**Methods**

In this paper, we aim to estimate the burden of childhood asthma due to NO2 exposure using state specific asthma incidence rates and compare the change in the estimated from those produced by Alotaibi et al. (2019).

*Census data*

We included populated census blocks of the contiguous United States (U.S.) for the year 2010 obtained from the National Historical Geographic Information System (NHGIS) website (Manson et al., 2018; US Census Bureau, 2010). Each block included information on total population of children <18 years, and whether the census block was designated as an urban or rural block. Urban blocks are stratified into urban clusters (≥2,500 and <50,000 people living in them) or urbanized areas (≥50,000 people). Median household income was available only for census block groups, which is a level higher than census block. We divided median household income into five categorized: <$20,000, $20,000 to <$35,000, $35,000 to <$50,000, $50,000 to <$75,000 and ≥$75,000 (Clark et al., 2017). There were 2686 (0.04%) census blocks with missing median income data in 2010 which were assigned as “Not defined” in the analysis of median household income. Table 1 summarizes the geographical and demographic data. .

*NO2 exposure assessment*

Annual average NO2 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 utilizing Environmental Protection Agency (EPA), satellite data and several GIS covariates. A detailed description of the model can be found at Bechle et al. (2015). NO2 concentrations were converted from ppb to ug/m3through multiplying by 1.88 (WHO, 2005).

The mean (min-max) NO2 concentrations were 13.3 (1.5-58.3) ug/m3 (Table 2). By living location the mean NO2 concentrations was highest at (living location)-(NO2 conc), while mean NO2 concentration was highest among (income group)-(NO2 conc) (Table 3 and Figures 2-5). South Dakota had the lowest ***median*** NO2 concentration (conc), while the District of Columbia had the highest (conc) (Table 4 and Figure 6). Figures 7-8 shows NO2 concentrations across living location and median household income for each state.

*Concentration-response function*

We used a concentration-response function (CRF) of 1.05 (95% CI = 1.02-1.07) per 4ug/m3 of NO2. The CRF was obtained from a meta-analysis of 20 studies examining the association between exposure to traffic-related air pollution (TRAP) and risk of developing asthma among children (Khreis et al., 2017).

*Asthma incidence and prevalence rates*

An incidence rate is defined as the number of new cases of a disease within a specified time period among an at-risk population. To estimate the childhood asthma incidence rate, we extracted the number of new asthma childhood cases and at-risk children for the year 2006 through 2010 using the Asthma Call Back Survey (ACBS) and Behavioral Risk Factor Surveillance System (BRFSS) (CDC, 2009, 2011) and following the methods described by Winer et al. (2012). In brief, participants in the BRFSS were asked “Has a doctor, nurse, or other health professional ever said that the [name of child] has asthma?” if the answer is “yes”, the respondent is requested to participate in the ACBS follow up survey. The ACBS survey further asks “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?”, an asthma incident case is defined as answering “within the past 12 months”. At-risk children are the sum of new childhood asthma cases and total children who never had asthma (I.e. those who answered no to “Has a doctor, nurse, or other health professional ever said that the [name of child] has asthma?”) (Figure 1).

*Data analysis* *method*

We obtained the BRFSS and ACBS child data sets for the years 2006-2010 from the CDC website <https://www.cdc.gov/brfss/>. All analysis was conducted using R statistical software (R Core Team, 2018). States not within the contiguous U.S. were excluded from the analysis. States with missing data from the BRFSS or ACBS were excluded for the year of missing data.

Each sample was weighted; the sum of the BRFSS weights represents the total children population of the state, while the sum of the ACBS weights represent the total children with ever asthma. We extracted the variable for the question “Has a doctor, nurse or other health professional EVER said that the child has asthma?” from the BRFSS data set and “How long ago was that?” from the ACBS data set. The weights for each answer across available states was than summed, which represents the population estimate of children for each answer (Table 11 & 12). We then estimated the following for each state and year separately:

At-risk children = Total incident cases + Total children with never asthma.

Asthma Incidence rate = Total incident cases / At-risk children.

Asthma prevalence rate = Ever asthma / Total children.

The overall average asthma incident rate is then estimated by taking the sum of incident case and dividing it with the sum of at-risk children across all available years. We then estimated the state-specific average asthma incidence rates for the years 2006 through 2010 following a similar fashion. Not all states participated in the ACBS each year. States that did not participate in the ACBCS were assigned the overall average asthma incidence rate.

*Burden of disease estimate*

To estimate the burden of disease, we used a standard assessment methods described by Mueller et al. (2017) with the following steps:

We estimated the at-risk children for each state by subtracting the total number of prevalent cases from the total children within the state. We then estimated the number of asthma cases for each state by multiplying the state-specific childhood asthma incidence rate with at-risk children for each census block.

*At-risk children = Total children – (Total children \* Prevalence rate) (1)*

*Asthma incident cases = At-risk children \* Incidence rate (2)*

We then calculated the relative risk (RRdiff) for asthma due to exposure difference between estimated exposure levels (NO2 concentration at the census block level) and no exposure (zero NO2 concentration).

*RRdiff = e((ln(RR)/RRunit\*Exposure level) (3)*

Where RR is the CRF and RRunit is the exposure unit for the CRF. The population attributable fraction (PAF) is then estimated.

*PAF = (RRdiff – 1)/(RRdiff) (4)*

The attributable number of asthma incident cases (AC) is estimated by multiplying the PAF with the number of incident asthma cases at each census block. The AC is then summed up to get the total AC.

* Add graphic section describing analysis flow (Figure 1)

**Results**

*ACBS and BRFSS results*

Overall, there were 32 states with available childhood asthma incidence rates (Table 10, 11, 12 & 13). The total childhood samples collected for the period (2006-2008) are shown in tables 10 & 12. Table 12 also shows the year’s available incidence rate data for each state. BRFSS weighted estimates representing the total childhood population of available states and ACBS weighted estimates representing total children with ever asthma of available states are shown in tables 11 &13.

The average national incidence rate for the years 2006-2010 was 12.1 per 1,000. The state of Montana had the lowest average childhood asthma incidence rate (IR = 4.3 per 1,000), while District of Columbia had the highest average childhood asthma incidence rate (IR = 17.7 per 1,000). States that did not have an incidence rate (add number of states) available were assigned the national incidence rate of 12.1 per 1,000.

*Asthma incident cases*

Using state-specific asthma incidence rates the estimated number of childhood asthma incident cases were 754,893 in 2010 (Table 3). 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 (28%) 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 6).

*Attributable number of cases and fraction*

On average, we estimated a total of 132,829 childhood asthma cases attributable to NO2 exposure which accounted for 17.6% of all childhood asthma cases (Table 3). By living location, urbanized areas had the largest number of attributable cases totaling 109,581 cases and highest percentage of all asthma cases of 20.3%. Rural areas had total of 13,951 cases but accounting for the east percentage of all asthma cases with 9.8%, while urban clusters had only 9,296 cases representing 13% of all asthma cases (Figure 9). By income, $50,000 to <$75,000 had the largest number of cases attributable to NO2, 37,559 cases accounting for 16.8% of all asthma cases. However, the income group with the largest percentage of asthma cases was the lowest income group <$20,000, accounting for 20.8% of all asthma cases (Figure 10). The median value of 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 11&12).

The state with the lowest number of estimated AC was Montana with 70 cases, while the state with the largest AC was California with 19,200 cases. The state with the lowest AF was South Dakota (7.6%), while the state with the highest AF was District of Columbia (26.9) (Table 6 and Figure 6).

Figures 14&15 present the distribution of AF by living location and median income group for each state. The majority of states follow a distribution similar to the national level with a few exceptions (e.g. see Arizona, Montana, Rhode Island & Wyoming).

*Comparison with the main paper*

*Comparing total asthma cases*

Using state-specific asthma incidence rates the overall number of cases reduced by an average of 40,041 (5%) cases compared to estimates in the main paper (Table 7). By living location, the largest reduction was among urban clusters with a decrease by 4,204 (5.6%) cases followed by urbanized areas which reduced by 29,926 (5.2%) cases. By income group, the largest decrease in the number of cases was among the highest income groups by 13,123 (6.8%) cases, while the least decrease was among the lowest income group by 168 (0.6%) cases.

*Comparing attributable cases*

The total attributable cases reduced by 9,103 (6.4%) cases when compared to the main paper (Table 7). By living location, urbanized areas had the largest reduction of 8,040 (6.8%) cases while rural areas had the least reduction by 514 (3.6%) cases attributable to NO2 exposure. By income group, the highest income group also had the largest decrease in attributable cases by 2.994 (8.5%) and the lowest income group had the least decrease by 58 (1%) cases.

*Comparing attributable fractions*

The overall attributable fraction reduced 1.4% with urbanized areas having the largest reduction by 1.7% in terms of living location. In terms of income group the largest reduction was 1.8% for both $50,000 to <$75,000 and ≥$75,000 (Table 8).

*Comparing state estimates*

Table 9 summarizes the changes in total asthma incident cases and AC by state after applying state specific asthma incidence rates. In brief, the state of Montana had the largest percent reduction in total childhood asthma incident cases and AC of 64.1% while the state of Texas had the largest percent increase of 33.8%. The state of California had the largest decrease in numbers of total childhood asthma incident cases of 24,442 cases while the state of Texas had the largest increase in numbers by 25,019 cases. The state of California had the largest decrease in AC by 6,190 cases while the state of Texas had the largest increase by 3,615 cases.

**Discussion (bullet points)**

* Using state specific asthma incidence rates did not change the results much (within the range of the sensitivity analysis from the main paper)
* The state specific total number of asthma cases and attributable cases changed when applying state specific incidence rates (Table 9)
* 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 but not the AF. The AF 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 won’t in incidence rate won’t be uniform within the state.
* The percentage of all asthma cases has a J shaped distribution when examining income groups. The lowest income group had the highest % then drops and rises again with the highest income group.
* Explore why the U shaped distribution is there,

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