Daily Associations of Air Pollution and Pediatric Asthma Risk Using the Biomedical REAL-Time Health Evaluation (BREATHE) Kit

Hua Hao 1, Sandrah P. Eckel 1, Anahita Hosseini 2, Eleanne D. S. Van Vliet 3, Eldin Dzubur 1, Genevieve Dunton 1, Shih Ying Chang 4, Kenneth Craig 4, Rose Rocchio 5, Theresa Bastain 1, Frank Gilliland 1, Sande Okelo 6, Mindy K. Ross 6*, Majid Sarrafzadeh 2, Alex A. T. Bui 7 and Rima Habre 1,*

1 Department of Population and Public Health Sciences, University of Southern California, Los Angeles, CA 90039, USA; hha0@usc.edu (H.H.); eckel@usc.edu (S.P.E.); eldind@gmail.com (E.D.); dunton@usc.edu (G.D.); bastain@usc.edu (T.B.); gillilan@usc.edu (F.G.)
2 Department of Computer Science, University of California Los Angeles, Los Angeles, CA 90095, USA; ani.dachia@gmail.com (A.H.); majid@cs.ucla.edu (M.S.)
3 Health Effects Institute, Boston, MA 02110, USA; evanvliet@healtheffects.org
4 Sonoma Technology, Inc., Petaluma, CA 94954, USA; cchang@sonomatech.com (S.Y.C.); kcrig@sonomatech.com (K.C.)
5 Mobilize Labs, University of California Los Angeles, Los Angeles, CA 90095, USA; rroccchio@oarc.ucla.edu
6 Department of Pediatrics, University of California Los Angeles, Los Angeles, CA 90095, USA; sokelo@mednet.ucla.edu (S.O.); mross@mednet.ucla.edu (M.K.R.)
7 Medical & Imaging Informatics Group, Department of Radiological Sciences, University of California Los Angeles, Los Angeles, CA 90095, USA; buia@mi.ucla.edu
* Correspondence: habre@usc.edu

Abstract: Background: Exposure to air pollution is associated with acute pediatric asthma exacerbations, including reduced lung function, rescue medication usage, and increased symptoms; however, most studies are limited in investigating longitudinal changes in these acute effects. This study aims to investigate the effects of daily air pollution exposure on acute pediatric asthma exacerbation risk using a repeated-measures design. Methods: We conducted a panel study of 40 children aged 8–16 years with moderate-to-severe asthma. We deployed the Biomedical REAL-Time Health Evaluation (BREATHE) Kit developed in the Los Angeles PRISMS Center to continuously monitor personal exposure to particulate matter of aerodynamic diameter < 2.5 µm (PM2.5), relative humidity and temperature, geolocation (GPS), and asthma outcomes including lung function, medication use, and symptoms for 14 days. Hourly ambient (PM2.5, nitrogen dioxide (NO2), ozone (O3)) and traffic-related (nitrogen oxides (NOx) and PM2.5) air pollution exposures were modeled based on location. We used mixed-effects models to examine the association of same day and lagged (up to 2 days) exposures with daily changes in % predicted forced expiratory volume in 1 s (FEV1) and % predicted peak expiratory flow (PEF), count of rescue inhaler puffs, and symptoms. Results: Participants were on average 12.0 years old (range: 8.4–16.8) with mean (SD) morning %predicted FEV1 and PEF of 69.1% (18.4%) and 1.4 (3.5) puffs per day of rescue inhaler use. Participants reported chest tightness, wheeze, trouble breathing, and cough symptoms on 36.4%, 17.5%, 32.3%, and 42.9%, respectively (n = 217 person-days). One SD increase in previous day O3 exposure was associated with reduced morning (beta [95% CI]: −4.11 [−6.86, −1.36]), evening (−2.65 [−5.19, −0.10]) and daily average %predicted FEV1 (−3.45 [−6.42, −0.47]). Daily (lag 0) exposure to traffic-related PM2.5 exposure was associated with reduced morning %predicted PEF (−3.97 [−7.69, −0.26]) and greater odds of “feeling scared of trouble breathing” symptom (odds ratio [95% CI]: 1.83 [1.03, 3.24]). Exposure to ambient O3, NOx, and NO was significantly associated with increased rescue inhaler use (rate ratio [95% CI]: O3 1.52 [1.02, 2.27], NOx 1.61 [1.23, 2.11], NO 1.80 [1.37, 2.35]). Conclusions: We found significant associations of air pollution exposure with lung function, rescue inhaler use, and “feeling scared of trouble breathing.” Our study demonstrates the potential of informatics and wearable sensor technologies at collecting highly resolved, contextual, and personal exposure data for understanding acute pediatric asthma triggers.
1. Introduction

Asthma affects more than 25 million Americans, representing 8% of adults and 7% of children [1]. Asthma prevalence has been increasing over the last few decades in all age, sex, and racial groups, especially in children [2]. Children with asthma are significantly burdened by asthma morbidity, with higher rates of emergency department visits, hospitalizations, and deaths [3,4]. A large proportion of the asthma burden is the consequence of poor asthma control [5]. Children with poorly controlled asthma report a decreased health-related quality of life [6]. Asthma guidelines emphasize the importance of achieving asthma control to minimize or prevent exacerbations; however, several asthma triggers are known to exacerbate asthma resulting in increased symptoms, reduced lung function, and the need to use rescue inhaler medications [7,8]. Major determinants of the severity and persistence of asthma described in the literature include genetics [9], atopy [10], pollution [11], environmental tobacco smoke [12], respiratory infections [13], etc.

Environmental exposures, including air pollution and reduced temperature or humidity, are among the many recognized asthma triggers [14]. Previous studies exposure to ozone (O$_3$), nitrogen dioxide (NO$_2$), and particulate matter (PM) may induce or aggravate asthma [15], and air pollution exposure is associated with increased emergency department visits for asthma [16], reduced %predicted forced expiratory volume in 1 s (FEV$_1$) [17], rescue medication use [18], and increased cough and wheeze symptoms [19].

Evidence on within-person acute effects (daily to sub-daily) of air pollution exposure on asthma is more limited than evidence on chronic effects, largely because of the challenges involved in collecting highly resolved exposure and outcome information over extended periods of time at a personal level. However, advances in mobile health (mHealth) technologies including wearables, sensors, smartphone applications (apps), and informatics are enabling these studies. Toward this goal, the Biomedical REAL-Time Health Evaluation (BREATHE) Kit was developed in the Los Angeles Pediatric Research Using Integrated Sensor Monitoring Systems (PRISMS) Center as a sensor-based informatics platform for environmental health studies of pediatric asthma to enable such studies [20]. In this first analysis, we deployed the BREATHE Kit in a panel study aimed to investigate the association of acute (daily) air pollution exposure with risks of reduced lung function, rescue inhaler use, and increased symptoms in children with moderate-to-severe asthma [20]. Subsequent research will expand these analyses to investigate the association of sub-daily, acute, and peak exposures on pediatric asthma risk.

2. Materials and Methods

2.1. Study Design and Population

We recruited 40 children with moderate-to-severe asthma from the University of California, Los Angeles Pediatric Asthma Center of Excellence clinics located in Los Angeles, CA, and Santa Monica, CA, from February 2019 through December 2019. Eligibility criteria included English-speaking children aged 8–16 years with doctor-diagnosed asthma. Participants were prescreened for eligibility based on their medical records and recruited by a dedicated study coordinator within the clinic during their routine appointments. Each child was given a Biomedical REAL-Time Health Evaluation (BREATHE) Kit [20] (Figure 1), which included an Android smartphone (Samsung S4) with a custom app to display sensor data and deliver Ecological Momentary Assessment (EMA) surveys; a smartwatch (Motorola Moto 360) with a custom app; an Airbeam I (HabitatMap) personal air pollution exposure sensor (measuring PM$_{2.5}$ particulate matter less than 2.5 µm in aerodynamic diameter, relative humidity, and temperature); handheld spirometer (Asma-1 BT, Vitalograph Inc., Lenexa, KS, USA); rescue and control medication inhaler sensors (Propeller Health, Inc., Madison, WI, USA) matched to their medication regimen. Every data point collected...
with the BREATHE Kit is geotagged with latitude and longitude coordinates and location metadata and timestamped, as described in more detail in Bui et al. [20].

Figure 1. The Biomedical REAL-Time Health Evaluation (BREATHE) Kit developed in the Los Angeles PRISMS Center.

Children and their caretakers were trained on how to properly use and charge the BREATHE Kit and its components in the clinic, including how to initiate and perform proper spirometry maneuvers, respond to smartphone surveys, charge devices, and verify data communications connectivity. The day following recruitment, a detailed baseline questionnaire was conducted over the phone with the child and their caregiver to collect asthma-related health and environmental data (e.g., typical activity patterns of the child, household ventilation conditions, indoor sources of air pollution, etc.).

Subjects were monitored for 14 days during which data collection and transmission status were continuously monitored in real time by the research coordinator in a dedicated researcher dashboard. When the researcher dashboard indicated sensors were offline or missing data for an extended period of time (generally 1+ days), participants were contacted to help troubleshoot issues or encourage compliance with data collection. Once the monitoring period was completed, participants mailed their kits back in prelabeled packages and completed an interviewer-administered exit survey over the phone asking about their experience with the BREATHE Kit and the study. The institutional review board of the University of California Los Angeles approved the study protocol (Protocol #15-001402). Informed consent and assent were obtained in the clinic from the primary legal guardian accompanying the child and the child participant, respectively, upon recruitment.

2.2. Asthma Outcomes

2.2.1. Lung Function

Subjects measured their forced expiratory volume in 1 s (FEV₁) and peak expiratory flow (PEF) twice a day at home using the Vitalograph Asma-1 BT Bluetooth-enabled
monitor. The handheld device provided immediate feedback (beeping tone and visual symbol on display) to indicate when a “good” maneuver was obtained. These data on maneuver quality were captured with the lung readings and transmitted to the BREATHE Kit in real time. Participants were instructed to collect three “good” maneuvers in the morning and in the evening every day, with up to six attempts per session, at the same time every day. Morning and evening measurement times were decided upon in the clinic during recruitment based on typical wake and sleep times, within predefined time windows.

The maximum (best effort) lung function was calculated from at least two reproducible maneuvers (as the average of the two) and selected for analysis. If no reproducible value was found, the maximum value was selected. We calculated % predicted lung function based on age, sex, and height for FEV\(_1\) and PEF based on equations from Knudson et al. [21].

We also fit a linear regression of FEV\(_1\) measured using clinical-grade spirometers (Morgan rolling seal LT spirometers, Morgan Scientific, Inc., Haverhill, MA, USA) at the clinic during the recruitment appointment (or closest date retrieved from medical records when not scheduled for the same day) on FEV\(_1\) measured after coaching with the Asma-1 BT in the participant’s BREATHE Kit to assess the correlation between the two as an indicator of data quality.

2.2.2. Inhaler Use

We provided Bluetooth\textsuperscript{®}-enabled Propeller Health Inc. inhaler sensors integrated with the BREATHE Kit to track puffs of controller and rescue inhaler dispensed. Sensors were attached to the participant’s medications, tested for data connectivity, and demonstrated in the clinic upon recruitment. We aimed to provide one sensor per regularly used inhaler medication; however, compatible sensors were not always available for every type of medication. If participants did not bring their medications to the clinic visit, their parent/caretaker was provided with a sensor(s) and instructed to attach and test it at home with phone coaching by the study coordinator. However, this self-setup scenario was more technically challenging for participants and did not always result in properly connected sensors. Medication data were summarized on a person-day level for rescue (puffs count, modeled as outcome) and control inhaler use (binary for any use, adjusted for as potential confounder in health models described below).

2.2.3. Asthma Symptoms

Self-reported asthma symptoms were collected via ecological momentary assessment (EMA) surveys deployed on a custom app with the BREATHE Kit using four types of surveys (morning/end of day, after-school (on weekdays), random (within predesignated 2 h windows), and context-sensitive sensor-triggered) to minimize recall bias, maximize validity, and capture participants’ symptoms in context. A detailed survey prioritization and suppression logic was designed to manage the burden on participants while capturing potentially rare or important events [20]. Briefly, scheduled (morning/after-school/end of day) and inhaler- or lung-function-sensor-triggered surveys were prioritized. A limit of \(\leq 1\) per 10 min (inhaler) and \(\leq 1/h\) (lung function) were imposed. Random and remaining context-sensitive surveys (detailed below) were managed with a variety of limits, including a daily cap (maximum 2/day), \(\leq 1/h\), 10 min rest period in between any consecutive survey, and a 2 h density limit. The following questions based on the Asthma Control Test (ACT) [22] were asked but rephrased to refer to either the past hour, the previous night, the day, or during school time.

Morning surveys: Questions on asthma experienced in the previous night were delivered at respondents’ wake-up time as determined by participants and their caretaker at recruitment (between 6.30 a.m. and 9.00 a.m.). These included the following: “Did you wake up because of your asthma?” (response choices: Yes/No); “How many times did you use your inhaler during the night?” (Never/One time/Two times/Three times/Four or more times, which was recorded to Never/One or more times in this analysis).
Random and sensor-triggered surveys: Additional asthma symptoms were collected via EMAs surveys sent out at random times within predesignated 2 h windows throughout the day or triggered in real time based on sensor data streams. Context-sensitive surveys were triggered after rescue inhaler use, lung function testing, peak in PM$_{2.5}$ concentrations, and following a sustained (>5 min) increase in heart rate corresponding to moderate exercise intensity (defined as heart rate (average in 2 min sliding window) > 0.5 (HR$_{\text{max}}$ − HR$_{\text{rest}}$) + HR$_{\text{rest}}$, where HR$_{\text{rest}}$ is calculated based on child’s age and resting heart rate collected at recruitment. These are described in more detail in Bui et al. [20]. Questions on asthma symptoms in the last hour included the following: “In the past hour, did your chest feel tight because of asthma?”; “In the past hour, did you feel wheezy (whistling in the chest) because of asthma?”; “In the past hour, did you have trouble breathing because of your asthma?”; “In the past hour, did you cough because of your asthma?”; “In the past hour, how much of a problem was your asthma when you ran, exercised or played sports?”; “In the past hour, did you feel scared that you might have trouble breathing because of your asthma?”; and “In the past hour, have you avoided strenuous activities, or had to slow down or stop exercising because of your asthma?” Response choices for all these questions were “Not at all/A little/Quite a bit/Very much so” except for asthma being a problem when exercising which included an additional option of “I did not run, exercise, or play sports.” Dichotomous symptom variables were created at the daily level as “Not at all” in all completed surveys versus any other report (A little, Quite a bit, Very much so).

After School: Questions were the same as the random survey described above, except they started with “At school today” instead of “In the past hour.”

End of the day: This last EMA survey of the day was scheduled for 7:00 p.m. and collected day-level information. Questions included the random survey symptom questions (referring to the past hour) as well as the following: “How much of the time did your asthma keep you from getting as much done at school or at home today?” Response choices were summarized similarly to the random survey questions at the daily level.

2.3. Environmental Exposure Assessment

Personal monitoring. Personal exposure to particulate matter with aerodynamic diameter < 2.5 µm (PM$_{2.5}$), relative humidity (RH), and temperature were continuously measured using the AirBeam 1.0 (HabitatMap) following the BREATHE Kit energy optimization cycle (15 secs data collection every 1 min) [20]. A running median filter (within a centered window of 10 observations) was applied to personal RH to remove outliers. As the degree of missingness in personal RH was high, we developed a model to impute it on the person-day level for use in health models. The imputation used the following predictors in a mixed-effects model: daily ambient RH (calculated from ambient dew point and temperature [23], described below), daily ambient temperature, and the visit-level difference between mean ambient and personal RH. The model included a random intercept for a subject to account for person-level clustering in the data. It also included a random slope for ambient RH to allow the relationship between daily ambient and personal RH to vary by person depending on their typical activity patterns or household characteristics. The Pearson correlation between daily predicted and measured personal RH was 0.97.

Modeled ambient air pollution and meteorology. An Environmental Data Web Service was built by Sonoma Technology Inc. (STI, Petaluma, CA, USA), to provide real-time and archived weather (ambient temperature and dew point) and ambient air pollution data streams based on user location (determined by GPS), date, and hour to support the BREATHE Kit. Meteorological data were extracted from the NOAA Real-Time Mesoscale Analysis (RTMA) hourly, 2.5 km × 2.5 km data assimilation product (https://www.nco.ncep.noaa.gov/pmb/products/rtma/#RTMA2p5, accessed 5 June 2020). Hourly ambient air pollution exposures were modeled using inverse-distance squared spatial interpolation from surrounding regulatory monitors for PM$_{2.5}$, ozone (O$_3$), nitrogen dioxide (NO$_2$), nitrogen oxide (NO), and nitrogen oxides (NOx). These reflect hourly concentrations of air pollutants from general background or regional sources. Los Angeles, CA, has one
of the densest regulatory ambient air monitoring networks in the US, which provided comprehensive coverage in our study area.

Modeled traffic-related air pollution. Air pollutant concentrations from vehicular traffic on nearby roads, referred to as traffic-related PM$_{2.5}$, NO$_x$, and NO$_2$, were modeled using the RLINE line source dispersion model and provided in the STI web service. RLINE uses local weather data and a comprehensive database of roadways, annual traffic volume, and vehicle emission factors for southern California to estimate pollutant concentrations contributed by on-road mobile source emissions at the participant receptor points [24].

Daily exposure averaging windows. To investigate the association of these exposures with morning, evening, and day-average outcomes, two averaging intervals were used to calculate 24 h exposure averages that precede the outcomes as follows: For morning outcomes such as morning lung function, 24 h averages were calculated starting from 6.00 a.m. the previous day to 6.00 a.m. of the current day. For evening (e.g., evening lung function) and daily outcomes (e.g., daily average lung function), 24 h averages were calculated starting from 6.00 p.m. the previous day to 6.00 p.m. of the current day. The cut points of 6.00 a.m. and 6.00 p.m. were selected because most participants completed their morning and evening lung function tests after 6.00 a.m. and 6.00 p.m., respectively (Supplementary Figure S1). Moreover, 24 h averages were calculated using 30% completeness criteria, which is more relaxed than typical air pollution investigations utilizing modeled ambient data given the greater chance of missing data using personal sensors and real-time data transmission.

2.4. Covariate Information

Based on previous air pollution and asthma literature [9–13], we considered the following covariates a priori as potential confounders: sex, race, Hispanic ethnicity, caretaker’s education level, household income, personal and ambient relative humidity and temperature, subject’s person-day level time–activity patterns, asthma medication use, outdoor physical activities, exposure to smoking (exposure to secondhand smoking in the home and in utero exposure to maternal smoking), home characteristics (kitchen ventilation, fuel use, presence of pets) and day of the week. Of this list, only Hispanic ethnicity and personal relative humidity were selected to be included in the final model since they were significant predictors, and their inclusion resulted in greater than roughly 10% change in the main pollutant effect estimate. This decision was guided by a priori selection of potential covariates and balanced the need to minimize degrees of freedom in the models and ensure comparable adjustments across health models. Given the importance of asthma control on the risk of these outcomes, we further adjusted for same-day use of controller medication in sensitivity analyses as a potential confounder.

2.5. Statistical Analysis

Spearman correlations were calculated to assess correlations between different pollutants given their non-normal distribution. We tested the association between daily air pollution exposures and lung function (% predicted FEV$_1$ and PEF), the daily count of rescue inhaler medication use, and asthma symptoms using mixed-effects models with a random intercept for each subject to account for the repeated-measures design. We investigated these associations for the preceding 24 h (lag 0) as well as lags 1 and 2 days. Daily lags followed the 6.00 a.m. to 6.00 a.m. or 6.00 p.m. to 6.00 p.m. definitions explained above, depending on whether the outcome was assessed in the morning or during the day/in the evening, respectively. For example, lag 1 was defined as the preceding 25–48 h and lag 2 as the preceding 49–72 h for daily or evening outcomes.

We reported results as a change in %predicted value for lung function, the rate ratio for rescue inhaler use, and odds ratios of experiencing symptoms. All effects estimates were scaled to a standard deviation (SD) increase in each pollutant (based on lag 0 distributions) to allow standardized inter-pollutant comparisons of health effects. We also fit two-pollutant models to test whether pollutant effects were potentially confounded by
co-exposure to another pollutant, in cases in which the two pollutants were not highly correlated (Spearman correlation < 0.5). Statistical significance was determined based on a $p$-value < 0.05. All analyses were conducted in SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Descriptive Summaries

Children were 12 years old on average (range 8–16 years, $n = 40$), 45% female, and 42.5% of Hispanic ethnicity. Descriptive statistics are presented in Table 1 and Supplementary Table S1. All participants were enrolled for 14 days in the study, except for 3 who withdrew and only completed 2, 3, and 5 days of follow-up, respectively. Overall, 1172 spirometry maneuvers were attempted and 887 (76%) were classified as “good”. Of 218 person-days with lung function data, 78 (36%) achieved a minimum of 6 attempts (3 maneuvers in each of morning and evening test sessions as instructed). Among days with <6 attempts, a median of three “good” attempts was obtained. On average, %predicted FEV$_1$ and PEF were lower in the morning and increased in the evening (Table 2). The fitted regression line between the FEV$_1$ measurements obtained with the Asma-1 BT handheld spirometer on recruitment day and clinic measurements using clinical-grade spirometers had an $R^2 = 0.68$ (Supplementary Figure S1). On average, subjects used 1.4 puffs/day of rescue medication, with a range of 0–24 puffs/day (Table 2 and Supplementary Figure S2). In general, subjects answered more morning and end-of-day symptom survey questions compared to random surveys (Table 2).

Table 1. Descriptive statistics of participant characteristics ($n = 40$).

| Characteristics | Statistics |
|-----------------|------------|
| Age (years, mean (range)) | 12.0 (8.4–16.8) |
| Sex ($n$ (%)) | |
| Female | 18 (45.0) |
| Male | 22 (55.0) |
| Race ($n$ (%)) | |
| White | 15 (37.5) |
| Black/African American | 2 (5.0) |
| Black/Not African American | 1 (2.5) |
| Asian | 4 (10.0) |
| Other | 15 (37.5) |
| Missing | 3 (7.5) |
| Hispanic Ethnicity ($n$ (%)) | |
| No | 19 (47.5) |
| Yes | 17 (42.5) |
| Missing | 4 (10.0) |
| Caretaker’s highest completed educational grade ($n$ (%)) | |
| High school or GED | 3 (7.5) |
| Some college or trade school | 9 (22.5) |
| College | 9 (22.5) |
| Graduate school | 15 (37.5) |
| Missing | 4 (10.0) |
| Total household income per year ($n$ (%)) | |
| Prefer not to say | 12 (30) |
| USD 30,000–40,000 | 2 (5.0) |
| Over USD 50,000 | 23 (57.5) |
| Missing | 3 (7.5) |
| Type of Health Insurance ($n$ (%)) | |
| HMO | 18 (45.0) |
| PPO or POS | 20 (50.0) |
| Missing | 2 (5.0) |
Table 2. Distributions of outcomes on the person-day level, including lung function, inhaler medication use, and asthma symptoms.

| Lung Function            | Mean ± SD  |
|--------------------------|------------|
| Percent-predicted FEV₁ (%) |            |
| Morning (n = 175)        | 67.9 ± 17.3|
| Evening (n = 147)        | 70.9 ± 17.7|
| Daily Average (n = 96)   | 68.7 ± 15.7|
| Percent-predicted PEF (%) |            |
| Morning (n = 175)        | 69.1 ± 18.4|
| Evening (n = 147)        | 73.8 ± 18.3|
| Daily Average (n = 96)   | 69.3 ± 15.8|

| Inhaler Medication        | Mean ± SD  |
|---------------------------|------------|
| Number of rescue inhaler puffs per day (n = 324) | 1.4 ± 3.5 |
| Number of control inhaler puffs per day (n = 312) | 1.5 ± 1.9 |

| Asthma Symptoms           | n (%)      |
|---------------------------|------------|
| Did you wake up last night because of your asthma? |            |
| No                        | 123 (93.2) |
| Yes                       | 9 (6.8)    |
| How many times did you use your inhaler during the night? |          |
| Never                     | 111 (84.1) |
| One or more times         | 21 (15.9)  |
| How much of the time did your asthma keep you from getting as much done at school or at home today? |          |
| Not at all                | 94 (86.2)  |
| A little/Quite a bit/Very much so | 15 (13.8)  |
| Did your chest feel tight because of asthma today? |          |
| Not at all                | 138 (63.6) |
| A little/Quite a bit/Very much so | 79 (26.4)  |
| Did you feel wheezy because of your asthma today? |          |
| Not at all                | 179 (82.5) |
| A little/Quite a bit/Very much so | 38 (17.5)  |
| Did you have trouble breathing because of your asthma today? |          |
| Not at all                | 147 (67.7) |
| A little/Quite a bit/Very much so | 70 (32.3)  |
| Did you cough because of your asthma today? |          |
| Not at all                | 124 (57.1) |
| A little/Quite a bit/Very much so | 93 (42.9)  |
| How much of a problem was your asthma when you ran, exercised, or played sports today? |          |
| Not at all                | 79 (71.8)  |
| A little/Quite a bit/Very much so | 31 (28.2)  |
| In the past hour, did you feel scared that you might have trouble breathing because of your asthma? |          |
| Not at all                | 152 (81.7) |
| A little/Quite a bit/Very much so | 34 (18.3)  |
| In the past hour, have you avoided strenuous activities, or had to slow down or stop exercising because of your asthma? |          |
| Not at all                | 155 (83.3) |
| A little/Quite a bit/Very much so | 31 (16.7)  |

Measured personal exposures had greater missingness than modeled ambient and traffic-related environmental exposures (Supplementary Table S2). Concentrations of personal 24 h PM$_{2.5}$ were highly variable between and within subjects, with a maximum reaching 64.7 µg/m$^3$ (Supplementary Figure S3). Personal PM$_{2.5}$ exposure was also more variable than ambient PM$_{2.5}$. Personal and ambient PM$_{2.5}$ were moderately correlated (Spearman $r = 0.39$), while personal and traffic-related PM$_{2.5}$ were weakly correlated ($r = 0.14$). Ambient pollutants had moderate-to-high correlations with each other, similar
to traffic-related pollutants. However, ambient O\textsubscript{3} was weakly correlated with remaining pollutants (Supplementary Table S3).

### 3.2. Air Pollution and Health Models

Final sample sizes for different outcome models varied based on exposure and outcome data completeness from \( n = 39 \) to 167 person-days (in the ambient O\textsubscript{3} (lag 0) and rescue inhaler use model). Supplementary Table S4 presents results of %predicted FEV\textsubscript{1} models (interpreted as a percentage point change). One SD increase in same-day (lag 0) O\textsubscript{3} (9.2 ppb) was associated with a 4.11% lower [95% CI: \(-6.86, -1.36\)] morning %predicted FEV\textsubscript{1}. O\textsubscript{3} was also significantly inversely associated with evening (\(-2.65 [\sim 5.19, -0.10]\)) and daily average %predicted FEV\textsubscript{1} (\(-3.45 [\sim 6.42, -0.47]\)). Similarly, lag 1 (previous day) O\textsubscript{3} exposure was associated with lower evening (\(-4.90 [\sim 7.94, -1.85]\)) and daily %predicted FEV\textsubscript{1} (\(-4.92 [\sim 8.44, -1.40]\)); however, only the association with morning %predicted FEV\textsubscript{1} marginally remained at lag 2 (\(-2.94 [\sim 5.93, 0.05]\)).

For traffic-related pollutants (PM\textsubscript{2.5}, NO\textsubscript{x}, NO\textsubscript{2}), lag 1 exposure was significantly and inversely associated with morning %predicted FEV\textsubscript{1}. Overall, most same-day (lag 0) air pollutant exposures were inversely associated with morning %predicted FEV\textsubscript{1}, although some were not significant (Figure 2). Supplementary Table S5 presents results for %predicted PEF. Previous-day (lag 1) traffic-related PM\textsubscript{2.5} exposure was associated with 3.97% lower [95% CI: \(-7.69, -0.26\)] morning %predicted PEF per SD (0.7 µg/m\textsuperscript{3}). Associations were marginal at lag 1 (\(-3.35 [\sim 6.89, 0.19]\)) and lag 2 (\(-6.27 [\sim 12.75, 0.21]\)). Traffic-related NO\textsubscript{x} and NO\textsubscript{2} were significantly associated with lower morning PEF at lag 1 (traffic-related NO\textsubscript{x}: \(-4.91 [\sim 9.28, -0.54]\), traffic-related NO\textsubscript{2}: \(-4.57 [\sim 8.51, -0.63]\)). Personal PM\textsubscript{2.5} exposure was not significantly associated with lung function (Figure 2). Adjusting for control inhaler use did not meaningfully change any of the observed results (Supplementary Tables S6 and S7).

Supplementary Table S8 reports associations between rescue inhaler use and air pollutants. Most significant associations were found for same-day (lag 0) exposures. Ambient air pollutants (PM\textsubscript{2.5}, O\textsubscript{3}, NO\textsubscript{x}, NO, NO\textsubscript{2}) on lag 0 days were all positively associated with daily rescue inhaler use; however, this association was not significant for ambient PM\textsubscript{2.5} and NO\textsubscript{2}. An increase of 1 SD (9.2 ppb) in O\textsubscript{3} was associated with 1.52 times greater rate of rescue inhaler use [95% CI: \(1.02, 2.27\)]. In contrast, same-day exposure to traffic-related PM\textsubscript{2.5}, NO\textsubscript{x}, NO\textsubscript{2} was significantly negatively associated with rescue inhaler use. However, these associations became non-significant in two-pollutant models adjusted for O\textsubscript{3} (Supplementary Figure S4). Although positive, personal PM\textsubscript{2.5} on lag 0 was not significantly associated with rescue inhaler use.

Supplementary Table S9 presents findings for asthma symptoms. One-SD increase in traffic-related PM\textsubscript{2.5} (lag 0) was significantly associated with 83% (95% CI: \(3\%\), \(224\%\)) higher odds of feeling scared of having trouble breathing because of asthma. Most associations were variable and not significant for cough, wheeze, chest tightness, trouble breathing, avoiding strenuous activities because of asthma, and asthma interfering with daily activities, although sample sizes for symptoms were more limited than the other outcomes (ranged from 52 person-days for personal PM\textsubscript{2.5} models to maximum 154 person-days for other pollutants). Finally, Supplementary Table S10 presents results for all outcomes in models adjusted for parental asthma status, caretaker education level, Hispanic ethnicity, and personal relative humidity to compare to the final models presented in this analysis.
Figure 2. Association of daily air pollution exposure (lag 0) with %predicted FEV₁ and PEF. Effect estimates and 95% confidence intervals are scaled to a standard deviation change in exposure. Effect estimates were scaled to a standard deviation change in pollutant concentrations as follows: personal PM$_{2.5}$: 9.1 µg/m$^3$; traffic-related PM$_{2.5}$: 0.7 µg/m$^3$; traffic-related NO$_x$: 14.7 ppb; traffic-related NO$_2$: 7.1 ppb; ambient PM$_{2.5}$: 3.7 µg/m$^3$; ambient O$_3$: 9.2 ppb; ambient NO$_x$: 6.1 ppb; ambient NO: 2.4 ppb; ambient NO$_2$: 4.6 ppb.

4. Discussion

Our findings revealed significant associations between same-day and previous-day exposure to air pollution and risk of reduced lung function, rescue inhaler use, and symp-
Symptoms in a panel study of 40 children with moderate to severe asthma in Los Angeles, CA. In general, we found the strongest associations for O3 and traffic-related PM_{2.5} with lung function, and with ambient pollutants and rescue inhaler use. Although limited in sample size, the risk of feeling scared of having trouble breathing because of asthma was also associated with traffic-related PM_{2.5} exposure. In contrast, total personal PM_{2.5} exposure—although marginal in some cases—was not associated with any of our outcomes. To the best of our knowledge, our study is the first to deploy a wearable, sensor-based informatics platform to monitor and model such an extensive suite of environmental exposures and potential acute asthma triggers at the personal level, in context, and with such high spatiotemporal resolution. As such, important data considerations, methodological challenges, and lessons learned will also be shared and discussed below.

For lung function, our findings generally agree with the literature, although the effects of ambient versus traffic-related pollutants were more pronounced for FEV\textsubscript{1}, while the inverse was true for PEF. Several studies reported short-term exposure to O3 was associated with lung function decrements [25–28], which is consistent with our O3 and FEV\textsubscript{1} results. Ozone is a strong oxidant that is formed in the troposphere via chemical reactions in the presence of precursor pollutants, such as volatile organic compounds, nitrogen oxides, and solar radiation [29]. Ozone concentrations are generally higher outdoors compared with indoors; therefore, human exposures to ozone mainly occur in the outdoor environment [30]. The World Health Organization (WHO) [31] states that there is more consistent evidence on the short-term rather than the long-term effects of O3, which include increases in daily mortality and morbidity, especially for respiratory causes [32]. As up to 90% of inhaled ozone is absorbed in the respiratory tract along the bronchial tree [33], O3 responses are likely initiated and localized in the respiratory tract lining fluid due to the low solubility and high reactivity of O3 [34]. Once inhaled, O3 reacts with proteins and lipids of the lung lining fluid resulting in cytokines generation leading to an increase in lung permeability and edema development [35]. Consequently, O3 exposure is believed to result in acute oxidative stress and lung inflammation, contributing to respiratory morbidities such as reduced lung function [36]. The range of magnitude in the association we found between short-term O3 and evening FEV\textsubscript{1} is comparable to previous studies, with a lower limit of −5.2% expected reduction in %predicted FEV\textsubscript{1} (−2.65 [−5.19, −0.10]). For example, a previous literature review reported that short-term O3 exposure was associated with a wide range of reduction in %predicted FEV\textsubscript{1} in children (−0.01% to −9% reduction per 10 ppb change in O3), for periods ranging from 1 day to 2 weeks [37]. Similarly, expected changes as large as −9.3% reduction in morning %predicted FEV\textsubscript{1} and −9.3% reduction in morning %predicted PEF were seen with lag 1 traffic-related NO\textsubscript{2} exposure (lower 95% CI limit, Supplementary Tables S4 and S5). Similarly, rate ratios of rescue inhaler use were as high as 2.3 for same-day ambient O3 exposure and 2.4 for same-day ambient NO\textsubscript{2} exposure (upper 95% CI, Supplementary Table S8). The full confidence interval should, therefore, be taken into consideration in the interpretation of our results, which could range from subtle to more noticeable effects on morbidity and quality of life for children with asthma on a day-to-day basis.

A 2001 study in The Netherlands reported significant decreases in PEF in children following exposures to PM_{10} (lags 1 and 3 days), NO\textsubscript{2} (lags 0 and 1), and NO (lag 3) [38]. In our study, we found same-day and up to 2 days lag exposure to traffic-related pollutants (PM_{2.5} on lag 0, 1, 2 days; NO\textsubscript{2} and NO\textsubscript{3} on lag 1 day) was associated with reduced morning PEF. Traffic is one of the most important sources of NO\textsubscript{3} in southern California, and a large contributor to overall PM_{2.5} concentrations [38]. Although other pollutants could be present in the near-roadway mixture and could contribute to these effects, in general, our findings seem consistent with the literature. Moreover, Li et al. [39] reviewed more than 30 panel studies on the effects of air pollution on children’s lung function and respiratory symptoms. They reported that PM and NO\textsubscript{2} showed more significant associations with PEF, but findings for many outcomes depended on the number of lag days similarly to our results.
In addition, previous studies investigated the biological mechanisms contributing to decreased lung function as a result of PM$_{2.5}$ exposure. They reported that PM$_{2.5}$ could reach the alveoli, and up to 50% may remain in the lung tissue [40]. Additionally, because of their deep deposition in the alveoli, their removal or clearance rate (via mucociliary transport) can be slow [41]. This further supports lagged effects and could provide actionable information to physicians to consider warning pediatric asthma patients and parents to be more vigilant about symptom monitoring both on particular poor air quality days, as well as for the following 1–2 days, to adequately prepare for potential symptom flares.

Similarly, several previous studies reported daily associations of ambient PM, O$_3$, and NO$_x$ exposure with rescue inhaler use [42,43], consistent with our findings for O$_3$, NO$_x$, and NO. However, ambient PM$_{2.5}$ was positively but non-significantly associated with rescue inhaler use in our study. Existing evidence suggests that short-term exposure to O$_3$ and NO$_2$ can cause airway inflammation, reduced pulmonary function, and exacerbation in individuals with asthma [44]. While consistent with the literature, it is possible our study was underpowered to detect significant associations with ambient PM$_{2.5}$. Exposure measurement error inherent in the ambient and traffic-related estimates could also lead to weaker statistical power to detect effects in our study. Ambient PM$_{2.5}$ does not fully capture personal exposure to PM$_{2.5}$ of outdoor origin. Ambient and personal PM$_{2.5}$ were weakly correlated in our data ($r = 0.39$), which also suggests personal PM$_{2.5}$ exposures in our population are heavily impacted by indoor and personal activity-related sources and do not correlate with outdoor variations in ambient PM. For traffic-related PM$_{2.5}$, NO and NO$_x$, we found increased exposure to those pollutants was associated with a decreased rate of rescue inhaler use. However, after we adjusted ozone in the same model, these associations became non-significant, but the point estimate was still negative. The possible explanation could be residual confounding due to other co-occurring exposures, behaviors, or time–activity patterns.

As for symptoms, sample sizes available for analysis were generally much lower relative to other sensor-measured outcomes, likely due to the additional burden involved in actively responding to multiple EMA surveys during the day. We only found significant associations between exposure to traffic-related PM$_{2.5}$ and feeling scared of having trouble breathing. Despite a roughly similar sample size, we did not find significant associations of traffic-related PM$_{2.5}$ with daily trouble breathing symptoms. One possible explanation could be the increased perception of risk or anticipation of an asthma attack when children are exposed to traffic for long periods of time, perhaps based on prior experiences, and thus might increase stress and anxiety levels. Several studies reported the associations between increased air pollution levels and asthma symptoms, and limited research has been conducted on the symptom of trouble/difficulty breathing. One study in Spokane, WA, investigated exposure to PM in several sizes and several asthma symptoms in children, including trouble breathing [45]. They found positive but non-significant results, similar to our study. We also found positive but non-significant associations between ambient PM$_{2.5}$ and some traffic-related air pollutants with cough, wheeze, asthma being a problem when running, exercising, or playing sports. Cough is a commonly studied asthma symptom in many previous studies [46–48], but with inconsistent findings. One study in New York found stronger daily associations of PM of indoor origin with wheeze, while O$_3$ and PM of outdoor origin were more strongly associated with cough [19]. However, given the limited sample size for symptoms and personal PM$_{2.5}$ in our study, we were not able to further model or disentangle the effects of PM$_{2.5}$ by origin or source. The higher concentrations and variability of personal PM$_{2.5}$, compared with ambient, further illustrate the diverse and complex sources, behaviors, and factors that contribute to true personal exposure which are often missed by using ambient estimates. Since PM composition and toxicity can vary considerably based on its contributing sources, this is an important future direction of research.

As for exposure patterns, ambient pollutants were more highly correlated with personal PM$_{2.5}$ exposure than traffic-related pollutants. This could be due to participants’
time–activity patterns and home operation characteristics (e.g., window opening), leading to infiltration of outdoor air pollution indoors. It is also possible that study participants did not spend too much time in transit or commuting during the monitoring period, or when they did, they were more isolated or protected from traffic emissions by operating air conditioners and closing car windows. We did not have data to ascertain these behaviors but believe this is possible for a pediatric population with moderate-to-severe asthma living in Los Angeles, CA.

Our study includes a number of limitations. First, the personal PM$_{2.5}$ exposure was measured using commercial grade sensors that were challenging or not feasible to regularly calibrate while the study was operational. Low-cost optical PM sensors such as the one used in this study tend to overestimate PM$_{2.5}$ concentrations largely due to relative humidity interferences. In addition, they do not capture particles $<$~300 nm in aerodynamic diameter, and their response can vary based on the actual chemical composition and size distribution of the aerosol mixture [49]. Whether or not the overestimation can have any effect on the health model findings could be assessed in future analyses; however, it is unlikely to be differential in relation to the outcome. Second, although we relied on real-time data streaming checks built into the researcher dashboard to regularly manage and encourage compliance with data collection, on top of the built-in engagement features of the BREATHE Kit, it is still possible that participants were not always fully compliant in using or charging their devices or not always allowed to take them to school. These challenges—while common in personal monitoring studies—require more research in terms of encouraging and rewarding compliance and designing mHealth platforms with users in mind to balance burden with quality, completeness, and representativeness of data. We also recommend careful evaluation of temporal and spatial patterns of data missingness in future mHealth studies to determine whether these might correlate with behaviors or outcomes being assessed and might introduce bias. For example, device use or battery power might correlate with certain times of day, for example, or certain microenvironments (e.g., home) might be more represented in the data.

In addition, the generalizability of our findings is potentially limited. Our participants were recruited from a pediatric asthma specialty clinic and had moderate-to-severe asthma. As such, triggers and factors associated with exacerbations in this population might not necessarily translate to children with mild asthma or well-controlled asthma. In addition, the socioeconomic characteristics of our study sample are likely not representative of the general population or more disadvantaged or environmentally burdened populations, as 37.5% of participants’ caretakers had graduate-level degrees, 57.5% of participants’ caretakers reported over USD 50,000 household income annually, and all participants had health insurance coverage. Finally, selection bias may have influenced our results if parents living in areas with higher air pollution exposure were also more concerned about its impact on their child’s asthma and therefore more likely to participate in our study. However, it is difficult to ascertain the direction of this potential selection bias.

Strengths of our study include a repeated-measures design that allowed us to investigate associations at the daily, within-person level over an extended period of 14 days, in a highly susceptible pediatric asthma population. This is also the first study up to our knowledge to deploy a sophisticated sensor-based informatics platform that allowed us to continuously collect very highly spatiotemporally resolved, contextualized, and personal exposure, behavior, and outcome information. The BREATHE Kit was designed to minimize recall bias in the outcome and behavior data, ascertain context, and reduce exposure measurement error. GPS tracking and integration of modeled environmental exposure data also enabled us to expand the suite of exposures that could be investigated and provided a robust sample size for detecting associations, compared with personal measurements that had the highest degree of missingness. As sensors continue to advance, we expect battery life and burden issues to continue to improve, allowing longer deployments and more complete data streams.
In conclusion, we found evidence of daily air pollution effects on lung function, rescue inhaler use, and feeling scared of having trouble breathing because of asthma using a longitudinal panel design. Our study provides further support for considering the importance of air pollution in the management and treatment of asthma. Our study demonstrates how informatics platforms such as our Los Angeles PRISMS Center BREATHE Kit can enable researchers to collect and integrate highly resolved measured and modeled data for investigating acute triggers of pediatric asthma or risk factors for other chronic diseases. Future directions of research include incorporating activity space-based exposures to capture conditions within actual spaces participants visited throughout the day and investigate their relationships with different metrics of personal exposures, as well as investigating within-day, within-person associations between exposures, behaviors, and health outcomes in context.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph19063578/s1, Table S1. Descriptive statistics of participants characteristics (n = 40); Table S2. Descriptive statistics of daily (6 a.m.–6 a.m.) air pollution exposures and meteorology; Table S3. Exposure (daily average, 6 a.m.–6 a.m.) Spearman correlation matrix; Table S4. Change in %predicted morning, evening or daily averaged FEV1 (forced expiratory volume in 1 s) per standard deviation change in pollutant exposure; Table S5. Change in %predicted morning, evening or daily PEF (peak expiratory flow rate) (per standard deviation change) in pollutant exposure; Table S6. Change in %predicted morning, evening or daily FEV1 (forced expiratory volume in 1 s) per standard deviation change in pollutant exposure on lag 0 day adjusted personal relative humidity, Hispanic ethnicity, and daily control inhaler use; Table S7. Change in %predicted morning, evening or daily PEF (peak expiratory flow rate) (per standard deviation change) in pollutant exposure on lag 0 day adjusted personal relative humidity, Hispanic ethnicity, and daily control inhaler use; Table S8. Associations between daily air pollutant exposures and count of rescue inhaler puffs used (rate ratios per standard deviation change in pollutant); Table S9. Associations between same-day (lag 0) daily air pollutant exposures and asthma symptoms (odds ratio per standard deviation change in pollutant); Table S10. Associations between between forced expiratory volume in one second (FEV1) collected at recruitment with the Asma-1 BT sensor used in the BREATHE Kit and the and clinic spirometer tested FEV1 on same or closest previous day to recruitment (units of L/s); Figure S1. Rescue inhaler use outcomes to demonstrate the impact of adjustments on final reported effects; Figure S2. Comparison between forced expiratory volume in one second (FEV1) collected at recruitment with the Asma-1 BT sensor used in the BREATHE Kit and the and clinic spirometer tested FEV1 on same or closest previous day to recruitment (units of L/s); Figure S3. Distribution of daily average personal (measured), ambient (modeled) and traffic-related (modeled) PM2.5 exposures in µg/m³ across all subjects; Figure S4. Results of single- and two-pollutant models (rate ratio and 95% CI per standard deviation increase in exposure) for daily count of rescue inhaler use in relation to traffic-related PM2.5, NO, and NOx exposure in the last 24 h (lag 0).

**Author Contributions:** Conceptualization, A.A.T.B., F.G., R.H., S.O., M.K.R., M.S.; data curation, A.A.T.B., A.H., K.C., R.R., R.H. and S.Y.C.; formal analysis, H.H.; investigation, A.A.T.B., A.H., M.K.R., M.S., R.H. and S.O.; methodology, A.A.T.B., A.H., F.G., G.D., K.C., M.S., R.H, R.R., S.Y.C., S.P.E. and T.B.; resources, A.A.T.B., A.H., F.G., M.K.R., M.S., R.H. and S.O.; supervision, A.A.T.B., M.K.R., M.S., R.H. and S.O.; visualization, A.A.T.B., H.H., R.H.; writing—original draft, H.H.; writing—review and editing, H.H., S.P.E., A.H., E.D.S.V., E.D., G.D., S.Y.C., K.C., R.R., T.B., F.G., S.O., M.K.R., M.S., A.A.T.B. and R.H. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Los Angeles Pediatric Research Using Integrated Sensor Monitoring Systems (PRISMS) Center under NIH/NIBIB U54 EB022002. Additional support was provided by the USC Southern California Environmental Health Science Center (NIH/NIEHS P30ES007048).

**Institutional Review Board Statement:** The study was approved by the University of California Los Angeles Institutional Review Board under Protocol #15-001402.
Informed Consent Statement: Informed consent and permission for child to participate (caretaker) and informed assent (child) were obtained from all study participants involved in the study.

Acknowledgments: The authors would like to thank members of the PRISMS consortium, including Ed Sakabu, Wren Reynolds, Cathy Tranche, and Lauren Cullen of UCLA Mobilize Labs; Lisa Valencia of USC; Frederick Lumbran of Sonoma Technology, Inc.; Dimitrios Stripelis and Jose-Luis Ambite of the PRISMS Data and Software Coordination and Integration Center (U24 EB021996). The authors also thank all study participants and their families for their time and commitment to the study, and the medical doctors and staff at the UCLA Pediatric Asthma Center of Excellence for their assistance and contributions to the success of this study. Finally, the authors would also like to thank Meredith Barrett and the Propeller Health team for their contributions to the study and this manuscript.

Conflicts of Interest: The authors declare no conflict of interest. S.Y.C. and K.C. are employed at Sonoma Technology, Inc., and E.D.S.V. is currently employed at the Health Effects Institute (previously at USC for the duration of this work).

References

1. CDC National Asthma Data. Available online: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm (accessed on 13 September 2021).
2. Kuschner, W.G. The asthma epidemic. N. Engl. J. Med. 2007, 356, 1073. [CrossRef] [PubMed]
3. Van Dellen, Q.M.; Stronks, K.; Bindels, P.J.; Orly, F.G.; Bruij, J.; van Aalderen, W.M.; Group, P.S. Predictors of asthma control in children from different ethnic origins living in Amsterdam. Respir. Med. 2007, 101, 779–785. [CrossRef] [PubMed]
4. Akinbami, L. Centers for Disease Control and Prevention; National Center for Health Statistics. The state of childhood asthma, United States, 1980–2005. Adv. Data 2006, 381, 1–24.
5. Bartter, T.; Pratter, M.R. Asthma: Better outcome at lower cost? The role of the expert in the care system. Chest 1996, 110, 1589–1596. [CrossRef] [PubMed]
6. Juniper, E.F.; Guyatt, G.H.; Feeny, D.H.; Ferrie, P.J.; Griffith, L.E.; Townsend, M. Measuring quality of life in the parents of children with asthma. Qual. Life Res. 1996, 5, 27–34. [CrossRef] [PubMed]
7. Cloutier, M.M.; Teach, S.J.; Lemanske, R.F., Jr.; Blake, K.V. The 2020 Focused Updates to the NIH Asthma Management Guidelines: Key Points for Pediatricians. Pediatrics 2021, 147, e2021050286. [CrossRef] [PubMed]
8. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J. Allergy Clin. Immunol. 2007, 120, S94–S138. [CrossRef]
9. Burke, W.; Fesinmeyer, M.; Reed, K.; Hampson, L.; Carlsten, C. Family history as a predictor of asthma risk. Am. J. Prev. Med. 2003, 24, 160–169. [CrossRef]
10. Illi, S.; von Mutius, E.; Lau, S.; Niggemann, B.; Gruber, C.; Wahn, U.; Multicentre Allergy Study. g. Perennial allergen sensitisation early in life and chronic asthma in children: A birth cohort study. Lancet 2006, 368, 763–770. [CrossRef]
11. Holst, G.J.; Pedersen, C.B.; Thygesen, M.; Brandt, J.; Geels, C.; Bonlkke, J.H.; Sigsgaard, T. Air pollution and family related determinants of asthma onset and persistent wheezing in children: Nationwide case-control study. BMJ 2020, 370, m2791. [CrossRef]
12. Dezateux, C.; Stocks, J.; Dundas, I.; Fletcher, M.E. Impaired airway function and wheezing in infancy: The influence of maternal smoking and a genetic predisposition to asthma. Am. J. Respir. Crit. Care Med. 1999, 159, 403–410. [CrossRef] [PubMed]
13. Friedlander, S.L.; Jackson, D.J.; Gangnon, R.E.; Evans, M.D.; Li, Z.; Roberg, K.A.; Anderson, E.L.; Carlson-Dakes, K.T.; Adler, K.J.; Gilbertson-White, S.; et al. Viral infections, cytokine dysregulation and the origins of childhood asthma and allergic diseases. Pediatr. Infect. Dis. J. 2005, 24, S170–S176, discussion S174–S175. [CrossRef] [PubMed]
14. Etzel, R.A. How environmental exposures influence the development and exacerbation of asthma. Pediatrics 2003, 112, 233–239. [CrossRef] [PubMed]
15. Spann, K.; Snape, N.; Baturcam, E.; Fantino, E. The Impact of Early-Life Exposure to Air-borne Environmental Insults on the Function of the Airway Epithelium in Asthma. Ann. Glob. Health 2016, 82, 28–40. [CrossRef] [PubMed]
16. Bouazza, N.; Foissac, F.; Urien, S.; Guedj, R.; Carbajal, R.; Treluver, J.M.; Chappuy, H. Fine particulate pollution and asthma exacerbations. Arch. Dis. Child. 2018, 103, 828–831. [CrossRef] [PubMed]
17. Delfino, R.J.; Quintana, P.J.; Floro, J.; Gastanaga, V.M.; Samimi, B.S.; Kleinman, M.T.; Liu, L.J.; Bufalino, C.; Wu, C.F.; McLaren, C.E. Association of FEV1 in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. Environ. Health Perspect. 2004, 112, 932–941. [CrossRef] [PubMed]
18. Williams, A.M.; Planeuf, D.J.; Barrett, M.A.; Su, J.G. Short-term impact of PM2.5 on contemporaneous asthma medication use: Behavior and the value of pollution reductions. Proc. Natl. Acad. Sci. USA 2019, 116, 5246–5253. [CrossRef] [PubMed]
19. Habre, R.; Mosher, E.; Castro, W.; Nath, A.; Grunin, A.; Rohr, A.; Godbold, J.; Schachter, N.; Kattan, M.; Coull, B.; et al. The effects of PM2.5 and its components from indoor and outdoor sources on cough and wheeze symptoms in asthmatic children. J. Expo. Sci. Environ. Epidemiol. 2014, 24, 380–387. [CrossRef] [PubMed]
20. Bui, A.A.T.; Hosseini, A.; Rocchio, R.; Jacobs, N.; Ross, M.K.; Okelo, S.; Lurmann, F.; Eckel, S.; Dzubur, E.; Dunton, G.; et al. Biomedical REAI-Time Health Evaluation (BREATHE): Toward an mHealth informatics platform. JAMA Open 2020, 3, 190–200. [CrossRef] [PubMed]

21. Knudson, R.J.; Lebowitz, M.D.; Holberg, C.J.; Burrows, B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am. Rev. Respir. Dis. 1983, 127, 725–734. [CrossRef] [PubMed]

22. DuRavage, N.; Ross, M.; Mayne, S.L.; Suh, A.; Weng, D.; Grundmeier, R.W.; Fiks, A.G. Asthma Control Test. Clin. Pediatr. 2017, 56, 341–347. [CrossRef] [PubMed]

23. Alduchov, O.A. Improved Magnus Form Approximation of Saturation Vapor Pressure. J. Appl. Meteorology Climatol. 1996, 35, 601–609. [CrossRef]

24. Snyder, M.G.; Venkatram, A.; Heist, D.K.; Perry, S.G.; Petersen, W.B.; Isakov, V. RLINE: A line source dispersion model for near-surface releases. Atmos. Environ. 2013, 77, 748–756. [CrossRef] [PubMed]

25. Samoli, E.; Dimakopoulou, K.; Evangelopoulos, D.; Rodopoulou, S.; Karakatsani, A.; Veneti, L.; Sionidou, M.; Tsolakoglou, I.; Krasanaki, I.; Grivas, G.; et al. Is daily exposure to ozone associated with respiratory morbidity and lung function in a representative sample of schoolchildren? Results from a panel study in Greece. J. Expo. Sci. Environ. Epidemiol. 2017, 27, 346–351. [CrossRef] [PubMed]

26. Angelis, N.; Spyratos, D.; Domvri, K.; Dimakopoulou, K.; Samoli, E.; Kalamaras, G.; Karakatsani, A.; Grivas, G.; Katsouyanni, K.; Papakosta, D. Effect of Ambient Ozone Exposure Assessed by Individual Monitors on Nasal Function and Exhaled NO Among School Children in the Area of Thessaloniki, Greece. J. Occup. Environ. Med. 2017, 59, 505–515. [CrossRef] [PubMed]

27. Kopp, M.V.; Bohnet, W.; Frischer, T.; Ulmer, C.; Studnicka, M.; Horst, G.; Gardner, C.; Forster, J.; Urbanek, R.; Kuehr, J. Effects of ambient ozone on lung function in children over a two-summer period. Eur. Respir. J. 2000, 16, 893–900. [CrossRef] [PubMed]

28. Chang, Y.K.; Wu, C.C.; Lee, L.T.; Lin, R.S.; Yu, Y.H.; Chen, Y.C. The short-term effects of air pollution on adolescent lung function in Taiwan. Chemosphere 2012, 87, 26–30. [CrossRef] [PubMed]

29. Tager, I.B.; Balmes, J.; Lurmann, F.; Ngo, L.; Alcorn, S.; Kunzli, N. Chronic exposure to ambient ozone and lung function in young adults. Epidemiology 2005, 16, 751–759. [CrossRef] [PubMed]

30. Geyh, A.S.; Xue, J.; Ozkaynak, H.; Spengler, J.D. The Harvard Southern California Chronic Ozone Exposure Study: Assessing ozone exposure of grade-school-age children in two Southern California communities. Environ. Health Perspect. 2000, 108, 265–270. [CrossRef] [PubMed]

31. World Health Organization. Review of Evidence on Health Aspects of Air Pollution—REVIHAAP Project: Technical Report; World Health Organization: Geneva, Switzerland, 2013.

32. Bell, M.L.; Zanobetti, A.; Dominici, F. Who is more affected by ozone pollution? A systematic review and meta-analysis. Am. J. Epinemiol. 2014, 180, 15–28. [CrossRef] [PubMed]

33. Chen, C.; Arjomandi, M.; Tager, I.B.; Holland, N.; Balmes, J.R. Effects of antioxidant enzyme polymorphisms on ozone-induced lung function changes. Eur. Respir. J. 2007, 30, 677–683. [CrossRef] [PubMed]

34. Kelly, F.J. Dietary antioxidants and environmental stress. Proc. Nutr. Soc. 2004, 63, 579–585. [CrossRef] [PubMed]

35. Mudway, I.S.; Kelly, F.J. Ozone and the lung: A sensitive issue. Mol. Asp. Med. 2000, 21, 1–48. [CrossRef]

36. Steerenberg, P.A.; Nierkens, S.; Fischer, P.H.; van Loveren, H.; Opperhuizen, A.; Vos, J.G.; van Amsterdam, J.G. Traffic-related air pollution affects peak expiratory flow, exhaled nitric oxide, and inflammatory nasal markers. Arch. Environ. Health 2001, 56, 167–174. [CrossRef] [PubMed]

37. Holm, S.M.; Balmes, J.R. Systematic Review of Ozone Effects on Human Lung Function, 2013 Through 2020. Chest 2022, 161, 190–201. [CrossRef] [PubMed]

38. Lurmann, F.; Avol, E.; Gilliland, F. Emissions reduction policies and recent trends in Southern California’s ambient air quality. J. Air Waste Manag. Assoc. 2015, 65, 324–335. [CrossRef] [PubMed]

39. Li, S.; Williams, G.; Jalaludin, B.; Baker, P. Panel studies of air pollution on children’s lung function and respiratory symptoms: A literature review. J. Asthma 2012, 49, 895–910. [CrossRef] [PubMed]

40. Steerenberg, P.A.; Nierkens, S.; Fischer, P.H.; van Loveren, H.; Opperhuizen, A.; Vos, J.G.; van Amsterdam, J.G. Traffic-related air pollution affects peak expiratory flow, exhaled nitric oxide, and inflammatory nasal markers. Arch. Environ. Health 2001, 56, 167–174. [CrossRef] [PubMed]

41. See, S.W.; Balasubramanian, R. Chemical characteristics of fine particles emitted from different gas cooking methods. Atmos. Environ. 2008, 42, 8852–8862. [CrossRef]

42. Schildcrout, J.S.; Sheppard, L.; Lumley, T.; Slaughter, J.C.; Koenig, J.Q.; Shapiro, G.G. Ambient air pollution and asthma exacerbations in children: An eight-city analysis. Am. J. Epidemiol. 2006, 164, 505–517. [CrossRef]

43. Pepper, J.R.; Barrett, M.A.; Su, J.G.; Merchant, R.; Henderson, K.; Van Sickle, D.; Balmes, J.R. Geospatial-temporal analysis of the impact of ozone on asthma rescue inhaler use. Environ. Int. 2020, 136, 105331. [CrossRef] [PubMed]

44. Guarnieri, M.; Balmes, J.R. Outdoor air pollution and asthma. Lancet 2014, 383, 1581–1592. [CrossRef]

45. Mar, T.F.; Larson, T.V.; Stier, R.A.; Claiborn, C.; Koenig, J.Q. An analysis of the association between respiratory symptoms in subjects with asthma and daily air pollution in Spokane, Washington. Inhal. Toxicol. 2004, 16, 809–815. [CrossRef] [PubMed]

46. Esposito, S.; Galeone, C.; Lelii, M.; Longhi, B.; Ascolese, B.; Senatore, L.; Prada, E.; Montinaro, V.; Malerba, S.; Patria, M.E.; et al. Impact of air pollution on respiratory diseases in children with recurrent wheezing or asthma. BMC Pulm. Med. 2014, 14, 130. [CrossRef] [PubMed]
47. Timonen, K.L.; Pekkanen, J. Air pollution and respiratory health among children with asthmatic or cough symptoms. *Am. J. Respir. Crit. Care Med.* 1997, 156, 546–552. [CrossRef]

48. Jalaludin, B.B.; O’Toole, B.I.; Leeder, S.R. Acute effects of urban ambient air pollution on respiratory symptoms, asthma medication use, and doctor visits for asthma in a cohort of Australian children. *Environ. Res.* 2004, 95, 32–42. [CrossRef]

49. Williams, R.; Duvall, R.; Kilaru, V.; Hagler, G.; Hassinger, L.; Benedict, K.; Rice, J.; Kaufman, A.; Judge, R.; Pierce, G.; et al. Deliberating performance targets workshop: Potential paths for emerging PM2.5 and O3 air sensor progress. *Atmos. Environ. X* 2019, 2, 100031. [CrossRef]