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2017-04-01

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Mapping rescue asthma inhaler use and outdoor air pollution: a geospatial-temporal analysis

By

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A thesis submitted in partial satisfaction of the requirements for the degree of
Master of Science
in
Health and Medical Sciences
in the
Graduate Division
of the
University of California, Berkeley

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Spring 2017
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PART ONE: REVIEWING OUTDOOR AIR POLLUTANTS AND ASTHMA ASSOCIATIONS, EXPOSURE CLASSIFICATIONS, AND OUTCOME MEASURES

Asthma is the most common chronic respiratory disease in the Western world. In 2010, 13% of adults and 12.5% of children in California had been diagnosed with asthma at some point in their lives, and nearly 200,000 new cases are diagnosed each year. Prevalence of asthma is disproportionately higher in poor communities of color.

Asthma is also a costly disease, accounting for over $50 billion in direct costs and lost productivity in the United States, with one third of all incremental costs due to hospitalizations and emergency department visits.

Asthma is an acute-on-chronic disease characterized by episodes of coughing, wheezing, chest tightness and difficulty breathing, often called “asthma attacks”. These acute episodes of exacerbation are largely preventable with adequate medications, patient education and self-management.

Asthma is affected by the outdoor environment. There is good evidence to show that certain ambient air pollutants contribute to asthma exacerbations, and there is evidence suggesting links between asthma and increased temperature, temperature fluctuations, traffic-related pollution, and pesticide exposure.

This paper begins by reviewing the associations between major outdoor air pollutants and asthma. This section discusses the criteria air pollutants associated with asthma exacerbation and pays particular attention to the effects of traffic-related air pollution (TRAP) and pesticides.

It then examines how asthma researchers typically assign exposures of outdoor air pollution and measure asthma outcomes. These methods are complex, as environmental exposures occur across wide ranges of space and time, making it notoriously difficult to accurately assign exposures at high spatial or temporal resolutions. Home addresses have been used to improve exposure classification, but these studies do not account for exposures outside the home environment. Similarly, this paper shows that there is no gold standard in measuring asthma outcomes, and researchers typically rely on hospitalizations and emergency department visits as indicators of general asthma exacerbation. I primarily focus on the geospatial methods used in assigning exposure and outcomes and the limitations...
of these approaches. Finally, I discuss emerging research that uses real-time geospatial sensors for improving both exposures and outcomes.\textsuperscript{24-26}

This paper concludes by discussing the emerging role of ecological niche modeling (ENM) and machine-learning models in researching complex human diseases. I briefly discuss common methods for modeling species distribution and the possible role of these methods in modeling the complex and synergistic role of multiple air pollutants in causing asthma exacerbation.

\section*{REVIEW OF OUTDOOR AIR POLLUTANTS}

Outdoor air pollution is a combination of gases and particulates that negatively impact respiratory health. Outdoor air quality is affected by traffic, power generation, industrial and agricultural activities, climate and topography.\textsuperscript{12,27} In urban areas, traffic and power generation are the main sources of urban air pollution.\textsuperscript{12} Outdoor air pollutants are thought to cause exacerbations of pre-existing asthma and new evidence is suggesting that they may also contribute to new incidence of asthma. Children are particularly vulnerable to the effects of air pollution due to their narrow and developing airways, higher breathing rate, increased time spent outdoors, and relatively immature immune systems. This section briefly reviews the associations between the main outdoor air pollutants (TRAP, PM, ozone, nitrogen oxides, sulfur oxides, and pesticides) and asthma.

\textit{Traffic-related air pollution (TRAP)}

Traffic-related air pollution (TRAP) is a complex mixture of gaseous emissions from vehicular exhaust, particulate matter as a product of gasoline or diesel combustion, and non-combustible sources of particulates such as dust and brake/tire wear.\textsuperscript{12} Gaseous emissions include carbon dioxide (CO\textsubscript{2}), carbon monoxide (CO), hydrocarbons (HC), nitrogen oxides (NO\textsubscript{x}), and so-called mobile-source air toxics (MSATs) such as benzene, formaldehyde, acetaldehyde, 1,3-butadiene, and lead (only in areas where leaded fuel is still used).\textsuperscript{28} These emissions can act directly to harm the environment and human health, but can also undergo chemical reactions while volatile to create ozone, organic acids, nitrates and other secondary aerosols which likewise act as environmental pollutants.

By 2010, over 400 studies had attempted to look at traffic exposure and its affects on health.\textsuperscript{29} Due to the large number of studies with adequate control for confounding, a 2010 expert panel on the Health Effects of TRAP concluded that the evidence for an increased wheeze in asthmatic patients with an increasing exposure to NO\textsubscript{2} is sufficient for a causal association.\textsuperscript{10} Moreover, there is increasing evidence that TRAP exposure also plays a role in new asthma incidence in both children\textsuperscript{30-32} and adults\textsuperscript{33,34}. 
The effects of chronic exposure to TRAP are not well understood, and there is inconsistency in the quality of evidence. Studies that examine the exposure of TRAP within a community using fine-scale spatial methods, traffic proximity measure or geostatistical interpolation from monitoring stations frequently report positive associations of exposure and asthma prevalence. In contrast, studies that compare long-term exposure to TRAP between communities generally do not find a significant association. This discrepancy may be due to the difficulty in powering inter-community studies, as the number of communities assessed determines the statistical power of these studies. Alternatively, it is possible that neighborhood-level analyses show associations between TRAP exposure and asthma prevalence merely due to confounding by other neighborhood-level factors such as socioeconomic status. Lastly, it is possible that inter-community studies do not show a positive association because exposure classification is poor at this geographic scale. More research is needed on the small-scale changes of environmental exposures that occur within a community and whether these exposures are associated with asthma exacerbation.

As would be expected, distance from highways affects the concentration of TRAP, with concentrations dropping rapidly with increasing distance. A TRAP “exposure zone” has been defined as the region within 300-500 meters from a highway or a major road. In large North American cities, it is estimated that 30-45% of the population lives within a TRAP exposure zone. Across 10 major European cities, this value is estimated to be even higher, with an estimated 53% of the combined population living with 150 meters of busy roads (defined as roads with more than 10,000 vehicles travelling on this road per day).

**Particulate Matter (PM)**

Particulate matter is a complex mixture of small particles and suspended liquid droplets in the air. This mixture comes from both anthropogenic and natural sources and includes dust, dirt, soot, smoke and products of combustion. PM can form in the air during chemical reactions involving gaseous pollutants such as sulfur dioxides and nitrogen oxides. The specific composition of particulate matter varies by region, time of day/year, weather conditions and other factors. Particulate matter is typically classified by size, with PM10 indicating particles with a diameter less than 10 micrometres (course particles), PM2.5 indicating fine particles, and PM0.1 indicating ultrafine particles.

Particulate matter deposits in the airways and is known to cause oxidative stress, airway hyper-responsiveness and airway remodeling. Fine particles deposit in distal airways such as the alveoli, which can lead to acute respiratory effects such as asthma exacerbation, decreased lung function and increased mortality. The risk of asthma exacerbation is higher in children with allergic sensitization. Acute exposure to course and fine PM has been associated with asthma exacerbation, especially in
children. Long-term exposure may also lead to exacerbation and decreased lung function.\textsuperscript{12}

Many studies of associations between both short and long-term exposure to PM use health-care utilization as the outcome measure of choice.\textsuperscript{12,39–42} These data aggregate over large spatial regions and may not represent proximal locations of asthmatic symptoms. Moreover, they do not include sub-acute symptoms or those situations in which a patient did not present in the emergency room or hospital due to factors such as cost or distance.

\textit{Ozone (O}_3\textit{)}

Ground-level (tropospheric) ozone is generally considered a “secondary pollutant”, as the main source is photochemical reactions of volatile organic compounds (VOCs) and nitrogen dioxide in the presence of heat and sunlight.\textsuperscript{27} The other source is intrusion of stratospheric ozone, which can occur sporadically and dramatically increase regional levels of ozone concentrations.\textsuperscript{43} Sink processes of ozone in the troposphere include wind transport, deposition, and photochemical processes – most notably the oxidation of nitric oxide to nitrogen oxides (NO\textsubscript{x}) near roadways.\textsuperscript{12,44}

Ground-level concentrations of ozone have a seasonal cycle, with higher concentrations in the summer due to higher heat and sunlight. Similarly, the daily concentrations of ozone rise with both heat and temperature, and can vary with anthropogenic and natural emissions and precursors.

Ozone is a powerful oxidant that causes airway irritation and inflammation, impaired pulmonary function, and asthma exacerbation. Acute ozone exposure can impact healthy adult and children, and causes acute exacerbation of existing asthma.\textsuperscript{45} There is less evidence showing ozone causes new-onset asthma, and the effects may be more likely in certain sub-groups of children.\textsuperscript{12,46} Ozone has also been associated with allergic sensitization in children, which may increase the likelihood of new-onset asthma. Ozone has also been shown to increase wheeze and asthma as diagnosed by a doctor, though these associations need to be supported by further research. Socioeconomic characteristics may also contribute differential ozone-asthma associations, with poor populations at increased risk of hospital admission on days with high ozone concentrations.\textsuperscript{46}

\textit{Nitrous Oxides (NO}_x\textit{)}

Outdoor NO\textsubscript{x} is a product of vehicle combustion and is also formed in atmospheric reactions between ozone and nitric oxides. Since nitric oxides are also products of vehicle combustion, concentrations of NO\textsubscript{x} tend to increase near roadways as ozone concentrations decrease. Thus, NO\textsubscript{x} is a primary constituent in TRAP and is used as an indicator for levels of TRAP.
Experimental data shows that short exposures to high ambient levels of NO₂ can increase exercise-induced bronchospasm and cause mild airway hyperreactivity.⁴⁷ These high levels of NO₂, however, are unlikely to be encountered in non-experimental setting, and the experimental associations have been shown as small, inconsistent, and of unclear clinical significance.¹²

Despite the inconsistency of experimental data on NOₓ, much observational data exists on the role of nitrogen dioxide in asthma exacerbation and incidence. Recent studies have shown associations between NO2 and symptoms of asthma, reduced response to bronchodilators, decrements in lung function, and exacerbation of asthma.¹² Experimental animal data and controlled exposures of healthy and asthmatic adults provide biological plausibility for NO2 as a cause of asthma.⁴⁸–⁵⁰ The discrepancy between experimental and observational data may result from NOₓ’s possible role as a co-pollutant with other TRAP components, and in the potential for NOₓ to enhance the asthmatic response to inhaled allergen.⁵¹,⁵²

**Sulfur Dioxide**
Sulfur dioxide (SO₂) is a toxic, water-soluble, colorless gas produced from industrial processes. It can lead to irritation of the nose, eyes and respiratory tract, asthma symptoms, and decreased lung function.⁵³ Sulfur dioxide is a reducing agent, and the mechanism by which it causes bronchoconstriction in asthmatic patients is largely unknown.

The main source of sulfur dioxides in the developing world is primary emissions during energy production and industrial processes.¹³ Exposure to sulfur dioxides has been largely reduced due to scrubbing of coal-fired power plants. In California, coal combustion is not widely used and thus, exposure to sulfur dioxides is very low in California. Urban areas (South Central Coast, San Francisco Bay Area and South Coast Air Basins) tend to have the highest concentrations in California, but even these regions have concentrations well below the California Air Resources Board standard.⁵⁴

**Pesticides**
Over one billion pounds of chemical pesticide active ingredient are applied each year in the United States, with California accounting for over 20% of all agricultural pesticide use in the country.⁵⁵,⁵⁶ Despite this, much remains unknown about the real affects of pesticide exposure, both acute and chronic, on respiratory health.

Agricultural workers, pesticide applicators, processing/plant workers⁵⁷ and rural communities are at risk for exposure to pesticides, though non-rural communities can also be exposures through home and non-agricultural uses of herbicides and insecticides. Respiratory exposure typically accounts for less than 1% of total overall
pesticide exposure, with dermal exposure representing the major route for people who work directly with pesticides.58

Though they represent a small fraction of total exposures, respiratory exposures are receiving increased attention in the media and literature. This is due, in part, to the continued use of highly volatile pesticides, fumigant pesticides, and aerially applied pesticides that have high potential to drift into residential areas, schools and other public spaces. These “drift” exposures may result in sub-acute symptoms or delayed symptoms that may not be recognized, treated or reported.59

Pesticide volatility is strongly influenced by temperature, with increased ambient temperature increasing the vapor pressure of pesticides that are applied in liquid or aerosol form. Fumigant pesticides, in particular, tend to be highly volatile and thus pose a greater risk for exposure.57 These pesticides, which are often applied at rates of hundreds of pounds per acre, can drift from the site of application to expose neighboring communities,56,60 and have also been found at distant sites, such as the National Parks far to the East of California’s Central Valley.61

Many studies have demonstrated a relationship between pesticide exposure among agricultural workers and increases in asthma symptoms. Among nearly 20,000 male farmers included in the Agricultural Health Study, the use of certain pesticides (including the organophosphate insecticides coumaphos and parathion) was associated with increased prevalence of self-reported allergic asthma, controlling for age, state, smoking and body mass.62 Likewise, women who grew up on farms and applied pesticides were at increased risk of developing atopic asthma.63 Similar associations have also been shown in cohorts of 1246 male French farmers,64 1939 male Canadian farmers,65 1999 Australian insecticide applicators,66 and other studies of farmers and farm workers.

Fewer studies have examined the relationship between pesticides and asthma in the general public outside the farming and farmworker community. Preliminary studies of children in Lebanon67 and in the National Health And Nutritional Examinational Survey (NHANES) study68 link pesticide exposure with chronic respiratory symptoms. The Children’s Health Study69 and the CHAMACOS birth cohort70 both have shown associations between early-life pesticide exposures and respiratory symptoms or asthma diagnosis.

A recent systematic review of pesticide exposure and airway disease concluded exposures “may be associated with prevalent asthma” with stronger evidence to

1 Interestingly, women who grew up on farms but did not apply pesticides had lower rates of atopic asthma than non-farm raised, non-pesticide applying controls. This protective “farm effect” has been supported by a body of evidence including a meta-analysis of 52 original articles from 39 studies that revealed “substantial heterogeneity” across studies but nonetheless statistically significant results with approximately 25% lower asthma prevalence among those subjects raised in farm environments.63
support a link among children, but the analysis was limited due to methodological inconsistencies across studies.\textsuperscript{71}

The physiologic mechanisms behind pesticides and airway hyperreactivity are still not well understood. It is known that at high levels, some pesticides may cause direct damage to the respiratory mucosa.\textsuperscript{77} Moreover, pesticides can cause oxidative stress which leads to subsequent airway narrowing.\textsuperscript{72} At lower doses, pesticides still lead to neurogenic inflammation of the epithelial lining of the lungs by activating irritant-sensing ion channels on respiratory nerve endings.\textsuperscript{77} These C-nerve fibers carry sensory information to the nervous system, but also have efferent functions as mediators of allergic airway inflammation.\textsuperscript{73} When activated, proinflammatory cytokines and neuropeptides are released, resulting in bronchoconstriction, vasodilation, histamine release, mucous secretion and other symptoms of allergic reaction in the airways. Chemical irritants also activate similar transient receptor potential (TRP) channels on some non-neural cells, further increasing the release of proinflammatory peptides and subsequent inflammatory events. The effect of neuropeptides may be upregulated in the asthmatic patient, though this effect may not be specific to asthma, as it may also be upregulated in chronic obstructive pulmonary disease (COPD) and smoking.\textsuperscript{74}

More specific causal mechanisms of asthma have been proposed for some classes of pesticides. For example, several studies have implicated the effect of organophosphate pesticides (OP) on cholinergic function as a potential mechanism of airway hyperreactivity.\textsuperscript{62,70,75,76} The main mechanism implicated is inhibition of acetylcholinesterase (AChE), the same mechanism known to cause acute OP pesticide poisoning. In the bronchi, this increased cholinergic activity is postulated to lead to increased vagally-induced parasympathetic bronchoconstriction. Moreover, chronic low levels of OP exposure may alter cholinergic neurotransmission via actions on postsynaptic muscarinic and nicotinic receptors.\textsuperscript{77} At least one study found decreased neuronal M2 receptor (a type of muscarinic receptor) function,\textsuperscript{78} strengthening the direct evidence of a causal link between OP exposure and airway hyperreactivity. By blocking M2 receptors, release of acetylcholine (ACh) from presynaptic nerve endings is upregulated and could lead to increased cholinergic activity and resulting bronchospasm.

A major limitation in historical research on pesticides and asthma is the limited populations that have been studied. Most studies have relied on data from agricultural communities. As such, it is hard to extrapolate these results to non-agricultural populations, or even those living in agricultural communities that do not actively work on farms and fields (e.g. children who attend school adjacent to farm fields). Similarly, with only a few exceptions, the literature does not research associations among women farmworkers exposed to pesticides.\textsuperscript{79,80} This is particularly relevant given that two studies that did examined this relationship reported higher prevalence and stronger associations among women than in
men. More research is needed that examines the acute and chronic exposure of pesticides on the general public.

EXPOSURE CLASSIFICATION, OUTCOME MEASURES AND SPECIES DISTRIBUTION MODELING

Exposure classification for outdoor air pollutants
Methods for assessing air pollution exposure are primarily geospatial and include proximity-based, geostatistical interpolation, land-use regression, dispersion, and hybrid models. These models range in complexity from binary classifications based on distance to hybrid models that incorporate personal monitoring data and a variety of environmental factors such as historic wind speed and direction, land use, and historic traffic data. All methods can also be subject to significant confounding if neighborhood-level socioeconomic factors are not controlled for.

Proximity models are commonly used to evaluate associates between health effects and air pollution, particularly TRAP. These methods calculate the perpendicular distance from the site of interest to the nearest emission source of various classes (e.g. for TRAP, the source is the nearest road). Though they are the easiest models to implement, they have considerable limitations. First, they do not consider weather patterns (e.g. wind, precipitation, temperature) or topography which influence dispersion of pollutants from roadways and other sources. Second, they may only look at distance to the nearest road, rather than aggregating all proximal roads into a measure of exposure “density”. Lastly, proximity based methods rarely consider exposures at locations other than residence, work or school, which can lead to misclassification. Studies that better track the location of asthma exacerbations, such as tracking location of inhaler use, could mitigate the risk of misclassification of proximity models while still leveraging their relative easy of implementation.

Interpolation models use geostatistical techniques to estimate the concentration of a pollutant at any location in the study area, based on measured locations throughout the study area. The most common interpolation technique implemented in air pollution research is called ‘kriging’. Unlike inverse-distance weighting, kriging methods provide information about the uncertainty of the estimate at any given location, and allow for inclusion or exclusion of monitors from point to point based on the spatial autocorrelation structure of the monitoring data.

Dispersion models use Gaussian plume equations to estimate how known emission sources disperse over space and time, using meteorological data and topography. This represents an advantage over other models in that it becomes easier to account for temporal variation in environmental conditions. Moreover, these models can be
applied to different study sites with only minor alterations.\textsuperscript{83} This model relies heavily on the quality of the input data, and when data sources report values at different temporal scales, it can be difficult to reconcile into a meaningful emissions value. Therefore, obtaining high quality data for emission sources can be costly.

Land use regression (LUR) methods combine monitoring of air pollution at 20-100 locations across a study area with predictor variables such as traffic, population density, and areas of commercial development. These predictor variables represent emission sources for the pollutant of interest. Given the location of these sources and the measured values throughout a study site, a regression-based model is generated and applied to all points within the study site. The result is an estimate of pollution concentration at very high spatial resolution (5-10 meters).\textsuperscript{86} This high resolution relies on accurate monitoring data at a large number of sites, particularly for urban areas with a high number of emission sources.\textsuperscript{88} LUR models have been increasingly used to assess exposure to air pollution, including TRAP.\textsuperscript{89} The main limitation of LUR is its lack of geographic generalizability: LUR methods from one study site cannot be used in areas with very different land use and topography. A second limitation is the lack of temporality in the prediction. Predictor variables (population, land use, etc.) often do not change over time and thus LUR methods are most suited for annual
estimates of exposure. An emerging area of research is the temporal variation of predictor variables to estimate monthly or daily exposures using land use regression.\textsuperscript{86,90}

![Image of land use regression of ultra-fine particles (UFPs) in Toronto, Canada. Note the high spatial resolution and how this differs from spatial interpolation.\textsuperscript{91}}

Personal monitoring of air pollutants is another method for estimating exposure. Samplers are attached to clothing or placed in houses for a specific duration, and participants are often asked to fill out a daily diary. Personal monitoring appears to results in lower measurements of exposure, which may reflect a more accurate value that accounts for time spent indoors.\textsuperscript{83} The clear downsides of such studies are the high costs and logistic complexity of implementation. The pollutant under study also impacts the cost of a personal monitor. For example, passive sampling of NO$_2$, a commonly used TRAP surrogate, is relatively inexpensive.

It may be that “hybrid” models that combine personal exposure to TRAP surrogates as well as other exposure models may “come closest to a logistically feasible ‘best’ estimate of human exposure.”\textsuperscript{92,95} These geospatial methods have been employed to assess TRAP exposure from home residence,\textsuperscript{92} cumulative exposure across multiple addresses,\textsuperscript{93} during commute travel,\textsuperscript{94} and other measurements of exposure. As previously discussed, these methods become increasingly useful with better geospatial-temporal data about asthma exacerbations. With increasing resolution of
both environmental data and respiratory health data, it may be easier to draw causal inference between exposures and outcomes.

**Special cases of exposure classification: TRAP and pesticides**

Methods used for assessing exposure to TRAP can be broadly categorized into (1) measuring pollutant surrogates such as NO$_2$, CO, or benzene to serve as indirect metrics of traffic exposure, and (2) direct measures of traffic exposure, such as measuring distance from home residence to nearest roadway, or aggregating exposures to all nearby roadways within a specified buffer. This metric, which is often called “traffic density”, is calculated by summing the total vehicle miles travelled (VMT) for all roads within a buffer. VMT is calculated by multiplying the average annual daily traffic (AADT) by the length of a road segment. $^{95}$ Traffic data can be imputed for roads of similar classifications without measured data. $^{96}$

Exposure classification for pesticides is particularly difficult. In addition to the geospatial methods outlined above, pesticide exposure is often assigned using self-reported questionnaires, which are prone to recall bias and exposure misclassification. Moreover, these surveys rely on surrogates of exposure such as ever/never exposed, years of exposure, or a qualitative estimate of exposure based on task-exposure matrix (TEM) for pesticide use. $^{71,97}$ Spatial or temporal analysis can be difficult or impossible as recalling time and place of exposure is even less reliable, and is often not collected.

Acute exposures can be measured with urine metabolites, but many pesticides are rapidly metabolized and urine samples only reflect very recent exposures (often on the order of days). Many urine metabolites also often are nonspecific biomarkers that represent an “integrated measure of exposure” to a chemical class, rather than to a unique active ingredient. $^{70}$ This precludes the option to analyze effects of subclasses of chemicals, which may have varied strength and effects.

One method of improving pesticide exposure classification may be to use historic pesticide application data from California’s Pesticide Use Reporting (PUR) dataset. This system, overseen by the Department of Pesticide Regulation (DPR), was implemented following California’s Food Safety Act on 1989 and gave DPR the authority to mandate reporting of all commercial pesticide use. $^{66}$ The system is financed by a statewide tax on pesticides sales and is regarded as the most comprehensive pesticide reporting program in the world. $^{56}$ Individual pesticide uses are reported in the dataset with the date and time of each reported application. Location is reported according to the Public Land Survey System’s (PLSS) square mile sections, though methods have been published to improve the geospatial resolution of the reported data to individual agricultural fields. $^{98}$ This data has tremendous potential to improve geospatial-temporal analyses of pesticide exposure and symptom exacerbations, since it allows the researcher to retrospectively analyze exposures separated by chemical classification, time of day, season, method of
application (i.e. ground or aerial), and also to place the exposure into the daily historical context of climate (i.e. temperature, wind speed and direction). These data could be used for exposure classification based on location of subject residence, work or other geospatial coordinates.

**Outcome measures for asthma**

Asthma is a heterogeneous disease with environmental, genetic and behavioral factors and a spectrum of patient symptoms. Moreover, symptoms are often acute and episodic exacerbations from a baseline of chronic persistent inflammation and/or structural changes of the airway. As such, it is difficult to define a perfect outcome measure for asthma, and a variety of outcome measures are utilized in the literature.

Asthma exacerbations, and proxies of asthma exacerbation such as hospitalization, are one of the most commonly used outcome measures. The American Thoracic Society (ATS) / European Respiratory Society (ERS) jointly define an asthma exacerbation as an event that is characterized by a change from the patient’s baseline status. Severe asthma exacerbations require “urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma.” Moderate exacerbations are characterized by a rise in baseline that is not severe.

In population-level studies, hospitalization rates or emergency department (ED) visits are commonly used as a proxy for asthma exacerbations. These metrics do not capture moderate exacerbations, or severe exacerbations that are mitigated by the use of fast-acting medication (bronchodilator inhaler use). Moreover, this outcome measure disproportionally represents asthmatics with poor asthma control, as these patients are more likely to have severe symptoms and require acute treatment as a result. Lastly, these data omit patients with limited access to health care.

Questionnaires of self-reported asthma symptoms are another common outcome measure of asthma exacerbation and control. The Asthma Control Questionnaire includes lung function tests and is widely validated. The Asthma Control Test (ACT) and Childhood ACT do not include lung function tests but survey five metrics of asthma control: shortness of breath, night-time symptoms, use of rescue medications, daily functioning and overall perceptions of asthma control. Surveys are limited in that they rely on patient self-reporting and may be prone to errors and bias. Likewise, asthma diaries may have limitations as to the reliability of the reported data. A study in Canada demonstrated comparative validity between questionnaires and asthma diaries. Peak expiratory flow (PEF) measurements can also be recorded in asthma diaries though the accuracy of self-recording has been called into question. A study of “well-motivated, well-informed” families of affluent children in the Netherlands showed dramatic discordance between asthma diary entries of PEF performance and performance as automatically measured by the
device. As many as half of the entries in the written plans were incorrect or fabricated, raising significant concerns as to the validity of asthma diaries.

Physician-diagnosed asthma is also often used as an outcome measurement. These are often still patient reported (i.e. “Has a doctor ever diagnosed you with asthma?”) and may show disproportionately high rates of asthma that reflect increased likelihood of diagnosis given an occupational exposure.

Lung function tests, airway hyper-responsiveness and biomarkers significantly increase the complexity and cost of studies. Moreover, symptoms are not strongly associated with lung function tests or airway hyper-responsiveness. Likewise, no single biomarker has been recommended to assess asthma among all patients for all medications. Biomarkers are becoming more widely available in the clinical setting and may be useful as an outcome measure in future studies.

Ultimately, there is no gold standard for measuring asthma control and exacerbation. The range of outcome measures used, in combination with incomparable exposure metrics (e.g. “ever exposed to pesticides” vs “use of insecticides in the home” vs “applying pesticides for >3 days per month”) make it very difficult to conduct meta-analyses of the current literature. Moreover, since most outcome measures lack spatial or temporal components, it is difficult to prove causality. To improve this, more detailed, reliable and consistent outcomes measures and exposure classification methods are needed for studying pesticides effects on asthma.

New remote monitoring technology is allowing for individual tracking of inhaler actuations across time and space through the implementation of a small sensor that attaches to an asthma inhaler. This technology is currently being used to improve individual disease control through better symptom tracking and patient education, and is also being used to estimate the effects of potential impacts from community interventions and municipal policy. This technology provides a reliable log of rescue inhaler use, which can serve as an approximation of sub-acute asthma symptoms. Moreover, this log includes the location, as well as the time, of inhaler use, which may be used as a geospatial-temporal log of symptoms.

Finally, the geospatial-temporal tracking of inhaler use also holds potential to improve exposure classification. One major limitation in assigning exposures is lack of data on the movements of patients, and particularly the places and times in which asthma symptoms occur. Tracking inhaler use provides a potential solution to this problem, and may be used for retrospectively assigning exposures using historic weather and air pollution data.
Species distribution modeling of asthma and the environment

In ecology, a species’ niche defines the set of conditions in which a species can reproduce and maintain their population “in the long term without an in-migration of individuals”. Generally, a niche is classified using biotic and abiotic features, though a “temporal niche” has also been described which accounts for daily, lunar or seasonal changes such as the tidal cycle, seasonal weather patterns and fluctuations of daily temperature.

Environmental niche modeling (or environmental niche modeling, both of which are abbreviated “ENM”) is a set of techniques used for relating point occurrence data of a species to a predicted geographic and environmental range based on landscape characteristics. It has been characterized as the most effective way to evaluate the potential geographical distribution of species. Moreover, these models can then be used to predict potential distribution of a species given a new environment, such as the potential habitat of a species on a different continent, or the expanded/reduced habitat of a species given a changing climate. The use of these models has increased sharply in recent years.

Typically, these models are employed by first choosing a set of suitable environmental variables to be included in the model. Machine learning models then plot each variable in the model and separate presences from absences with minimal error.
Figure 3. ENMs build a predictive model of habitat suitability based on current observation, known as “presence points” as various environmental conditions noted in the presence locations. In the example above, notice how the predicted habitat is larger than the current observations, as it highlights other places in this ecosystem that have similar rainfall and altitude as the locations in which the species or disease is noted to have occurred. 111

Common machine-learning SDM methods include Maxent, support vector machines (SVM), boosted regression trees, and Random Forest. 112–115 These methods can turn relatively small geographic sample of occurrences into a highly parameterized landscape model of predicted occurrences.

SVMs, in particular, are a type of non-probabilistic binary linear classifiers that have been increasingly used across broad areas of science. They make use of the so-called “kernel trick” to map features into higher-dimensional “feature spaces” in order to find linear barrier for classification. This allows SVMs to learn by example to estimate whether a unique set of predictor variables will lead to the presence or absence or a point. 115 There has been growing interest in using SVMs for remote sensing, 116 and health research such as gene-function prediction 117 and imaging biomarkers. 118,119
Figure 4. In these graphics, white and black points represent two distinct classes of data, for example presence and absence data. This illustrates an example of a nonlinear kernel function ($\phi$) that transforms variables from “input space” to feature space, with the red line representing the maximum-margin hyperplane in the transformed feature space. Though this graphic depicts this transformation in two-dimensional space, in reality these algorithms can, and often are, calculated in hyperdimensional feature spaces.

These methods have been increasingly used in the research of fungal diseases\textsuperscript{120–124}, bacterial diseases\textsuperscript{125,126}, and vector-borne diseases\textsuperscript{127–135}. These studies tend to cover large geographical areas with relatively large spatial resolution, and study diseases where the geographic habitat of a vector or fungal is highly correlated with the likelihood of acquiring the disease.

Figure 5. Maxent ecologic niche model for distribution of mosquito species Aedes vexans, a potential vector for West Nile Virus, across Iowa. This model used rasterized layers of both climatic (eg. temperature, precipitation, freezing days, etc) and landscape (eg. aspect, slope, distance to rivers, land cover, soil features, etc) features in predicting species niche using Maxent.\textsuperscript{128}
It is possible that machine-learning algorithms such as Maxent and SVMs may hold future promise in the classification of asthma exacerbation. More specifically, given a set of environmental exposures, including air pollution, weather, proximity to highways, land use, and others, it may be possible to model the ‘niche’ of asthma exacerbations across geographic space. Such a map would reflect the so-called ‘hotspots’ of asthma exacerbation, based on environmental predictor variables. These models could be made for an entire community of patients with asthma exacerbation, or could be made uniquely for each patient. Furthermore, SVMs and some other SDM methods work exceedingly well in high-dimensional analyses, even with relatively small training and testing sets. Thus, they may be well suited to help us understand the synergistic and multifactorial relationship between asthma and environmental exposures. These same models could then be applied prospectively, such that future risk of asthma exacerbation could be predicted given a unique set of environmental conditions.

**CONCLUSION**

Asthma is a major health concern that causes considerable morbidity and mortality. These impacts disproportionately fall on children and poor communities of color. Much is known about the experimental exposure of criteria air pollutants in acute settings but more research is needed on the chronic effects of air pollution on asthma. Future research could also focus on the small-scale changes of environmental exposures that occur within a community. The respiratory effects of pesticides on the general population, particularly chronic effects, are also largely unstudied.

Better methods are needed to estimate environmental classification of exposures. These improved methods may include personal, wearable devices that validate geospatial techniques such as LUR that can map air pollution at high spatial resolution. Real-time sensors that attach to asthma inhalers may also be used to assigning environmental exposures that are proximal in time and location to inhaler use. Traffic density data and data from California’s Pesticide Use Reporting database may be helpful in improving exposure classification of TRAP and pesticides, respectively.

Outcome measures for asthma also vary in the literature. Hospitalization, ED visits, medication refills, questionnaires, physician diagnoses, lung-function tests and remote monitoring technologies have all been used and there remains no gold standard asthma outcome. Remote technologies may hold promise, as they require little effort on the part of a patient, better track sub-emergent asthma symptoms and track higher resolution spatial and temporal data.
With improved exposures and outcomes, the use of machine-learning tools such as SVM might eventually allow for better models that account for the synergistic and complex nature of asthma exacerbations. If the definition of ‘environment’ is expanded to include factors such as socioeconomic status and health risks, we begin to see how these methods could be used to build a more comprehensive model of environmental disease. Such a model might integrate air pollution, socioeconomic factors, genetics, family history, coincident diagnoses, and other ‘exposures’ into a dynamic machine-learning model that classifies a person’s unique risk of asthma exacerbation at any particular place and time.
PART TWO: GEOSPATIAL-TEMPORAL ANALYSIS OF RESCUE ASTHMA INHALER USE AND OUTDOOR AIR POLLUTION

BACKGROUND

Asthma is a common chronic respiratory disease. Over 13% of adults in California have been diagnosed with asthma at some point in their lives, and the Sacramento and San Joaquin Valleys demonstrate particularly high levels of asthma-related emergency department (ED) visits and hospitalizations. 

Asthma is a chronic illness with acute episodes of worsening symptoms characterized by coughing, wheezing, chest tightness and difficulty breathing. These acute symptoms may be triggered by factors such as exercise, smoking, viral respiratory infections, and both indoor and outdoor pollutants. Acute asthma symptoms are largely preventable with adequate medications, patient education, avoidance of triggers, and self-management.

Several common outdoor air pollutants have been implicated in aggravating asthma symptoms. Particulate matter of 2.5 microns or smaller (PM2.5) and particulate matter of 10 microns or smaller (PM10) can deposit in the airways to cause oxidative stress and asthma exacerbations. Controlled ozone exposure has been shown to cause airway inflammation and reduction in pulmonary function in patients with existing asthma. Ambient ozone concentrations have also be positively correlated with increased emergency department (ED) visits and hospitalization rates for asthma. Traffic-related air pollution (TRAP) has been associated with increased wheeze in asthmatic patients, and may play a role in new asthma incidence in both children and adults. Pesticide exposure has been implicated in asthma exacerbations, although there is a paucity of research limited to occupational exposure among farmers and insecticide applicators. Fumigant pesticides are often highly volatile by design and may pose a greater risk for ambient environmental exposure. Studies disagree on the effect of temperature with some research indicating that increased temperatures and temperature fluctuations exacerbate asthma, while other research suggests that cold temperatures exacerbate asthma.

Previous studies have been limited by inconsistent environmental exposure classification and asthma outcome measures. Exposure classification involves spatio-temporal analysis, as the concentration of air pollutants can change dramatically across time and space. Most often, the address of a patient’s home, work or school is used as an estimate of patient location and when assigning exposures. This can lead
to exposure misclassification since patients are not always at a fixed location. Moreover, there is no gold standard for asthma outcomes, and studies have cited the limitation of reproducible outcome measures in asthma research. Research often relies on a combination of patient surveys and asthma diaries, which rely on patient self-report and records of ED visits or hospitalizations. The results of several studies question the accuracy of self-reported asthma adherence, particularly for patients who underuse their medications. ED visits and hospitalizations also have limitations, as they do not capture subacute symptoms, disproportionately represent asthmatics with poor asthma control, and are often aggregated spatially or provided with a long time lag.

This study uses a novel method of tracking bronchodilator medication use that improves exposure classification and outcome measurement. Several studies have measured bronchodilator medication use as an outcome measure, but these studies have occurred over short time periods. Our research utilized a small sensor that tracked the time, and in many cases the location, of short-acting beta-2 agonist (SABA) actuation. One study has been published on the feasibility of using this device to identify the impact of environmental triggers. We expand upon this analysis by (1) testing the feasibility of using these devices to assess exposures and outcomes in a new patient population in a different geographic area, (2) estimating individual-level environmental exposures and measuring inhaler use for each participant, rather than using daily aggregates across the entire population, and (3) estimating exposure to TRAP and pesticides as a function of proximity to sources.

**METHODS**

**Original study**

**Study design**
The Dignity Propeller Health Clinical Trial (NCT01509183), referred herein as the “original study”, took place between April 2012 and October 2014. The trial's protocol and amendments have been approved through the Dignity Health Institutional Review Board.

In the original study, all participants were given a sensor to attach to their SABA medication inhaler (Propeller Health, Madison, WI). The sensor tracked the date and time of each SABA actuation and, if the subject had a smartphone or Bluetooth device, also tracked the location of that actuation. The study followed a prospective, equivalent group design in which subjects were randomly assigned to either the intervention or control group. Members of the intervention group and their healthcare providers received weekly reports from Propeller Health and access to online interfaces that summarized patterns of asthma control and provided
suggestions about management, whereas the control group subjects did not receive any access to online information. The study was designed to provide equivalent treatment to members of the intervention and control groups except for the availability of the timing and frequency of SABA use.

All subjects went through the same intake process regardless of study group affiliation and participated in the study for a period of 12 months. At the conclusion of their involvement in the 12-month study, all members of the control group were presented with the option of continuing in the study for another four months. The last patient in the extension study completed it in October 2014, but additional subjects were enrolled through a non-study, commercial expansion at the Woodland Healthcare site. All patients in the commercial expansion received the same sensors and same standard of care as the intervention group in the original study.

Eligibility
Inclusion and exclusion criteria of participants were designed to reflect a typical practice of patients with asthma. As such, children and pregnant women were included in the study. Criteria were as follows:

Inclusion criteria
• Provider diagnosis of asthma (ICD9 493.xx);
• Prescription for a short-acting beta-2 agonist (SABA) at study intake.
• Age equal to or greater than 5 at the beginning of the study

Exclusion criteria
• Did not speak either English or Spanish;
• No access to the Internet or email to receive reports; or
• Substantial co-morbidity (e.g., provider diagnosis of COPD).

The aim was to recruit 50% publicly-insured subjects and 50% privately-insured subjects.

Study site
Study subjects were recruited from Woodland Healthcare (WHC) in Yolo County and Mercy Medical Group (MMG) in Sacramento County, both of which are health care units of Dignity Health. Referral to the study was primarily through the specialty allergy clinic at both locations, but also occurred through primary care clinics as well.

Collection of rescue inhaler use
The sensor tracked the date and time of each inhaler actuation and, for subjects with a smartphone or Bluetooth device, the location of the actuation. The location data of inhaler actuations are accurate within 10 m. The actuation data were securely transmitted to Propeller Health where they were maintained on a secure, HIPAA-
compliant server. Loss of actuation data due to device malfunction or exhausted batteries was limited by monitoring of the device's “heartbeat,” an automatically generated periodic signal that indicated that the device was active. Propeller Health sent an alert to both the subject and the Study Coordinator if the heartbeat was lost for any device. The Study Coordinator contacted subjects whose sensor had lost their heartbeat signal to assist them in reestablishing actuation monitoring. Replacement devices were available as needed. Heartbeats were also used in several analyses as absence points during days for which there were no rescue inhaler events (see statistical analyses).

Actuations occurring within a two-minute time period were considered a single rescue inhaler use “event”. Inhaler events were removed if they:

1. Did not have geospatial (latitude/longitude) coordinates;
2. The geospatial coordinates were located outside California; or
3. The date of event occurred outside of the study period.

**Defining active participants**
For each participant, an active timespan was defined as the period between the first sensor sync and the last sensor sync with the Propeller Health servers. Some patients transitioned from the original study to the commercial expansion, as outlined above. For these patients, the period between the last actuation in the original study and the first actuation in the commercial study was removed from the active timespan. The total number of active patients was calculated for each day of the study.

**EXPOSURE CLASSIFICATION**
Exposure to the following outdoor air pollutants was estimated for the time and location associated with each SABA actuation and heartbeat:

1. Traffic density;
2. Air pollution concentrations (PM2.5, PM10, Ozone); and
3. Aerially-applied and fumigant pesticides.

Additionally, wind speed, wind direction, daily mean temperature and daily standard deviation of temperature were calculated for each actuation and heartbeat. The remainder of this section outlines the methodologies for estimating each of the exposures.

**Traffic density**
Measured values of traffic flow for road segments across the state of California were obtained from the US Department of Transportation Highway Performance Monitoring System (HPMS). These data include a measure of average annual daily traffic (AADT) in number of cars per day. They also include a “functional class” for
each road, with values between 1 (interstate highways) and 5 (small roads with low daily traffic).

Geospatial road network data were also obtained from Esri (Redlands, CA) for the following counties: Sacramento, Yolo, El Dorado, Napa, Sutter, Calaveras, Solano, San Joaquin, Contra Costa, Amador, Colusa, Placer, Stanislaus. These data similarly contain functional classes, and represent a more complete network of roads, though they do not contain values for AADT (see Figure 6).

![Figure 6. Road network in Woodland, CA. Data is from complete ESRI road network and is color-coded by functional class. Lower functional classes (i.e. interstates and highways) generally have higher rates of average annual daily traffic.](image)

Road segments with measured values of traffic represent a small fraction of the complete road network. Thus, a method was developed for imputing traffic data for roads without measured AADT. The Esri road network data was isolated for each city in the study region, and a square-bounding box was generated. HPMS data were geospatially overlapped with this bounding box, to only include measured traffic data within one city’s border. Average AADT was calculated across all measured road segments for each functional class, and these values were assigned to road segments with unknown AADT based on their functional class.

The following method was used to combine the HPMS and Esri road network files. Buffers of various widths were generated around HPMS data and intersected with Esri data of matching functional class. Any road segments with imputed data that intersected with HPMS road segments were removed, to avoid including both the
measured and imputed road segments. To ensure that roads of lower functional class (interstates and highways) were not included in both data sets, these roads received proportionately larger buffers (see Table 1).

<table>
<thead>
<tr>
<th>Functional Class</th>
<th>Buffer width (meters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60m</td>
</tr>
<tr>
<td>2</td>
<td>30m</td>
</tr>
<tr>
<td>3</td>
<td>20m</td>
</tr>
<tr>
<td>4</td>
<td>15m</td>
</tr>
<tr>
<td>5</td>
<td>12m</td>
</tr>
</tbody>
</table>

Table 1. Buffers assigned by functional class of road. These buffers were assigned to measured HPMS road segments and used to remove imputed Esri road segments, so as to not include both measured and imputed values in the data set.

Figure 7. Map of Woodland with road segments from the HPMS data set in red. These roads have measured values of average annual daily traffic. Road segments in blue are from the Esri data set (see Figure 6). Estimated values of daily traffic for the ESRI road network were imputed from roads of matching functional class in HPMS data. Notice that in most cases, these roads do not overlap, due to the above-mentioned method for removing overlapping road segments.
Figure 8. This map shows average annual daily traffic from both measured (HPMS) and imputed (Esri) sources. Road segments are color-coded by AADT, with warmer hues representing higher rates of traffic.

For each inhaler event and heartbeat, buffers of 250m were generated around the point of use. All road segments within the buffer were isolated. AADT was multiplied by the length of road to calculate the daily vehicle miles travelled (VMT) for each road segment. The total VMT was summed for each point as the traffic density (Figure 10). This method of VMT calculation has been used in other studies.\textsuperscript{96,149}
Figure 9. Example inhaler event with buffer of 1000m for ease of visualizing methodology (buffer of 250m used in analysis). Color scale shows AADT of each road segment. Values of AADT are then multiplied by length of road segment to calculate VMT (see Figure 10).

Figure 10. Sample example inhaler event with color scale showing VMT of each road segment. VMTs for each road segment are summed to calculate total traffic density for each inhaler event or heartbeat. Notice that road segments with equal AADT but shorter length (see Figure 9) have correspondingly lower values of VMT.

To test for variability in predicted traffic exposure due to uncertainty of reported device location, we randomly selected 1000 SABA events and created false events 20
meters north, east, south and west of the actual event location. Traffic estimates were calculated for each false event and paired t-tests were conducted comparing the traffic exposures at measured locations versus the traffic exposures calculated at each set of pseudopoints.

**Air pollution concentrations**

Hourly samples of air pollution data for PM10, PM2.5, and ozone were obtained for the years 2012-2016 from the U.S. Environmental Protection Agency (EPA) AQS Datamart. These data were limited to include only stations located in the following California counties: Sacramento, Yolo, El Dorado, Napa, Sutter, Calaveras, Solano, San Joaquin, Contra Costa, Amador, Colusa, Placer, Stanislaus. For each inhaler use with geospatial coordinates, the air quality monitoring stations within a 50km circular buffer were isolated. The hourly values for ozone, PM2.5 and PM10 during the 24 hours preceding an inhaler actuation were obtained for each monitoring station. Maximum and mean values of air pollutants were calculated for each air quality monitoring station. These values were then spatially interpolated between stations using the inverse distance-squared algorithm. Different power values were tested and a power of 6 was found to give a smooth result between air quality monitoring stations without overestimating local effects. Values were assigned at the location of the inhaler use using raster extraction (Figure 11). Identical methods were employed to estimate criteria air pollutant exposure for inhaler heartbeats.
Figure 11. Map showing sample inhaler use (inhaler icon) with location of air quality monitoring stations within a 50km buffer (blue markers). Color raster indicates interpolated values of mean 24-hour ozone within the buffer zone. Estimated exposure of ozone was then assigned as the interpolated value at the location of inhaler use. Analogous methods were used to estimate background levels of other outdoor air pollutants. These methods interpolated maximum 24-hour values and mean 24-hour values for these air quality parameters.

**Pesticides**

Pesticide data were obtained from the California Department of Pesticide Regulation’s (DPR) Pesticide Use Reporting (PUR) database for years 2012-2014.\textsuperscript{56} Data for years 2015-2016 were not available from the DPR at the time of analysis. To limit the analyses to pesticides likely to aerosolize and travel greater distances, PUR data were limited to pesticides that were either 1) aerially applied, or 2) classified with the primary chemical use as a fumigant pesticide.

Pesticide use is reported according to the Public Land Survey System’s (PLSS) square mile sections, and shapefiles for these sections were obtained from United States Department of the Interior - Bureau of Land Management (BLM).\textsuperscript{151} PLSS sections with no reported pesticide applications over the study time period were removed from the analysis.

For each inhaler event and heartbeat, a buffer of 1km was created around the location of use. All reported pesticide use in sections that had any overlap with this 1km buffer during the 3 days preceding an inhaler event or heartbeat were included.
in the analysis. Total pounds of active ingredient and total number of acres treated were summed for all sections in this buffer. The pesticide with the highest number of pounds applied was also recorded for each inhaler event and heartbeat.

Figure 12. Map showing example inhaler event (inhaler icons). A buffer of 1km was drawn around this buffer and aerial and fumigant pesticide use was summed for all pesticide applications occurring 3 or fewer days before the event or heartbeat. Note: buffer in this example is greater than 1km for illustrative purposes.

Weather

Historic hourly weather data were obtained from the National Oceanic and Atmospheric Administration (NOAA) Quality Controlled Local Climatological Data (QCLCD). QCLCD data were downloaded in plain text for years 2012-2016, and stations in California were extracted for analysis. For each inhaler actuation, the closest weather station was identified. Inhaler actuations that were greater than 20km from the closest weather station were not assigned weather data. QCLCD data for the closest weather station were queried for weather data during the hour of the reported inhaler actuation. If hourly data were not available for the exact hour of actuation, data from previous hours were sequentially queried (i.e., 1 hour prior, 2 hours prior, etc.) and assigned to the inhaler actuation, up to a maximum of 4 hours prior to actuation.
STATISTICAL ANALYSIS

*Descriptive*

Descriptive characteristics were calculated for the patient population, including age, sex and city of residence. Socioeconomic indicators including race or income were not available for this analysis.

Descriptive characteristics were calculated for rescue inhaler events and inhaler heartbeats. A timeline of rescue events over the study period was generated, as was a graph showing the normalized use of inhaler actuations and heartbeats over a 24-hour cycle. Total number of events and heartbeats were totaled for administrative boundaries of each city, as defined by 2012 California Department of Transportation (DOT) city boundary GIS data.¹⁵³

Descriptive statistics were calculated for all environmental exposures and histograms were generated to show occurrence of exposure values across all inhaler events.

*Calculation of daily means and daily count of events*

Daily means of all exposures were calculated for each participant on every day they were active in the study. Mean exposures were calculated across all heartbeats and any SABA events that may have occurred on a given day. The total number of SABA events in a day was summed and recorded as the “event count”. Days with no SABA events were assigned an event count of zero.

This approach aggregated inhaler events using the unit of person-day – meaning for each participant, on each day of the study, the total number of events was counted. This allowed days with higher inhaler counts to serve as incrementally more severe outcome measures, rather than treating multiple events in one day as independent from one another. A model that aggregated daily use by geographic space was considered for this analysis, but ultimately a person-day aggregation was used as it allowed us to include a unique identifier for each participant as a random effect in the model, and therefore control for variations in expected exposures and inhaler use patterns from one participant to another.

*Model*

Pairwise Pearson correlation coefficients were calculated for daily mean temperature, daily standard deviation of temperature, daily mean wind speed, daily mean wind direction, daily mean relative humidity, daily mean acres treated with pesticides, daily mean pounds of pesticides applied, daily mean VMT, and daily means of both mean and max 24-hour ozone, PM2.5, and PM10.
A generalized linear model with Poisson distribution was developed, with daily inhaler use count for each participant as the outcome measure and mean daily exposure as the fixed effect. Age was included as a binary outcome indicating whether the participant was under age 18. Age variation above 18 was not accounted for, as we did not believe it would significantly change exposure to outdoor air pollutants. We included a random intercept for participant ID to control for expected similarity in exposures within actuations from a unique participant. We also included categorical wind direction (e.g., “N”, “NNE”, “NE”, etc.) as a second random effect in the model.

Pesticide use was removed from the model due to a high percentage of zero exposures. PM10 was removed from the analysis due to lack of adequate data, resulting in high percentage of zero values. Max and mean measures for 24-hour PM2.5 and ozone were tested in the models, separately and together. Temporal changes throughout the year were accounted for by including season as a fixed variable in the models.

This model was used to estimate the effect of each variable. The estimated effect was used to calculate the expected change of rate in daily count of events associated with each interquartile range (IQR) increase in exposure level. The model was rerun to assess the impact of adding the following variables as fixed effects: (1) number of days the participant was enrolled in study on date of event/heartbeat, (2) participation in control or intervention group in original study, and (3) participation in original study or commercial expansion.

**RESULTS**

*Participants and inhaler use*

Participants (n=278)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Primary language</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min.</td>
<td>4</td>
<td>English 284</td>
</tr>
<tr>
<td>1st Qu.</td>
<td>21</td>
<td>Spanish 3</td>
</tr>
<tr>
<td>Median</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>37.54</td>
<td></td>
</tr>
<tr>
<td>3rd Qu.</td>
<td>53.5</td>
<td></td>
</tr>
<tr>
<td>Max.</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>(NULL)</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>232</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

31
287 participants met inclusion criteria for the study and had at least one SABA use with geospatially resolved information. The average age of participants was 37.5 years, with standard deviation of 18.4 years. Sex was reported for only 55 participants (male = 22, female = 33) and not reported for 232 participants. The primary language of most participants was English (98.8%, n=284). The median number of days active in the original study and/or project expansion was 461.4, and the maximum number of days was 1,580.

**Inhaler use**

From an original set of 49,726 events, 4,294 rescue inhaler events (8.6%) met the criteria for inclusion in the study. 45,152 events were excluded for not having latitude and longitude data. One event was excluded for having incorrect date recording (date prior to January 1st, 2012). 279 events were excluded for occurring outside the geographic bounds of California, likely during participant travel.

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Number of unique users</th>
<th>First date</th>
<th>Last date</th>
</tr>
</thead>
</table>

Figure 13. Descriptive characteristics of events and heartbeats. ‘Number’ refers to the total number of events or heartbeats included in the analysis.

The first heartbeat occurred on 4/13/2012 and the last event in the data set occurred on 8/31/2016. The minimum number of active participants on any given day was one, and the maximum was 163. The minimum number of total events for a participant was one, and the maximum was 204. The minimum number of total heartbeats for a participant was one, and maximum was 3,880.
Figure 14 shows inhaler events and heartbeats by time of day, normalized by the respective peak hour of events or heartbeats. Peak rescue inhaler use had a bimodal distribution, with the highest number of actuations in the morning (6AM-9AM) and in the evening (6PM-10PM). The number of inhaler events between 12AM-4AM was low (6.9%). Heartbeats varied less by time of day, with slightly higher rate of heartbeats from 12AM-6AM.

<table>
<thead>
<tr>
<th>City</th>
<th>Events</th>
<th>Heartbeats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodland</td>
<td>1455 (34%)</td>
<td>42856 (32%)</td>
</tr>
<tr>
<td>NA's</td>
<td>822 (19%)</td>
<td>25812 (19%)</td>
</tr>
<tr>
<td>Sacramento</td>
<td>570 (13%)</td>
<td>23199 (17%)</td>
</tr>
<tr>
<td>Davis</td>
<td>297 (7%)</td>
<td>10189 (8%)</td>
</tr>
<tr>
<td>Citrus Heights</td>
<td>281 (7%)</td>
<td>2648 (2%)</td>
</tr>
<tr>
<td>West Sacramento</td>
<td>247 (6%)</td>
<td>7247 (5%)</td>
</tr>
<tr>
<td>Roseville</td>
<td>185 (4%)</td>
<td>1751 (1%)</td>
</tr>
<tr>
<td>Elk Grove</td>
<td>128 (3%)</td>
<td>4805 (4%)</td>
</tr>
<tr>
<td>Winters</td>
<td>63 (1%)</td>
<td>2312 (2%)</td>
</tr>
<tr>
<td>Vacaville</td>
<td>23 (1%)</td>
<td>1688 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>223 (5%)</td>
<td>11538 (9%)</td>
</tr>
</tbody>
</table>

Table 2. Total count of heartbeats and events (and percent of total), by the geographic city bounds in which they occurred. NA values occurred outside the bounds of city polygons (e.g., unincorporated county areas).
Woodland had the highest number of inhaler events (34%, n=1455) and heartbeats (32%, n=42856). Cities were not assigned to 19% of events (n = 822) and 19% of heartbeats (n=25812), as the geographic coordinates were not located within the administrative bounds of any incorporated city in the California DOT database.

**Environmental exposures**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Type</th>
<th>Mean (SD) (Range)</th>
<th>Median (IQR)</th>
<th>Null values</th>
<th>Zero values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acres treated with pesticides</td>
<td>Events</td>
<td>27.2 (137.4) [0–2189]</td>
<td>0 (0)</td>
<td>0%</td>
<td>91.2%</td>
</tr>
<tr>
<td>Acres treated with pesticides</td>
<td>Heartbeats</td>
<td>42.3 (199.8) [0–5717.8]</td>
<td>0 (0)</td>
<td>0%</td>
<td>88.8%</td>
</tr>
<tr>
<td>Daily mean temperature, F</td>
<td>Events</td>
<td>61.4 (11.2) [31.7–88.8]</td>
<td>61.6 (17.3)</td>
<td>1.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Daily mean temperature, F</td>
<td>Heartbeats</td>
<td>62.8 (11.4) [4.5–101.2]</td>
<td>63.7 (17.1)</td>
<td>2.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Daily SD temperature, F</td>
<td>Events</td>
<td>8.9 (3.3) [0–18.4]</td>
<td>9.3 (4.6)</td>
<td>1.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Daily SD temperature, F</td>
<td>Heartbeats</td>
<td>9.2 (3.2) [0–18.4]</td>
<td>9.6 (4.4)</td>
<td>2.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Ozone – 24 hr max, ppb</td>
<td>Events</td>
<td>46.5 (13.5) [5–101]</td>
<td>45.2 (18)</td>
<td>7.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Ozone – 24 hr max, ppb</td>
<td>Heartbeats</td>
<td>46.4 (13.5) [2–116.7]</td>
<td>45 (18)</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Ozone – 24 hr mean, ppb</td>
<td>Events</td>
<td>26.2 (9.5) [2–63.4]</td>
<td>26.1 (12.8)</td>
<td>7.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Ozone – 24 hr mean, ppb</td>
<td>Heartbeats</td>
<td>25.5 (9.2) [1–67]</td>
<td>26 (12.3)</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>PM10 – 24 hr max, micrograms/m³</td>
<td>Events</td>
<td>31.3 (20.8) [5.7–159.6]</td>
<td>27.1 (18.2)</td>
<td>95.4%</td>
<td>0%</td>
</tr>
<tr>
<td>PM10 – 24 hr max, micrograms/m³</td>
<td>Heartbeats</td>
<td>39.1 (25.1) [4–254]</td>
<td>33 (21.8)</td>
<td>19.2%</td>
<td>0%</td>
</tr>
<tr>
<td>PM10 – 24 hr mean, micrograms/m³</td>
<td>Events</td>
<td>15.9 (8.8) [3.6–54.4]</td>
<td>14.6 (10.6)</td>
<td>95.4%</td>
<td>0%</td>
</tr>
<tr>
<td>PM10 – 24 hr mean, micrograms/m³</td>
<td>Heartbeats</td>
<td>19 (10.9) [0.9–97.2]</td>
<td>16.6 (10.8)</td>
<td>19.2%</td>
<td>0%</td>
</tr>
<tr>
<td>PM2.5 – 24 hr max, micrograms/m³</td>
<td>Events</td>
<td>19.9 (13.6) [0.1–157]</td>
<td>17 (13)</td>
<td>11.5%</td>
<td>0%</td>
</tr>
<tr>
<td>PM2.5 – 24 hr max, micrograms/m³</td>
<td>Heartbeats</td>
<td>19.9 (18.3) [0–997.9]</td>
<td>16.1 (12.9)</td>
<td>15.9%</td>
<td>0%</td>
</tr>
<tr>
<td>PM2.5 – 24 hr mean, micrograms/m³</td>
<td>Events</td>
<td>9.4 (5.7) [–1–55.8]</td>
<td>8.2 (6)</td>
<td>11.5%</td>
<td>0%</td>
</tr>
<tr>
<td>PM2.5 – 24 hr mean, micrograms/m³</td>
<td>Heartbeats</td>
<td>9.3 (6.2) [–1–60.3]</td>
<td>8 (6.4)</td>
<td>15.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Pounds pesticides</td>
<td>Events</td>
<td>52 (743.9) [0–25276.1]</td>
<td>0 (0)</td>
<td>0%</td>
<td>91.2%</td>
</tr>
<tr>
<td>Pounds pesticides</td>
<td>Heartbeats</td>
<td>71.4 (778.5) [0–30458.9]</td>
<td>0 (0)</td>
<td>0%</td>
<td>88.8%</td>
</tr>
<tr>
<td>Traffic density – 250m, VMT</td>
<td>Events</td>
<td>10373.1 (18276.4) [0–307364]</td>
<td>5960 (6900.8)</td>
<td>0%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Traffic density – 250m, VMT</td>
<td>Heartbeats</td>
<td>10469.6 (18281.9) [0–444452.7]</td>
<td>6277.7 (5578.8)</td>
<td>0%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Wind speed, mph</td>
<td>Events</td>
<td>5.4 (4.6) [0–28]</td>
<td>5 (8)</td>
<td>1.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Wind speed, mph</td>
<td>Heartbeats</td>
<td>6.2 (5) [0–115]</td>
<td>6 (6)</td>
<td>2.5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 3. Descriptive statistics of environmental exposures estimated across all events and heartbeats in the analysis. Null values could not be calculated due to absent data. Zero values were calculated with available data, but resulted in estimated exposure equal to zero.

Estimated PM10 was zero in 95.4% of events, and in 19.2% of heartbeats, indicating that it was not possible to estimate exposure. Estimated PM2.5 was zero in 11.5% of events, and in 15.9% of heartbeats. All other exposures had low values of zero exposure. Pounds of pesticides applied and acres treated with pesticides had greater than 88% of reported values equal to zero. Events and heartbeats with zero traffic density exposure were low (events=6.7%, heartbeats=9.9%).
Figure 15. Histograms showing occurrence of events with given exposure values. Note: events with zero VMT or zero pounds/ acres of pesticide exposure are not included in these histograms. See Table 3 for percent of events/heartbeats with no exposure.
Figure 16. Wind rose showing frequency of wind from directions.

Wind direction was from the southeast for the majority of events (Figure 16). Mean distance to a weather station was 15.8 miles.
Table 4. Mean and standard deviation of vehicle miles travelled (VMT) for events in the study, aggregated by city. Events that occurred outside the geographic bounds of a city are not included in this table.

Inhaler events in Sacramento had the highest mean VMT exposure of any city in the study, followed by Roseville, and Elk Grove. Woodland had a mean traffic density of 6,787 VMT.

P-values for paired t-tests comparing pseudoevent traffic exposure with actual event traffic exposure revealed non-significant differences (north= 0.20, east= 0.61, south= 0.10, west= 0.44).
Pairwise correlation analysis (Figure 17) revealed strong positive correlations between daily mean temperature and both mean (0.54) and max (0.66) 24-hour ozone. Daily standard deviation of temperature and daily mean temperature were positively correlated (0.56). Daily standard deviation was therefore not included in the model. There was a high level of positive correlation between the mean and max 24-hour exposures of each air quality parameter, and the mean values were selected for inclusion in the model. Relative humidity was negatively correlated with daily mean temperature (-0.47) and wind speed (-0.25), and was therefore removed from the model.
Table 5. Result from generalized linear model, Poisson distribution. Unique participant ID and wind direction are used as a random effects in this model. *** = p-value <0.001, ** = p-value <0.01, * = p-value <0.05.

DailyMeanTemperature = daily temperature on date of event or heartbeat. Ozone.mean24 = daily mean of ozone levels at locations of events or heartbeats during preceding 24 hours. PM2.5.mean24 = daily mean levels of particulate matter 2.5 microns or smaller at location of event or heartbeat during preceding 24 hours. trafficDensity250 = daily mean of exposure to traffic density (VMT) within a 250m buffer.

For every increase in ozone of one part per billion (ppb), our model predicted a 1.07% increase in daily count of inhaler events (p=<0.001). For every increase in temperature by one degree, our model predicted a decrease in daily count of inhaler events by 0.84% (p=0.001). For every increase in wind speed by one mile per hour (mph), our model predicted a decrease in daily count of inhaler events by 2.24% (p<0.001). Age, PM2.5, and VMT were not significantly associated with changes in daily count of inhaler events.

Inhaler events in the Spring had an increase in daily count of inhaler events of 38.67% as compared to events in the Fall. The counts of inhaler events in the Summer and Winter were not significantly different from events in the Fall.
These model estimates were then used to estimate the change in rate of daily inhaler events across one interquartile range (IQR) of exposure (Figure 18). For one IQR increase of daily mean temperature (17.3 degrees Fahrenheit), our model estimates a decrease in rate of daily event count by 13.5%. For one IQR increase of ozone exposure (12.8 ppb), our model estimates an increase in rate of daily event count by 14.8%. For one IQR increase of wind speed (8 mph), our model estimates a decrease in rate of daily event count by 16.4%.

The direction and statistical significance of the effects of daily mean temperature, daily mean ozone, daily mean PM2.5, daily mean VMT, and daily mean wind speed were unchanged when adding the following variables as fixed effects into the model: 1) participation in control or intervention group of original study, 2) number of days in original study, 3) participation in original study or project expansion.

**DISCUSSION**

*Feasibility of sensor use*

287 participants were active in the study for an average of 461.4 days. In total, this yielded 49,726 unique SABA inhaler events. All inhaler events successfully recorded information on the date, time and the number of actuations. Of these, most (90.8%) were removed due to absent latitude and longitude data, leaving 4,294 (3.4%) of all
events eligible for inclusion. This loss of data was expected, as events without geospatial data most likely represent use by participants without Bluetooth compatible smartphones. Increasing prevalence of Bluetooth-compatible smartphones will help mitigate this limitation in the future. Additionally, it would be possible to assign secondary estimates of location using latitude and longitude of home address, work address and/or location of healthcare facility. These secondary locations could be useful in measuring exposure to pollutants with relatively uniform regional distributions like ozone\textsuperscript{154}, but would be less accurate for pollutants with a high resolution of spatial variability such as TRAP. Additionally, future analyses that focus only on temporal patterns of use over time – and not spatial patterns – would dramatically increase the number of available sample points, at the cost of limiting exposure classification across space.

There were many more heartbeats included in the analysis (n=134,045) than events (n=4,294). The percentage of heartbeats that occurred from 8PM-7AM (53.2\%) was higher than the percentage that occurred from 8AM-7PM (46.8\%), as shown in Figure 14. This most likely reflects the higher likelihood of cell service, and therefore reported latitude and longitude, during the time the sensor is at home. The difference is small, but since our exposure model assesses the 24-hour mean ozone, this could result in decreased estimates of daily mean ozone since ozone levels tend to be higher during the day due to increased sunlight.\textsuperscript{27} In contrast, SABA events were much higher during waking hours, with peaks in the morning (7AM) and evening (10PM).

The ability to assign ambient air pollution exposure varied depending on available data. Ozone and PM\textsubscript{2.5} values were assigned to most events and heartbeats (Table 3). PM\textsubscript{10} had high zero values for events (95.4\%), as the monitoring station in Woodland does not record PM\textsubscript{10} values and monitoring stations more than 50km from an event were not used in the exposure model. NO\textsubscript{2} was not included in the study due to insufficient air quality monitoring data. Mean and max 24-hour exposures were used in this analysis and are both common reporting metrics.\textsuperscript{146} Due to the high temporal granularity of the outcome measure, these methods could be easily replicated with 1-hour and 8-hour peak exposures, both of which have been used in other studies to account for diurnal patterns of ozone concentration.\textsuperscript{155–157} Future analyses might also consider the distance to air quality monitoring stations as a measure of uncertainty in the model.

Pesticide exposure for events was low (zero in 91.2\% of events) despite using a lag time of 3 days and buffer of 1 kilometer. This most likely represents the lack of spatial overlap between pesticide applications and inhaler use. Thus, our exposure classification likely inflated the number of events with zero pounds/acidres of pesticide exposure, minimizing the effect of pesticides in our model. Future research on the impact of pesticides on inhaler use might be better applied within a targeted population of agricultural workers, farmers, or people living in rural conditions who
would presumably have higher rates of environmental and occupational exposure to pesticides. Additionally, as some pesticides may drift across large distances\textsuperscript{17,60,61}, it may be worth further exploration into the effects of pesticide use on a population of participants across a larger area with more variation in exposure. This model would also be improved by incorporating temperature, chemical volatility, wind speed and wind direction into a more rigorous model of pesticide exposure over space and time. Despite these limitations, the methods outlined in this research represent the first attempt, to our knowledge, to associate bronchodilator use with non-occupational environmental pesticide exposure.

Lastly, the traffic exposure method resulted in more than 90\% of events and heartbeats showing traffic exposure greater than zero. Events with an estimated traffic exposure of zero VMT most likely represent: (1) inhaler use outside the available road network data, (2) inhaler use in cities which have no measured data for a given functional class, which would result in an imputed AADT value of zero, or (3) inhaler use in very remote areas with no road traffic.

**Associations**

For every IQR increase of ozone exposure (IQR=12.8 ppb), our model estimates an increase in daily SABA use by 14.8\%. This estimate was significant in a single pollutant model and remained significant in a two-pollutant model with PM\textsubscript{2.5}. It remained significant when daily mean temperature, wind speed, wind direction, age, season, and participant ID were included in the model. This finding is consistent with existing evidence that short-term exposure to ambient ozone can cause airway irritation and inflammation, impaired pulmonary function, and asthma exacerbation\textsuperscript{12,45,146}. The association between ozone and SABA use was present despite relatively low-level exposure to ozone (mean=26.2 ppb, $\sigma$=9.5 ppb). The current California EPA standard for 8-hour mean ozone levels is 70 ppb.\textsuperscript{158} No events or heartbeats had mean 24-hour ozone levels that exceeded this standard. 8-hour mean ozone levels were not assessed in the analysis.

Our model showed an inverse association between inhaler use and daily mean temperature, indicating less inhaler use on hotter days. This result contrasts with the majority of previous research which associates aggravation of asthma symptoms with cold weather.\textsuperscript{142,143,159} There is also previous evidence to suggest that higher humidity may improve asthma symptoms.\textsuperscript{160} However, cold weather in California’s Mediterranean climate tends to also be relatively humid as compared to the dry summers, as is reflected in the strong negative relationship between daily mean temperature and relative humidity in our data (Figure 17). It is possible that the dry, warm air of California summers may aggravate airways less than the relatively humid, cold winter air. This finding would suggest that temperature might play a more important role than humidity in airway aggravation. Alternatively, our finding may
represent confounding such as increased time spent indoors during hot days, leading to less outdoor air exposure.

The model associated decreased wind speed with increased rate of inhaler use. This result remained significant when including categorical wind direction as a random effect in the model. Previous literature shows mixed effects of wind speed on worsening of asthma symptoms. Some evidence shows that low wind speeds and stagnant air increase asthma-related emergency department visits, presumably due to decreased clearance of airborne irritants such as products of combustion. This can be seen in these data as the negative relationship between wind speed and PM2.5 (Figure 17). Conversely, larger particulate such as pollen and dust are more likely to be present in the air on days with high wind speed. Our result suggest that the role of larger particulates in exacerbating asthma may be less significant than the role of smaller particulates and aerosolized pollutants in this study site. This interpretation faces the same limitation as temperature in that it is also possible that participants spent less time outdoors on windy days and therefore had less exposure to outdoor air pollutants. This point underscores a primary limitation of the study in that participant behavior cannot be accounted for in the model.

Exposure to PM2.5 did not have a significant effect on inhaler use. This finding is contradictory to the majority of evidence, which suggests that acute exposure to particulate matter is associated with asthma exacerbation in patients with pre-existing asthma. It is possible that the average values of PM2.5 exposure in this study may have been too low to appreciate an effect on asthma. The Air Quality Index for particulate pollution defines a “Good” index value as 0-12 mg/m³ PM2.5. The average PM2.5 exposure for inhaler events (mean = 9.4; σ = 5.7; median=8.2) falls well within with the “Good” range. Additionally, it is possible that our model did not accurately estimate exposure to PM2.5. Previous research on the spatial variability of PM2.5 in urban areas has highlighted the potential for exposure misclassification. This is in contrast to ozone, which often has a more uniform regional distribution. This study was limited by the relatively small number of air quality monitoring stations and the large distances between them. The air quality monitoring station in Woodland measured ozone concentration but not PM2.5, adding additional error as estimates had to be interpolated from stations in Sacramento and Davis. Moreover, the inverse distance weighting method of exposure assessment does not consider geographic or climate factors such as topography and wind. Increasing the number of air quality sensors would reduce misclassification, and would allow for methods such as land use regression that provide higher spatial resolution of air quality variability.

Traffic density was also not significantly correlated with daily count of inhaler events. This is contradictory to the overwhelming evidence suggesting a strong relationship between traffic-related exposure to NO2 and increased wheeze in asthmatic patients with pre-existing asthma. Unlike our model for ambient air pollution, our estimate
of traffic density can change dramatically over short distances, based on proximity to highways. The results of the paired t-test between pseudoevents and actual events are reassuring that inaccuracy in device recording of location was unlikely to play a role in exposure misclassification.

**Limitations**

There are four main limitations we identify with our method of traffic density exposure. First, our estimate of traffic exposure does not account for the behavior of the participant. Specifically, for participants who use their inhalers while driving on highways with closed-circuit air conditioning, they may in fact have relatively low levels of air pollution exposure despite our model estimating very high levels of proximal traffic density. Future studies might leverage the Propeller Health smartphone application to track speed of movement at time of event, and thereby classify events occurring in a moving vehicle. Second, exposure to traffic-related air pollution may have been too low in this study to cause an increase in bronchodilator use, relative to other exacerbating factors. While there is no standard index of VMT exposure, Gunier et al. found a statewide mean of 132,472 VMT per square mile when measuring census block traffic density. The mean exposure of VMT for Woodland (6,787 VMT in a 250m buffer; n=1455) can be converted to exposure per square mile (89,554 VMT per square mile), which is well below the statewide mean. Moreover, mean traffic density in Woodland was lower than mean traffic density in Sacramento (26,378 VMT in 250m buffer) in this analysis (Figure 9). Repeating this analysis in areas of higher traffic density may show relationships between TRAP exposure and inhaler use. Third, there are limitations to our method of imputing missing traffic data. Roads of low functional class (i.e. small, residential roads) often have very few measured road segments, despite often being the most common class of road in a city. Additional analyses could assess the impact of excluding roads with low AADT on the model estimates. Fourth, there were limitations in the geospatial method developed for estimating traffic exposure. We believe this method represents a more accurate representation of true traffic density than methods that use linear distance to highway. However, future exposure models might improve these methods by introducing a decay coefficient to proportionately weight closer roads, and investigating the effect of both larger and smaller buffer sizes.

Our model aggregates inhaler events at the level of the person-day. This approach did not allow us to measure the influence of unique geographic spaces on inhaler use, as we only used location as a means to estimate exposures. An alternative model could aggregate events across space-day by creating a geographic grid, calculating exposures for each cell in the grid, and counting the number of events occurring within each cell. The benefit of a space-day aggregation would be the ability to estimate use in any cell for the given patient population, and the ability to include additional characteristics that do not change over space (such as land use or crime...
index) that could not be included in a person-day model. Future models should also assess the autocorrelation and spatial autocorrelation of inhaler uses.

More research is needed on the spatial and temporal variability of heartbeats. It may be that both heartbeats and inhaler use events both simply represent a sampling of the normal range of locations in which a participant travels. Clustering analyses could help identify whether the geospatial patterns of SABA events differ from the normal patterns of travel (i.e., heartbeat locations). A population level analysis that aggregates daily exposures across the entire study population might help mitigate this limitation by removing the need to use heartbeats, though such a model may not be able to control for variation in patterns of use from one participant to another.

Our study was also limited by the available patient characteristics. There was no available data on socioeconomic status, smoking status, or race/ethnicity. Sex was reported for only a small minority of the participants. Including such demographic information as covariates in future studies will be necessary.

**CONCLUSION, IMPLICATIONS, AND FUTURE DIRECTIONS**

In summary, we found associations between increased rescue asthma inhaler use and both increasing ozone exposure and increasing daily mean temperature. No associations were found for PM2.5 and TRAP. There was insufficient exposure to pesticide applications to analyze an effect. Ozone and weather patterns are generally considered regional exposures, whereas PM2.5 and TRAP can vary across small spatial scales. Thus, it remains unclear if location contributed to the model, or if the associations are simply a product of temporal changes in regional ozone and weather. Future studies might further explore this question by comparing two parallel models: one that uses the location of home address to assign exposures, and a second that uses the location of inhaler event to assign exposures. If there is no distinguishable difference in the two model outputs, we might infer that using home address is an effective estimate for assigning regional exposures like ozone and weather. This would imply that future studies might use home address as a proxy for exposure, while also using the timestamp of use from the sensor. This would allow for the inclusion of events without measured geospatial data, thus dramatically increasing the number of events in the analysis.

The results of this study add to the body of evidence documenting an association between ozone and asthma symptoms. The longitudinal nature of the study and the subacute outcome measures provide further support for the plausibility of the association. Understanding the effect of ozone on respiratory health is increasingly
important in the context of climate change – multiple models have predicted a rise in urban ozone exposure and subsequent impact on human health.\textsuperscript{168,169}

The Propeller Health sensor served as an objective, accurate outcome measure in this study. Previous studies on the influence of exposure to ozone on asthma exacerbations have primarily focused on hospital admissions and emergency department visits as the outcomes of interest.\textsuperscript{23,35,156,170–172} While hospitalizations and ED visits are useful metrics of a severe exacerbation, they are relatively infrequent events that affect only a minority of asthmatics each year. Some meta-analyses have also reported SABA use as a measure of asthma control,\textsuperscript{173} although many of the included studies used shorter periods of use monitoring on the order of days to months, require medical record reviews, and rely on self-reported SABA use or medication refills. Future studies could include hospitalizations and ED visits alongside inhaler sensors to capture both emergent and daily symptoms.

In contrast, our outcome measure provides a log of bronchodilator use that (1) passively captures symptoms that reflect the daily burden of disease, (2) allows the assessment of severity of symptoms based on the number of times an inhaler is used in a time period, and (3) eliminates the need for a resource-intensive medical record review. We believe that the simplicity and consistency of our outcome measure makes it more reliable than asthma logs, more comprehensive than ED visits or hospitalizations, and more reproducible than current studies that track bronchodilator use over time.

The sensor data collection also appears to improve exposure classification. We were able to assign a wide range of environmental exposures across various scales of time and space. These data may allow for future studies that investigate short-term (i.e. hourly) changes in asthma symptoms. More research is needed on the reliability of our exposure models over high-resolution space-time, including more robust analyses to validate the accuracy of exposure classification methods. Future research might improve these methods by tracking a participant’s movement throughout the day to assign accumulated exposures, improve classification of time spent indoors or outdoors, or use smartphone location-tracking technology to classify events by speed of movement or type of transportation.\textsuperscript{174} Our research helps lay the groundwork for these future studies.

Finally, the Propeller Health system provides a mechanism to directly translate research findings into clinical practice. Participants in this study were given access to the Propeller Health mobile App and website. This platform has the capability of sending notifications to participants. As more is understood about a participant’s environmental triggers, it may be possible to alert patients when their risk of asthma exacerbation is high based on previous patterns of inhaler use and projected weather and air pollution forecasts.
ACKNOWLEDGEMENTS

• Propeller Health Team: Meredith Barrett, Kelly Henderson, Jason Su, Jesika Riley
• Thesis Committee: John Balmes, Justin Remais, Maggi Kelly
• Thesis working group: Ndola Prata, Wilson Ly, Alex Goodell, Raphaela Lipinsky-Degette, Elizabeth Johns, Daniel Morberg, Christa Morris
• Susan Kegley
• Bina, my family, and my friends.
• The OpenStreetMap community for their commitment to making a free, accurate, accessible map of the world.

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