material

Table S1: NO_2 concentration (ug/m^3) by state

State	Mean	Min	25%	Median	75%	Max
Alabama	10.3	3.0	7.1	9.3	12.5	33.8
Arizona	17.0	4.6	10.1	15.1	23.4	45.9
Arkansas	9.3	3.2	6.2	8.1	11.6	28.0
California	21.1	1.6	12.7	19.3	27.9	58.3
Colorado	18.1	3.4	9.3	15.2	24.8	56.9
Connecticut	15.6	7.3	11.9	15.0	18.6	36.2
Delaware	13.2	7.1	9.3	11.6	16.7	28.7
D.C.	26.3	20.2	24.2	25.4	28.5	36.1
Florida	10.7	1.8	7.4	10.2	13.7	29.2
Georgia	10.8	3.0	6.8	9.8	13.6	41.4
Idaho	9.8	3.1	6.4	8.8	12.6	26.9
Illinois	19.0	4.4	10.1	15.5	26.9	55.7
Indiana	15.4	6.7	10.7	14.4	18.7	38.9
Iowa	9.1	4.3	6.1	8.0	11.7	22.6
Kansas	9.7	4.5	6.3	8.8	12.4	28.7
Kentucky	12.4	6.1	8.9	10.8	14.8	33.3
Louisiana	9.6	3.0	5.3	8.0	12.6	31.4
Maine	6.3	2.0	4.4	5.8	7.5	18.7
Maryland	16.1	5.9	11.8	15.3	20.8	34.0
Massachusetts	14.1	3.7	10.3	13.2	17.0	42.5
Michigan	12.9	2.8	7.7	11.3	17.5	35.9
Minnesota	9.9	2.9	5.0	7.8	12.5	40.8
Mississippi	8.3	3.1	5.6	7.0	10.2	24.9
Missouri	9.3	4.4	6.8	8.4	11.0	23.8
Montana	6.2	1.7	4.0	5.5	8.0	14.8
Nebraska	8.6	3.0	5.2	7.7	11.1	26.5
Nevada	15.9	5.5	10.5	14.7	20.8	35.2
New Hampshire	9.1	5.0	7.4	8.4	10.3	20.2
New Jersey	21.0	7.1	15.8	20.2	25.7	48.1
New Mexico	12.1	4.7	7.9	11.0	14.8	35.0
New York	16.6	3.2	8.3	12.4	23.9	48.7
North Carolina	11.0	3.2	8.0	10.4	13.5	31.1
North Dakota	5.4	2.1	3.3	4.0	6.9	17.6
Ohio	14.3	7.5	10.7	13.6	17.3	35.2
Oklahoma	10.4	4.1	7.0	9.5	13.1	28.5
Oregon	11.1	1.5	7.0	10.1	14.3	31.0
Pennsylvania	16.6	6.4	12.2	15.5	20.1	43.7
Rhode Island	13.8	5.9	11.1	13.7	16.2	29.2
South Carolina	9.4	3.3	6.4	8.9	11.9	25.1
South Dakota	5.2	1.8	3.3	4.2	6.7	15.8
Tennessee	12.7	5.9	9.2	11.2	15.0	38.3
Texas	11.5	1.9	7.0	10.4	14.5	40.6
Utah	17.0	4.3	10.0	15.4	23.4	39.8
Vermont	8.3	3.3	7.1	7.9	9.1	18.7
Virginia	13.5	5.3	9.2	12.0	17.1	36.1
Washington	14.9	2.9	9.3	13.6	19.1	48.9
West Virginia	12.7	6.9	10.3	11.9	14.9	25.5
Wisconsin	10.6	2.8	6.6	9.3	13.5	35.7
Wyoming	7.6	2.0	4.5	6.7	10.1	21.4

Table S2: Available childhood asthma incidence rates by state and year

State	2006*	2007*	2008*	2009*	2010*	Aggregate IR*	Aggregate PR**
Alabama						11.6	14.4
Arizona	23.7	6.8				15.2	13.1
Arkansas						11.6	13.1
California	12.1	6.5				9.3	12.2
Colorado						11.6	13.1
Connecticut		9.9	14.1	10.8	13.5	12	16
Delaware						11.6	18.2
District of Columbia	5.3	28.8				17.7	19.9
Florida						11.6	13.1
Georgia	6.4	5.8	9.1	16.6	6.9	9.1	15.1
Idaho						11.6	9
Illinois		4.2		9.2		6.7	12.4
Indiana	25.4	9.3	13.4	9.9	17.6	15.2	12.8
Iowa	5	4	9.9			6.3	8.4
Kansas	7.8	9.9	9.9	8.3	9	9	11.6
Kentucky						11.6	14
Louisiana				5.8		5.8	13
Maine	13	8.7	5.8			9.2	13.2
Maryland	16.2	8.6	11	17.3	2.3	11.2	14.8
Massachusetts						11.6	13.1
Michigan	5.3	7.7	5.2	13.4	29.3	12	13.6
Minnesota						11.6	9.5
Mississippi		10.8			17.2	14	14.2
Missouri	21.2	10.3	7.2			12.9	13.9
Montana	2.8	2		3.7	8.5	4.3	9.7
Nebraska	11.9	8.3	8.9	3.3	12.9	9.1	9.3
Nevada						11.6	10.9
New Hampshire	11.5	13.8	10.4			12	12.1
New Jersey			6.3	12.5	10.5	9.8	14.3
New Mexico		3.2	9.5		7.2	6.7	12
New York	12.9	6.1	28.4	11.2		14.7	15.8
North Carolina						11.6	13.1
North Dakota						11.6	8.9
Ohio		13.1	17			15.1	12.3
Oklahoma		9.2	10.1		12.9	10.8	14
Oregon		11.1				11.1	11.1
Pennsylvania		21.8			4.3	13.2	13.9
Rhode Island			15.3	13.2		14.3	16.1
South Carolina						11.6	13.1
South Dakota						11.6	13.1
Tennessee						11.6	13.1
Texas	14.4		18.2	12.5	21	16.6	13.1
Utah		15.4	11.9	5.6	9.3	10.4	10.2
Vermont	13.5	4.4	8.5	21.2	10.4	11.5	13.8
Virginia						11.6	13.6
Washington				7.9	5.6	6.8	10.8
West Virginia		11.8				11.8	12.7
Wisconsin	12.3					12.3	10.6
Wyoming						11.6	9.5

*Incidence rate per 1,000 at-risk children

** Prevalence rate per 100 children

[Note: The grey highlight represent no available data]

Table S3: Childhood asthma survey summary by state (Total of 2006-2010)

State	Total ACBS sample	Total BRFSS sample	Total ever asthma	Total incident cases
Arizona	103	5,535	699	10
California	172	11,801	1,543	13
Connecticut	549	7,112	1,132	47
D.C.	69	4,101	685	6
Georgia	545	9,433	1,455	26
Illinois	122	6,187	778	6
Indiana	500	9,824	1,361	41
Iowa	245	8,084	724	19
Kansas	827	14,699	1,839	50
Louisiana	88	8,829	1,214	4
Maine	376	4,523	644	23
Maryland	624	13,093	1,897	44
Michigan	680	10,762	1,524	43
Mississippi	208	10,816	1,527	14
Missouri	262	5,646	814	20
Montana	286	8,609	909	17
Nebraska	717	17,883	1,644	53
New Hampshire	232	5,285	664	19
New Jersey	458	15,410	2,230	32
New Mexico	287	5,554	765	17
New York	404	7,083	1,079	28
Ohio	351	7,989	1,138	32
Oklahoma	299	8,611	1,291	21
Oregon	165	4,793	579	13
Pennsylvania	209	14,760	2,090	12
Rhode Island	169	7,127	1,209	11
Texas	780	16,749	2,293	55
Utah	573	14,417	1,617	45
Vermont	597	8,784	1,220	40
Washington	594	9,706	1,165	33
West Virginia	85	5,089	663	5
Wisconsin	140	5,170	611	10

**Incidence rate* per 1,000 at-risk children

**Prevalence rate per 100 children*

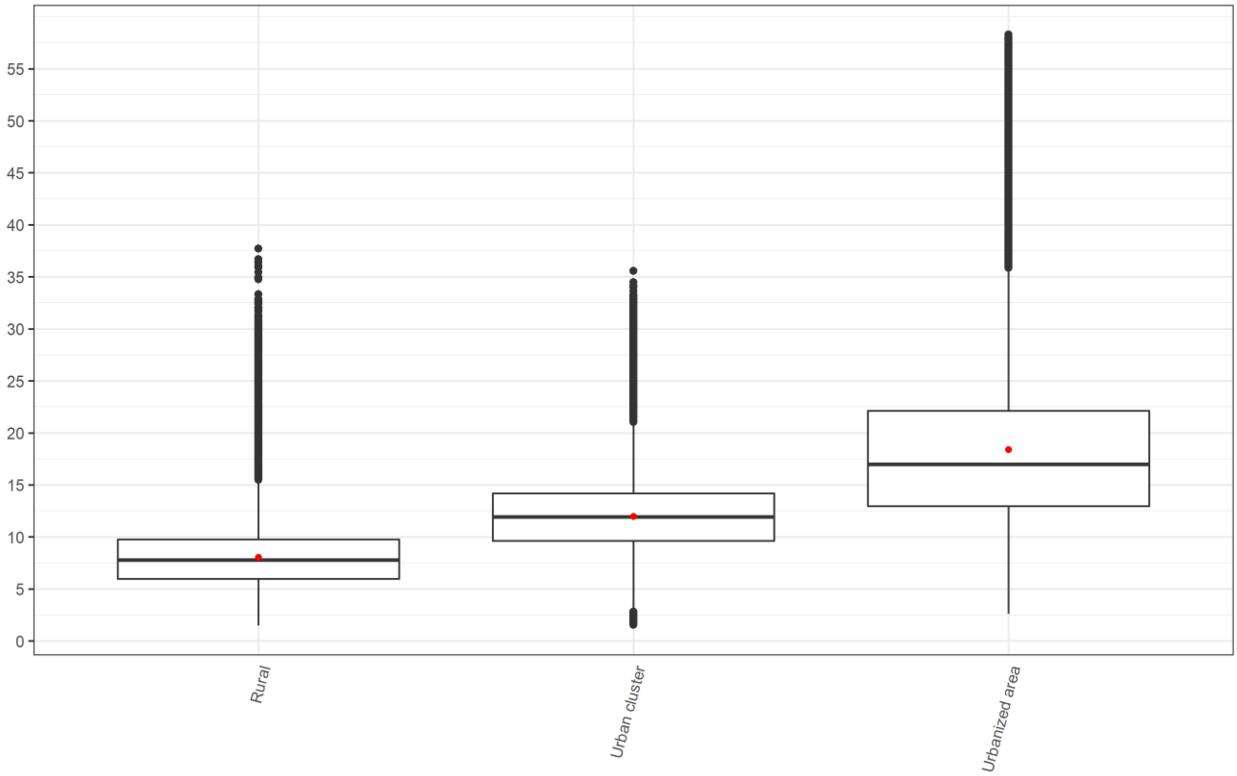
Table S4: Aggregated childhood asthma weighted survey summary (2006-2010)

State	Aggregated weighted incident cases	Aggregated at-risk children	Years of available data
Arizona	42,622	2,802,422	2
California	156,599	16,850,453	2
Connecticut	32,939	2,734,478	4
D.C.	3,184	179,493	2
Georgia	94,786	10,458,074	5
Illinois	37,799	5,673,571	2
Indiana	105,219	6,936,762	5
Iowa	11,510	1,829,734	3
Kansas	27,509	3,059,760	5
Louisiana	5,379	931,966	1
Maine	6,662	722,763	3
Maryland	64,871	5,816,584	5
Michigan	126,102	10,491,065	5
Mississippi	18,264	1,300,917	2
Missouri	46,410	3,600,272	3
Montana	3,296	768,012	4
Nebraska	18,262	2,014,605	5
New Hampshire	9,423	788,302	3
New Jersey	51,472	5,274,310	3
New Mexico	8,857	1,327,496	3
New York	221,226	15,027,481	4
Ohio	71,568	4,755,245	2
Oklahoma	24,628	2,285,659	3
Oregon	8,328	752,768	1
Pennsylvania	62,292	4,733,925	2
Rhode Island	5,476	384,117	2
Texas	381,999	22,992,023	4
Utah	30,221	2,902,955	4
Vermont	6,498	563,280	5
Washington	18,647	2,752,373	2
West Virginia	3,847	325,031	1
Wisconsin	14,404	1,174,447	1

Table S5: State-specific results and comparison

	Results using flat national-level IR			Results using state-specific IR			Difference			Difference (%)		
State	**Incident cases**	**AC**	**AF**	**Incident cases**	**AC**	**AF**	**Incident cases**	**AC**	**AF**	**Incident cases**	**AC**	**AF**
Alabama	12,200	1,400	11.5%	11,300	1,300	11.5%	-900	-100	0.0%	-7.4%	-7.1%	0.3%
Arizona	17,600	3,800	21.6%	21,500	4,600	21.4%	3,900	800	-0.2%	22.2%	21.1%	-0.9%
Arkansas	7,700	900	11.7%	7,200	800	11.1%	-500	-100	-0.6%	-6.5%	-11.1%	-4.9%
California	100,300	25,400	25.3%	75,800	19,200	25.3%	-24,500	-6,200	0.0%	-24.4%	-24.4%	0.0%
Colorado	13,200	3,100	23.5%	12,400	2,900	23.4%	-800	-200	-0.1%	-6.1%	-6.5%	-0.4%
Connecticut	8,800	1,600	18.2%	8,300	1,500	18.1%	-500	-100	-0.1%	-5.7%	-6.3%	-0.6%
Delaware	2,200	400	18.2%	2,000	300	15.0%	-200	-100	-3.2%	-9.1%	-25.0%	-17.5%
D.C.	1,100	300	27.3%	1,400	400	28.6%	300	100	1.3%	27.3%	33.3%	4.8%
Florida	43,200	5,500	12.7%	40,500	5,200	12.8%	-2,700	-300	0.1%	-6.3%	-5.5%	0.8%
Georgia	26,900	3,900	14.5%	19,200	2,800	14.6%	-7,700	-1,100	0.1%	-28.6%	-28.2%	0.6%
Idaho	4,600	600	13.0%	4,500	600	13.3%	-100	0	0.3%	-2.2%	0.0%	2.2%
Illinois	33,800	8,300	24.6%	18,300	4,500	24.6%	-15,500	-3,800	0.0%	-45.9%	-45.8%	0.1%
Indiana	17,300	3,100	17.9%	21,300	3,900	18.3%	4,000	800	0.4%	23.1%	25.8%	2.2%
Iowa	7,900	1,000	12.7%	4,200	500	11.9%	-3,700	-500	-0.8%	-46.8%	-50.0%	-6.0%
Kansas	7,800	1,100	14.1%	5,800	800	13.8%	-2,000	-300	-0.3%	-25.6%	-27.3%	-2.2%
Kentucky	11,000	1,600	14.5%	10,300	1,500	14.6%	-700	-100	0.0%	-6.4%	-6.3%	0.1%
Louisiana	12,100	1,400	11.6%	5,600	700	12.5%	-6,500	-700	0.9%	-53.7%	-50.0%	8.0%
Maine	3,000	200	6.7%	2,200	200	9.1%	-800	0	2.4%	-26.7%	0.0%	36.4%
Maryland	14,600	2,800	19.2%	12,800	2,500	19.5%	-1,800	-300	0.4%	-12.3%	-10.7%	1.8%
Massachusetts	15,300	2,500	16.3%	14,400	2,400	16.7%	-900	-100	0.3%	-5.9%	-4.0%	2.0%
Michigan	25,300	4,200	16.6%	24,400	4,100	16.8%	-900	-100	0.2%	-3.6%	-2.4%	1.2%
Minnesota	13,900	2,100	15.1%	13,500	2,100	15.6%	-400	0	0.4%	-2.9%	0.0%	3.0%
Mississippi	8,200	800	9.8%	9,100	900	9.9%	900	100	0.1%	11.0%	12.5%	1.4%
Missouri	15,400	1,800	11.7%	15,800	1,900	12.0%	400	100	0.3%	2.6%	5.6%	2.9%
Montana	2,400	200	8.3%	900	100	11.1%	-1,500	-100	2.8%	-62.5%	-50.0%	33.3%
Nebraska	5,000	600	12.0%	3,800	500	13.2%	-1,200	-100	1.2%	-24.0%	-16.7%	9.6%
Nevada	7,200	1,400	19.4%	6,900	1,400	20.3%	-300	0	0.8%	-4.2%	0.0%	4.3%
New Hampshire	3,100	300	9.7%	3,000	300	10.0%	-100	0	0.3%	-3.2%	0.0%	3.3%
New Jersey	22,300	5,400	24.2%	17,300	4,200	24.3%	-5,000	-1,200	0.1%	-22.4%	-22.2%	0.3%
New Mexico	5,600	900	16.1%	3,000	500	16.7%	-2,600	-400	0.6%	-46.4%	-44.4%	3.7%
New York	46,700	11,800	25.3%	53,600	13,500	25.2%	6,900	1,700	-0.1%	14.8%	14.4%	-0.3%
North Carolina	24,600	3,200	13.0%	23,100	3,000	13.0%	-1,500	-200	0.0%	-6.1%	-6.3%	-0.2%
North Dakota	1,600	100	6.3%	1,600	100	6.3%	0	0	0.0%	0.0%	0.0%	0.0%
Ohio	29,500	5,000	16.9%	36,100	6,200	17.2%	6,600	1,200	0.2%	22.4%	24.0%	1.3%
Oklahoma	10,000	1,300	13.0%	8,600	1,200	14.0%	-1,400	-100	1.0%	-14.0%	-7.7%	7.3%
Oregon	9,300	1,300	14.0%	8,500	1,200	14.1%	-800	-100	0.1%	-8.6%	-7.7%	1.0%
Pennsylvania	30,100	6,000	19.9%	31,600	6,300	19.9%	1,500	300	0.0%	5.0%	5.0%	0.0%
Rhode Island	2,400	400	16.7%	2,700	400	14.8%	300	0	-1.9%	12.5%	0.0%	-11.1%
South Carolina	11,700	1,300	11.1%	10,900	1,200	11.0%	-800	-100	-0.1%	-6.8%	-7.7%	-0.9%
South Dakota	2,200	200	9.1%	2,100	200	9.5%	-100	0	0.4%	-4.5%	0.0%	4.8%
Tennessee	16,100	2,500	15.5%	15,100	2,400	15.9%	-1,000	-100	0.4%	-6.2%	-4.0%	2.4%
Texas	74,100	10,700	14.4%	99,100	14,300	14.4%	25,000	3,600	0.0%	33.7%	33.6%	-0.1%
Utah	9,400	1,900	20.2%	8,100	1,700	21.0%	-1,300	-200	0.8%	-13.8%	-10.5%	3.8%
Vermont	1,400	100	7.1%	1,300	100	7.7%	-100	0	0.5%	-7.1%	0.0%	7.7%
Virginia	20,000	3,400	17.0%	18,700	3,200	17.1%	-1,300	-200	0.1%	-6.5%	-5.9%	0.7%
Washington	17,100	3,000	17.5%	9,600	1,700	17.7%	-7,500	-1,300	0.2%	-43.9%	-43.3%	0.9%
West Virginia	4,200	600	14.3%	4,000	600	15.0%	-200	0	0.7%	-4.8%	0.0%	5.0%
Wisconsin	14,400	2,100	14.6%	14,700	2,200	15.0%	300	100	0.4%	2.1%	4.8%	2.6%
Wyoming	1,500	100	6.7%	1,400	100	7.1%	-100	0	0.5%	-6.7%	0.0%	7.1%

Figure S1: NO_2 concentration (ug/m^3) by living location



**Red dot represents the mean value while the midline represents the median value*

Figure S2: NO_2 concentration (ug/m^3) by median household income group

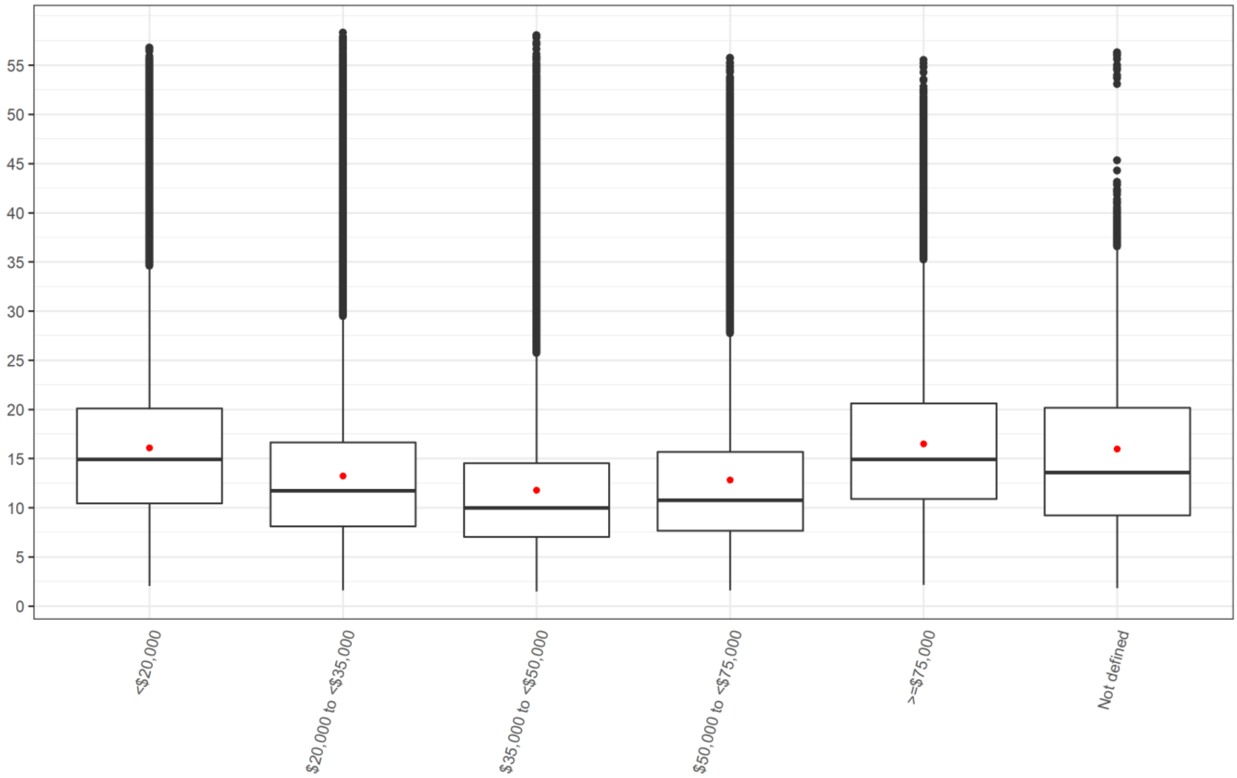


Figure S3: NO_2 concentration (ug/m^3) by living location stratified into median household income group

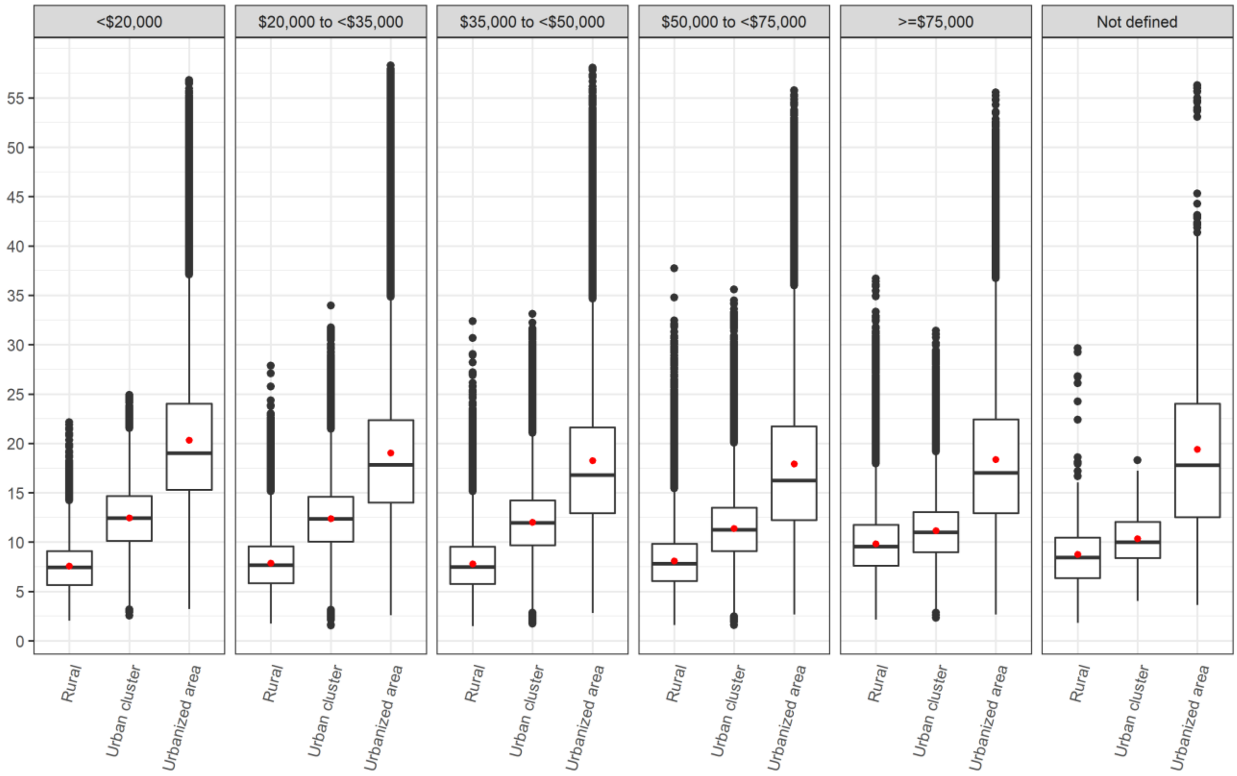


Figure S4: NO_2 concentration (ug/m^3) by median household income group stratified into living location

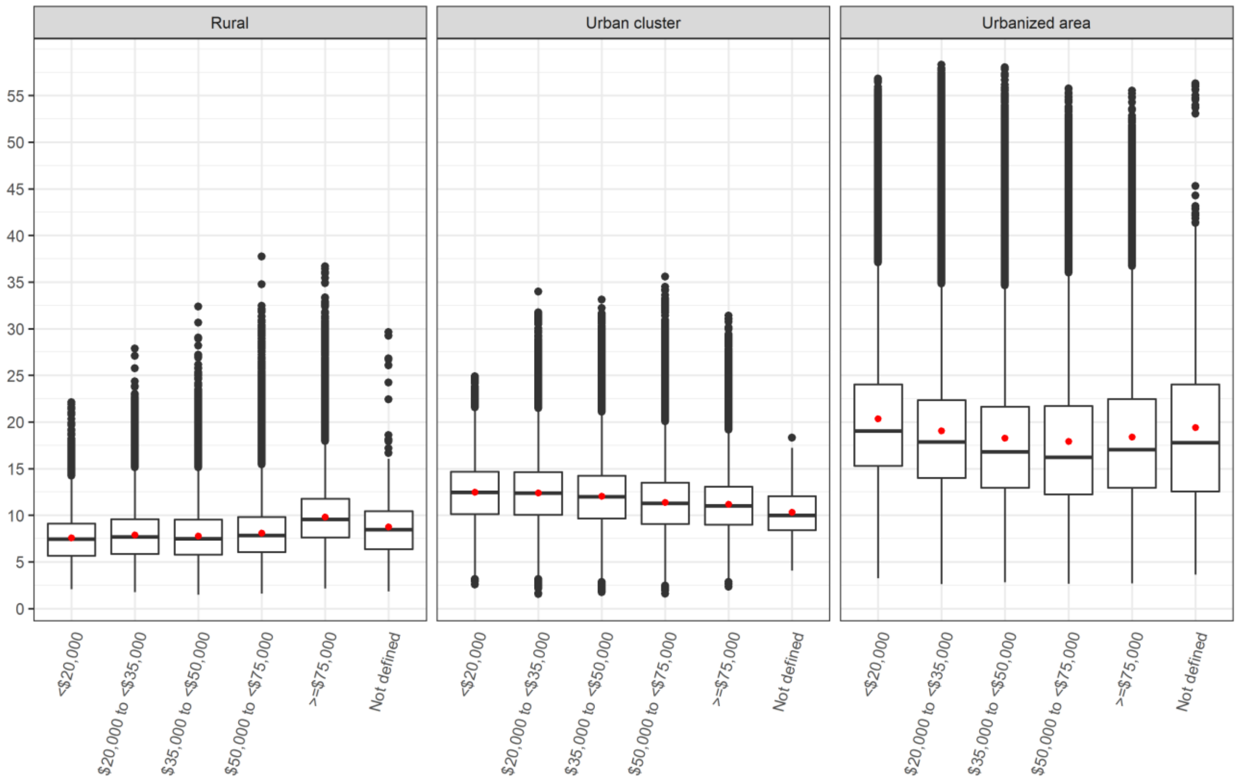


Figure S5: NO_2 concentration (ug/m^3) by state

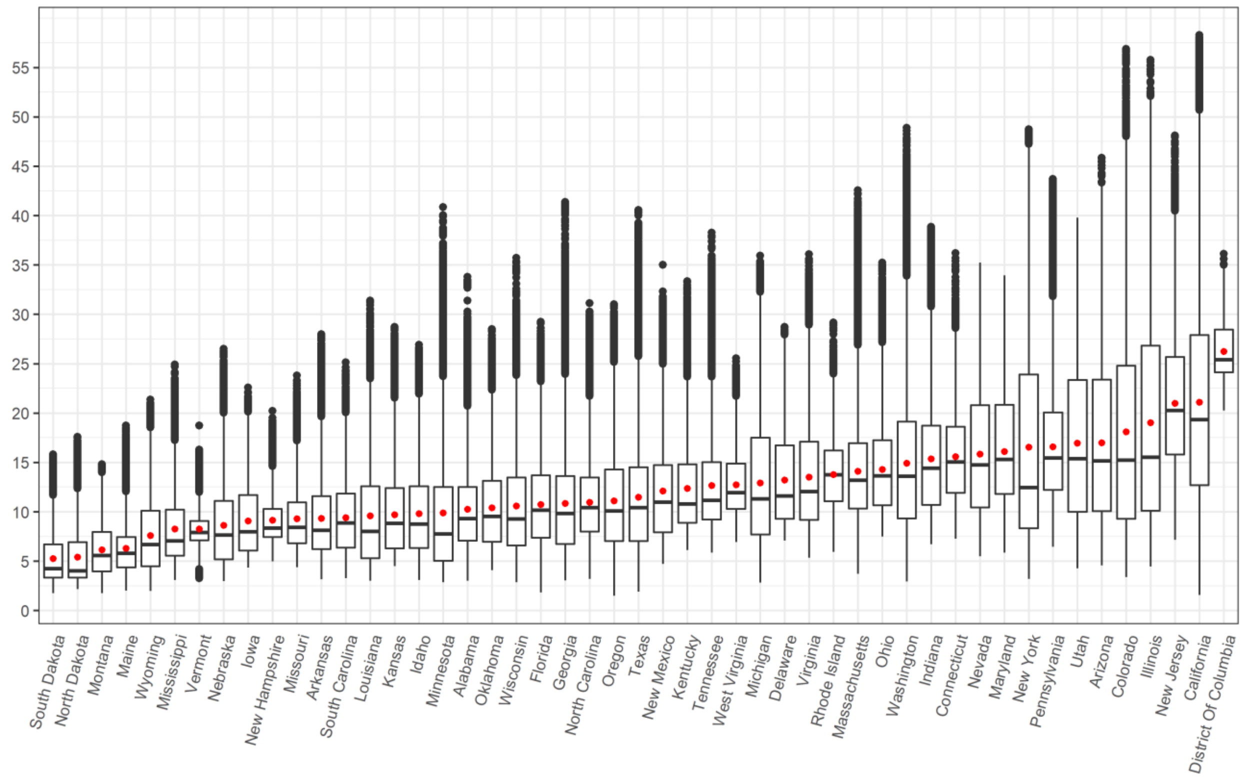
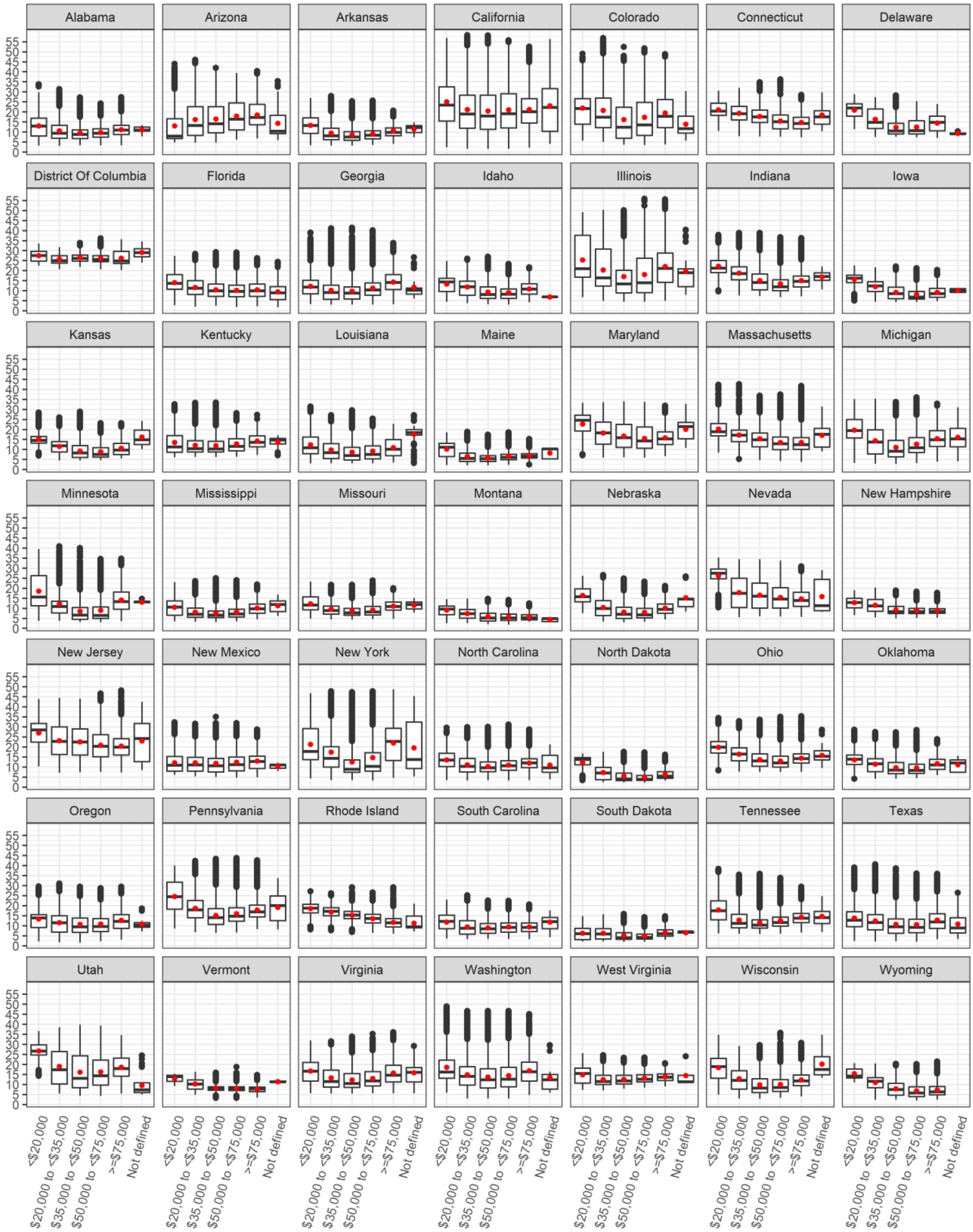
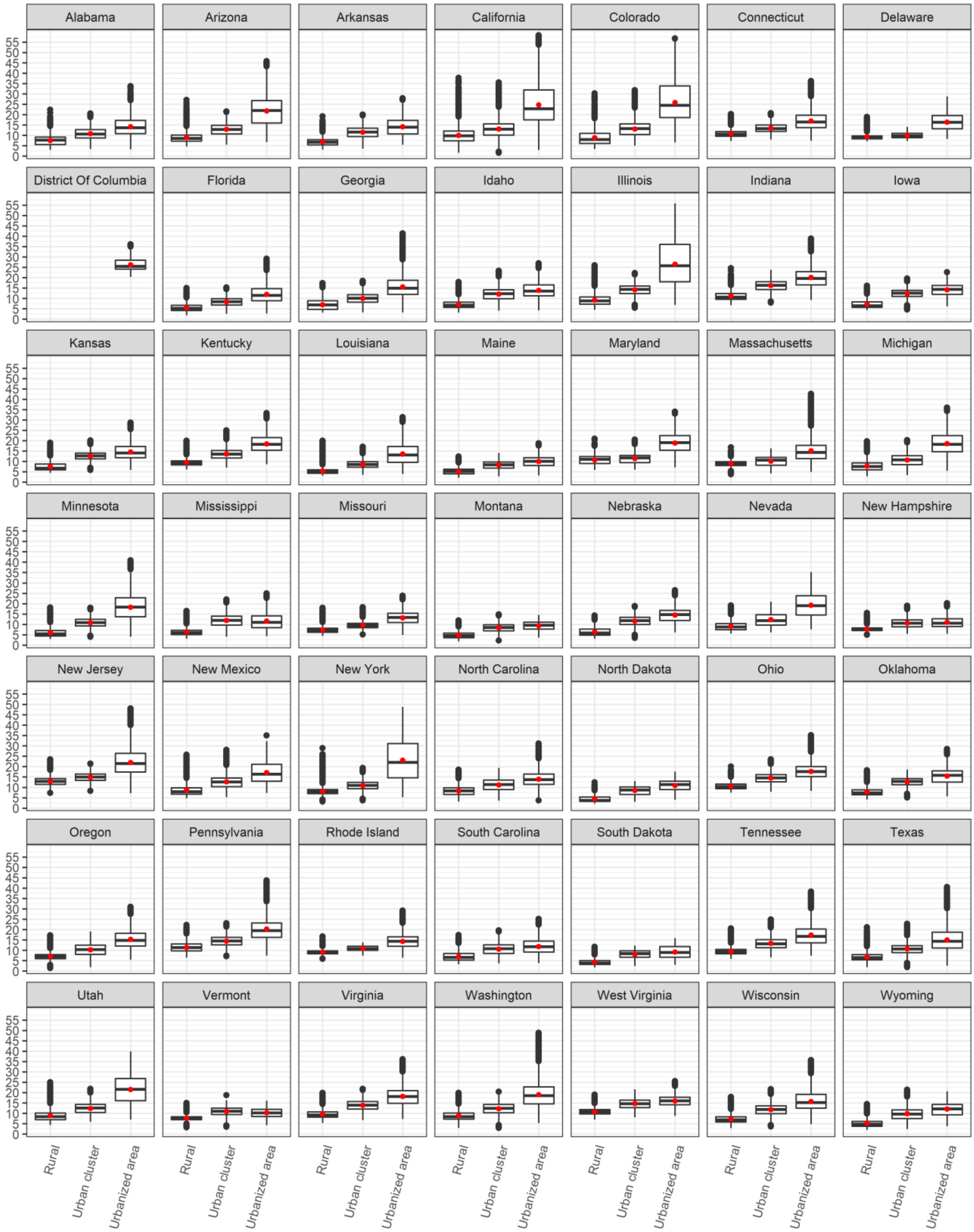


Figure S6: NO_2 concentration (ug/m³) by state and median household income group



569 *Figure S7: NO_2 concentration (ug/m^3) by state and living location*



570

Figure S8: Attributable Fraction by living location

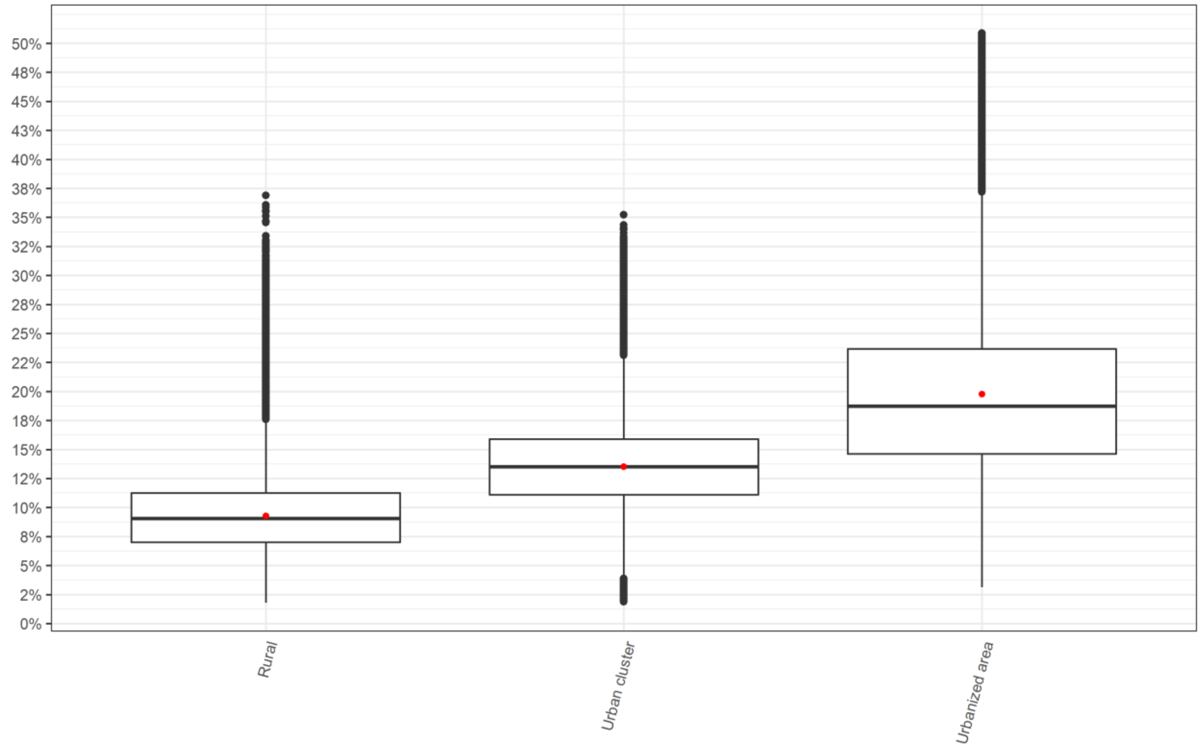


Figure S9: Attributable Fraction by median household income group

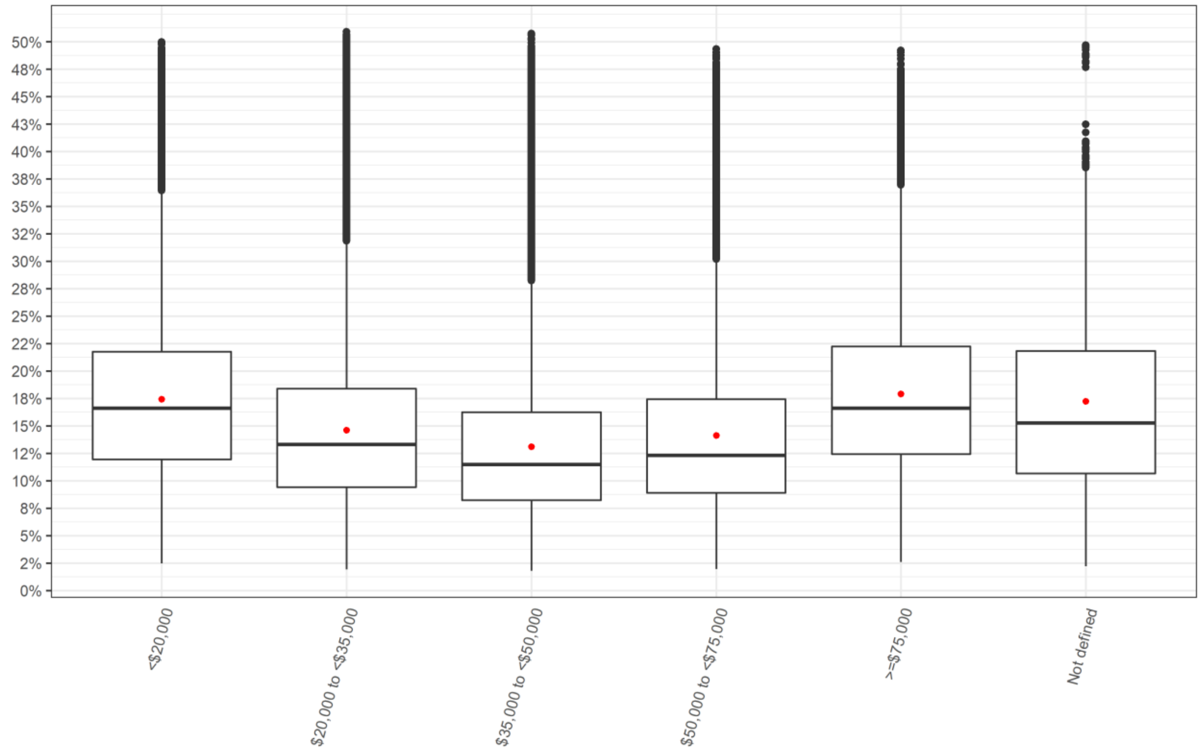


Figure S10: Attributable Fraction by median household income group stratified into living location