Neha Solanki MD1 | David Bruckman MS2 | Xiaofeng Wang PhD1 | Anne Tang MS2 | Amy Attaway MD1 | Sumita Khatri MD1

1Cleveland Clinic Respiratory Institute, Cleveland, Ohio, USA
2Cleveland Clinic Center for Populations Health Research, Lerner Research Institute, Cleveland, Ohio, USA

Correspondence
Neha Solanki, MD, Cleveland Clinic Respiratory Institute, 9500 Euclid Ave, Cleveland, OH 44195, USA.
Email: neha.solanki@gmail.com

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Abstract
Rationale: Efforts to reduce nitrogen dioxide (NO2) have the potential to reduce the morbidity and mortality related to asthma in children. We analyze the associations of pediatric hospital admission rates for asthma with Environmental Protection Agency (EPA) NO2 parameters at the patient zip code level.

Methods: We identified zip codes that had EPA monitors which monitored NO2 levels located in states with high asthma burden. We used the Healthcare Cost and Utilization Project (HCUP) State Inpatient Database (SID) to identify patients who were <17 years of age with diagnosis codes for asthma. We compared NO2 levels at the zip code level with the number of patients hospitalized for asthma from the HCUP SID database.

Results: Data from zip codes in Buffalo, Detroit, Phoenix, and Tucson from 2009 to 2011 demonstrated that the monthly mean NO2 levels predicted pediatric asthma hospital admission rates in six monitored zip codes in these four cities with time series modeling (Buffalo zip code 14206, p = 0.0089; Detroit zip code 48205, p = 0.0179; Phoenix zip code 85006, p = 0.0433; Phoenix zip code 85009, p = 0.0007; Phoenix zip code 85015, p = 0.0036; Tucson zip code 85711, p = 0.0004).

Conclusion: Pediatric admissions to the hospital for asthma exacerbations mirror the cyclic and seasonal pattern of NO2 levels in the cities of Detroit, Buffalo, Phoenix, and Tucson. While traffic density may be higher in cities with periodicity of NO2 and asthma exacerbations, other factors could be contributing to high NO2 levels.

KEYWORDS
asthma & early wheeze, environmental lung disease, pulmonology (general)
1 | INTRODUCTION

Asthma is a chronic lung disease that affects millions of lives in the United States, with certain areas of the country more affected than others. These areas are known as Asthma Capitals by the Asthma and Allergy Foundation of America (AAFA). Pollution is known to play a key role in the onset and severity of asthma, especially in the Asthma Capitals. Traffic-related air pollution (TRAP), composed of toxic gases and particles which include nitrogen dioxide (NO2), is known to significantly increase the odds of asthma related emergency department visits. The Clean Air Act, a comprehensive federal law that regulates air emissions, authorizes the Environmental Protection Agency (EPA) to establish National Ambient Air Quality Standards (NAAQS) to protect public health and public welfare and to regulate the emissions of hazardous air pollutants such as NO2 in high-risk areas. Currently, per the EPA, the NAAQS for NO2 is annually 53 parts per billion (ppb). Zip codes in the Asthma Capitals have NO2 levels below this level of 53 ppb, but the levels recorded may still be high enough to impact asthma control. Despite the NAAQS, TRAP, consisting of NO2, continues to significantly increase the odds of asthma related emergency department visits. Therefore, the current NO2 regulations are not strict enough to improve pediatric asthma health.

Previous studies have demonstrated that NO2 is a significant risk factor for asthma exacerbations in the pediatric population. NO2 plays an important role in asthma development, and there are longitudinal studies evaluating the relationship between early childhood exposure to NO2 and future asthma development. In fact, early exposures to NO2 are associated with a higher incidence of asthma until 20 years of age. However, the pattern of NO2 emissions and its relationship to asthma exacerbations in key urban areas with high asthma burden remain unknown. Though zip codes are known to vary in their emissions, the EPA reports its US air quality index data collected from air pollution monitors at the zip code level for urban regions that are known to have high levels of air pollution. Practically, we investigate the pattern of NO2 exposure at these zip codes because these are the zip codes that are of importance to the EPA. Understanding the exact interplay between nitrogen oxide levels and the incidence of asthma could help determine whether stronger regulations on air pollution levels are needed to benefit the pediatric asthma population.

Our study aimed to investigate the associations between pediatric hospital admission rates (primary outcome) for asthma and NO2 at the patient zip code and city level utilizing a time-series analysis of monthly admission rates and NO2. We hypothesized that higher levels of NO2 may be associated with increased risk for pediatric hospital admission rates for asthma and bronchiolitis.

2 | METHODS

The National Inpatient Sample (NIS) is a database maintained through the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ) which can be accessed at organizations can be found at http://www.hcup-us.ahrq.gov/db/hcupdatapartners.jsp. NIS data are available from HCUP, AHRQ, Rockville, MD (https://www.hcup-us.ahrq.gov/). Data are available to all researchers following a standard application process and signing of a data use agreement (DUAs). The authors confirm that they had no special access to the data used in this study (2002–2014 data from the HCUP NIS). The authors paid a fee to access the NIS data used in this study, with a fee schedule in accordance with the HCUP Central Distributor, the entity that accepts, processes, and fulfills applications for the purchase of HCUP databases, and manages DUAs for all data users (https://www.distributor.hcup-us.ahrq.gov/). Future researchers interested in purchasing and using HCUP databases will be required to complete the web-based HCUP DUA training (https://www.hcup-us.ahrq.gov/tech_assist-dua.jsp). Further instructions for submitting an application for purchasing HCUP databases can be found at https://www.distributor.hcup-us.ahrq.gov/. The NIS consists of data from approximately 8 million hospitalizations per year at approximately 1000 US community hospitals. NIS data include a sample of 20% of hospitalizations in the United States and are weighted statistically to provide nationwide estimates to assist in demographic calculations. Our retrospective observational study included data sources from the HCUP State Inpatient Database (SID) encompassing 2009–2011, EPA data on NO2 for states during the same time frame, US census tables, as well as AAFA Asthma Capitals Lists from 2015 to 2018 accessed at https://www.aafa.org/asthma-capitals/.

Eleven cities in five states were selected based on Asthma Capitals lists cited by the AAFA spanning the years 2015 through 2018. In these cities, we identified zip codes where NO2 levels were already recorded by EPA monitors. The selected cities included the following: New York City, Albany, Rochester, and Buffalo, NY; Phoenix and Tucson, AZ; Detroit and Grand Rapids, MI; Jefferson County/Louisville, KY; Seattle and Spokane, WA. Once these locations with monitored NO2 levels were identified, we then matched them to our available hospital data (HCUP-SID) to identify emergency department visits and hospitalizations for people with asthma. Admissions from HCUP-SID were defined as any inpatient admission of a person 17 years of age or under who had a primary ICD-9-CM diagnosis code of 493.XX (asthma) or 466.19 (bronchiolitis). These state-level data also included month of discharge and patient zip code, parameters necessary for this analysis.

Monthly averages of NO2 were calculated at the monitoring EPA site level, zip code, and city levels. Zip code lists per city were determined using US Postal Service listings at https://www.unitedstateszipcodes.org/. To control for the demographics, we used US census tables for 2010 using American Fact Finder web application, https://factfinder.census.gov/, which provided age-specific population denominators per zip code. SID data for Rochester, NY were excluded from data analysis due to the small admission numbers identified based on HCUP data reporting rules found at https://www.hcup-us.ahrq.gov/.

The main outcome evaluated in this study was the monthly mean rates of primary asthma admission per 10,000 population,
age-adjusted at the zip code level per city. In the EPA monitored zip codes, pollution measures were averaged to the month to determine associations between air pollution parameters and discharge rates. Only the month of discharge is available from the SID public use files, so monthly discharge rates adjusted for the census population were calculated which allowed us to interpret patterns at this scale. Please refer to Supporting Information: appendix for a table of asthma admission rates from HCUP SID files and monthly mean NO2 levels measured by EPA monitor for a particular zip code. Admission counts <11 are suppressed following the HCUP DUAs.

Locally weighted scatterplot smooth or LOESS regression was used to illustrate periodic or segmented linear trends in monthly mean admission rates and NO2 levels. LOESS regression makes use of least squares regression analysis to find the best fit curve for a set of points. Each point of data represents a relationship between a known independent and an unknown dependent variable. Please refer to the Supporting Information: appendix for more information regarding the SAS procedures used for analysis.

Time series modeling, a collection of observations sequentially in time with equal intervals of time between observations, was then used to determine the relationship between the monthly averages of NO2 and exacerbations of asthma among pediatric patients requiring hospital admission in select zip codes where EPA monitoring occurs. Zip codes included had at least 13 months of monthly data. See Supporting Information: appendix for more statistical modeling analysis.

In this study, spectral analysis was used to test whether observed periodicity or cyclic behavior in either admission rate or NO2 levels were significant. Spectral analysis is a method used with time series that separates out periodic components in a noisy environment. To perform a robust analysis, spectral analysis was limited to those zip codes having at least 27 months of admission and NO2 data.

To conclude the methods, an autoregressive model was used on the data. This type of model attempts to predict the future signal (forecasting) based on the prior signal. Maximum likelihood estimation, a method of estimating the probability of distribution under a statistical model, was used to determine model coefficients and significance. Time series and general linear models were compared within each zip code to determine which was most appropriate and robust, while also using Akaike informational criterion (AIC), minimal mean squared error, and highest R2. The AIC method finds the highest goodness of fit model so that the time series and general linear models can be compared. Minimal mean squared error is the average squared difference between the estimate value and the actual value, with values closest to zero signifying a stronger model.

### RESULTS

#### 3.1 Hospitalization rates and utilization of HCUP-SID data

In the 1643 zip codes located in 10 cities that were initially identified, we identified 41,483 pediatric hospitalizations of which 6310 admissions (15.2% of all admissions for asthma) were among patients in 62 zip codes colocated with EPA monitors. Table 1 demonstrates that Phoenix (n = 13), Tucson (n = 15), and New York City (n = 11) are represented.

| Factor City          | Total (N = 41,483) Admissions | Not in an EPA-monitored zip code (N = 35,173) Admissions | In a monitored zip code (N = 6310) Admissions | Zip codes |
|----------------------|-------------------------------|----------------------------------------------------------|---------------------------------------------|-----------|
| Albany               | 275 (0.66)                    | 229 (0.65)                                               | 46 (0.73)                                   | 2         |
| Buffalo              | 1495 (3.6)                    | 1357 (3.9)                                               | 138 (2.2)                                   | 3         |
| Detroit              | 3170 (7.6)                    | 2368 (6.7)                                               | 802 (12.7)                                  | 8         |
| Grand Rapids         | 488 (1.2)                     | 428 (1.2)                                                | 60 (0.95)                                   | 1         |
| Jefferson County     | 2430 (5.9)                    | 1805 (5.1)                                               | 625 (9.9)                                   | 6         |
| New York             | 25,051 (60.4)                 | 22,924 (65.2)                                            | 2127 (33.7)                                 | 11        |
| Phoenix              | 5732 (13.8)                   | 4209 (12.0)                                              | 1523 (24.1)                                 | 13        |
| Seattle              | 1071 (2.6)                    | 1010 (2.9)                                               | 61 (0.97)                                   | 1         |
| Spokane              | 449 (1.1)                     | 352 (1.0)                                                | 97 (1.5)                                    | 2         |
| Tucson               | 1322 (3.2)                    | 491 (1.4)                                                | 831 (13.2)                                  | 15        |
| Totals               | 41,483                        | 35,173 (84.8)                                            | 6310 (15.2)                                 | 62        |

Note: Statistics presented as N (column %). For admissions in a monitored zip code, statistics are N (column %) (row %). Data are not available for all subjects. Missing values: CITY = 35,173. Data for Rochester were removed due to suppression of admissions in one monitored zip code.

Abbreviation: EPA, Environmental Protection Agency.
were cities with the largest number of zip codes with EPA monitors. Table 2 categorizes asthma admissions in zip codes with EPA monitors. Age was similar when comparing zip codes with and without EPA monitors, although length of stay and healthcare charges were higher in the EPA-monitored zip codes. Table 3 demonstrates the demographics of children evaluated in the study; patients did not differ in mean age, sex categories, or disposition. More admissions among White and Hispanic pediatric populations than Black/African American patients were observed in the patient zip codes colocated with EPA monitors.

3.2 | Descriptive analysis of rate of hospitalizations for asthma exacerbations and NO₂ dynamics at EPA monitors

Figure 1, consisting of two panels, illustrates modeling of monthly NO₂ levels for the 11 of the 14 zip codes organized by city and also modeling of the monthly asthma admission rates by city. Zip codes with admission counts <11 are suppressed following the HCUP DUAs. Both panels of Figure 1 make use of LOESS regression and find that for most zip codes, NO₂ levels and the rate of asthma admissions by month follow a predictable cyclic pattern by zip code demonstrating maxima in between November through February of each year which have corresponding shaded areas seen in the imaging.

3.3 | Correlating hospitalization rates for asthma with NO₂ levels: Time series analysis and linear modeling

Of the 14 zip codes in five cities, 10 zip codes had at least 18 months of data and underwent time-series modeling. Six zip codes revealed adequate evidence that monthly mean NO₂ levels statistically predicted mean asthma admission rates over the 3 year study period (Table 4). Three zip codes in Phoenix demonstrated that NO₂ was positively associated \( (p = 0.04, 2 \text{ others } p < 0.004) \) with monthly asthma rate. Model \( R² \) were modest for the three models \( (R² \text{ range } = 0.297−0.538) \), the highest denoting that nearly 54% of the variation in the data was explained by the model. One zip code in Tucson demonstrated that NO₂ was positively associated \( (p = 0.0004, R² = 0.41) \) with monthly asthma rate, adjusted for first-order (Table 4). One of the 6 zip codes demonstrated a negative association with monthly mean admission rates. For zip code 48205 in Detroit,
The monthly mean NO2 level decreased the mean monthly rates by 0.543 (coefficient = −0.543, p < 0.0179). The model showed good prediction having over 64% of the data variation explained by the model (R² = 0.64) when a 12 month lag to the autocorrelation in admission rates was found to be most optimal (Table 4).

Figure 2A–H demonstrates the cyclical and seasonal pattern of NO2 levels in green which is closely correlated to the pediatric asthma admission rates in red for the 6 zip codes.

| TABLE 3 | Asthma admissions in selected cities among those living in EPA monitored and nonmonitored zip codes |
|-----------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Factor                      | Total (N = 41,483)                              | Not in an EPA-monitored zip code (N = 35,173)   | In an EPA-monitored zip code (N = 6310)         | p Value |
| Race (uniform)a             |                                                 |                                                 |                                                 | <0.001c |
| White                       | 6849 (17.0)                                     | 5527 (16.1)                                     | 1322 (21.5)                                     |         |
| Black                       | 15,992 (39.6)                                   | 14,046 (41.0)                                   | 1946 (31.6)                                     |         |
| Hispanic                    | 13,092 (32.4)                                   | 10,797 (31.5)                                   | 2295 (37.3)                                     |         |
| Asian/Pacific Islander      | 1147 (2.8)                                      | 1054 (3.1)                                      | 93 (1.5)                                        |         |
| Native American             | 344 (0.85)                                      | 230 (0.67)                                      | 114 (1.9)                                       |         |
| Other                       | 2968 (7.3)                                      | 2583 (7.5)                                      | 385 (6.3)                                       |         |
| Sex and age group           |                                                 |                                                 |                                                 | 0.33d   |
| Female (year)               |                                                 |                                                 |                                                 |         |
| 0–4                         | 9416 (22.7)                                     | 7968 (22.7)                                     | 1448 (22.9)                                     |         |
| 5–9                         | 3481 (8.4)                                      | 2966 (8.4)                                      | 515 (8.2)                                       |         |
| 10–14                       | 2010 (4.8)                                      | 1726 (4.9)                                      | 284 (4.5)                                       |         |
| 15–17                       | 932 (2.2)                                       | 801 (2.3)                                       | 131 (2.1)                                       |         |
| Male (year)                 |                                                 |                                                 |                                                 |         |
| 0–4                         | 16,298 (39.3)                                   | 13,818 (39.3)                                   | 2480 (39.3)                                     |         |
| 5–9                         | 5494 (13.2)                                     | 4684 (13.3)                                     | 810 (12.8)                                      |         |
| 10–14                       | 3005 (7.2)                                      | 2518 (7.2)                                      | 487 (7.7)                                       |         |
| 15–17                       | 847 (2.0)                                       | 692 (2.0)                                       | 155 (2.5)                                       |         |

Note: Statistics presented as N (column %).
Abbreviation: EPA, Environmental Protection Agency.
p Values: b, Wilcoxon rank sum test; c, Pearson’s χ² test; d, Fisher’s exact test.
aData are not available for all subjects. Missing values: Hispanic ethnicity (as received from source) = 7063; Race (uniform) = 1091.

4 | DISCUSSION

Our retrospective observational study demonstrates a novel methodology that uncovers cyclical and seasonal correlations between the rate of hospitalizations for asthma and NO2 levels in multiple urban zip codes across the United States. Time-series analysis with 6 zip codes that have at least 24 months of data demonstrated a significant (p < 0.05) cyclical association between NO2 levels and asthma exacerbations. Furthermore, we believe that based on the pattern that we have uncovered, it may be possible to forecast which urban areas are more likely to have higher rates of hospitalizations for asthma based upon their recorded levels of NO2 by zip codes. The earlier the at-risk population is identified, the sooner each individual with asthma can be referred to appropriate care and avoid the emergency department altogether. This would result in decreased healthcare dollars spent for pediatric asthma care. In fact, in cities such as Detroit, which houses the 48205 zip code, NO2 levels have only increased between 2016 and 2022, though still staying below the EPA guidelines. This differential in asthma prevalence between Detroit and the rest of Michigan did not exist in 2016. The conclusion is that the current EPA guidelines for NO2 levels are not strict enough to reduce or even maintain the rate of asthma exacerbations in certain urban regions. This study supports more stringent EPA monitoring of NO2 as it is predictive of asthma exacerbations requiring pediatric hospitalizations in the major cities studied. Our findings are novel highlight the need greater regulation of NO2 levels in certain urban locations.

In Phoenix and Tucson, the 4 zip codes we analyzed demonstrated a cyclic and seasonal pattern for NO2 which is strongly associated with the asthma exacerbations in those zip codes. We demonstrate the same pattern in the Buffalo zip code of 14206 and Detroit at the zip code of 48205. Interestingly, all 6 zip...
codes demonstrated a significant cyclical/seasonal relationship between hospital admissions for asthma and NO2 levels. In contrast, for hospitalizations for asthma in Detroit at zip code 48205, there is a negative correlation with NO2 levels which may be due to regional weather and traffic patterns for that particular zip code. Our data demonstrates that the peaks of asthma exacerbation are related to peaks in NO2 levels and occur mainly in the cold season. This finding supports a mechanism where NO2 could be contributory to an asthma exacerbation in an individual. There is a biological plausibility for NO2 as a cause of asthma exacerbations which is supported by animal models. Additionally, NO2 induces an inflammatory response in people with asthma. Even in healthy individuals, NO2 can exert an allergic effect on bronchial epithelium by upregulating ICAM-1 which is a major receptor for rhinovirus and respiratory syncytial viruses. Therefore, in the cold season, exogenous NO2 likely upregulate ICAM-1 in the bronchial epithelium in people with asthma causing a spike in acute asthma exacerbations. Children ages 2–18 also have a greater and faster
response to NO2 leading to emergency department visits for asthma exacerbations.\textsuperscript{16}

Our data also demonstrate that there are certain zip codes in Buffalo, Detroit, and Tucson, such as Tucson’s 85711, that have admission rates that do not demonstrate cyclicity in hospital admission for asthma while the zip code’s corresponding NO2 levels are demonstrated to be cyclical. One reason for the lack of cyclicity in the rate of asthma exacerbations in zip codes such as 85711 may be secondary to the census having less of a pediatric population to track. Zip code 85711 has over 10% less children compared to zip code 85006 which is also in Arizona. Unlike zip code 85711, zip code 85006 demonstrates cyclical/seasonal relationship for NO2 levels and pediatric asthma exacerbations. Additionally, zip code 85711 mostly has housing that was built after the 1950s, which means that their homes may have better insulation year-round compared to the homes in zip code 85006 which were mostly built before the 1950s. Better home insulation may be a protective factor against allergens and viruses from the exterior. Furthermore, zip code 85711 also is home to more high school graduates than 85006, so it is possible that the residents of this zip codes are better able to seek medical care earlier and less likely to have to go to the urgent care or ED for medical treatment for asthma. A separate analysis will need to take place to develop a deeper understanding as to why some zip codes show cyclic and seasonal patterns where other zip does do not.

Our findings are consistent with and also add to the important body of literature analyzing time-series studies of NO2 exposure and outcomes related to respiratory diagnoses. The strengths of this study include a robust population analysis with fully replicable and transparent methods. Additionally, we used the EPA reported monthly averages of NO2 instead of daily exposures averages in our study which are less impacted by the lag between exposure and admission, as previously noted. Adjusting for the lag between NO2 and exposure, Mills et al.\textsuperscript{17} conducted a quantitative systematic review of short term exposure to NO2 and its associations with mortality and hospital admissions for a wide range of respiratory conditions. Even using lag time, Mills et al found positive associations between 24 h NO2 and admission to the hospital for respiratory diseases.\textsuperscript{17} While our findings are consistent with these analyses, our study is unique because we have specifically examined asthma exacerbations where a person with asthma resides instead of where he or she is hospitalized, and we have demonstrated a novel cyclic pattern between hospitalizations for asthma exacerbations and NO2 levels.

One limitation of our study is the potential for unequal distribution of EPA monitors among zip codes. Zip codes were the lowest geographic units available to both HCUP SID and EPA Air Quality System data. Not all zip codes have EPA monitors, and some zip codes have several EPA monitors where others may have only one. Oftentimes, these monitors are placed in urban areas of known pollution but in locations that capture the influence of multiple pollution sources that may affect health.\textsuperscript{18} Therefore, it is difficult to study and compare NO2 levels in all regions due to lack of EPA monitoring. In the future, satellite data could be used to monitor NO2 levels by region instead of EPA monitors. A second limitation is that certain races (including Whites and Hispanics) were more likely to be included in EPA monitored zip codes as compared to the general population of the United States, although other important demographic features such as age and sex were similar between the monitored and nonmonitored cohorts. Finally, given our study is based on billing codes, certain confounders are not captured in the queried databases including indoor air pollution.

\textbf{5 | CONCLUSION}

In our retrospective analysis integrating databases from HCUP and the EPA, NO2 levels were significantly associated with an increased risk for asthma exacerbation. We found a cyclical and seasonal
pattern to NO₂ levels that correlated to the rate of hospital admissions for asthma. While future studies are needed in additional zip codes to replicate our results, our study can inform policy-making decisions and regulatory efforts to reduce air pollution across the United States. Given the strong correlation between asthma exacerbations and NO₂ levels in the pediatric population in certain urban locations even at NO₂ levels under EPA NAAQS guidelines, we advocate for lower and stricter cutoffs for NO₂ levels in the United States.

AUTHOR CONTRIBUTIONS
Neha Solanki: conceptualization, funding acquisition, investigation, methodology, project administration, visualization, writing original draft, writing–review and editing. David Bruckman: data curation, formal analysis, methodology, resources, writing–review and editing. Amy Attaway: data curation, formal analysis. Xiaofeng Wang: validation. Sumita Khatri: conceptualization, investigation, methodology, supervision, writing–review and editing.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
NIS data are available from HCUP, AHRQ, Rockville, MD (https://www.hcup-us.ahrq.gov/). Data are available to all researchers following a standard application process and signing of a data use agreement. The authors confirm that they had no special access to the data used in this study (2002–2014 data from the Healthcare Cost and Utilization Project’s National Inpatient Sample [NIS]). The authors paid a fee to access the NIS data used in this study, with a fee schedule in accordance with the HCUP Central Distributor, the entity that accepts, processes, and manages data use agreements (DUAs) for all data users (https://www.distributor.hcup-us.ahrq.gov/). Future researchers interested in purchasing and using HCUP databases will be required to complete the Web-based HCUP Data Use Agreement (DUA) Training (https://www.hcup-us.ahrq.gov/tech_assist/dua.jsp). Further instructions for submitting an application for purchasing HCUP Databases can be found at https://www.distributor.hcup-us.ahrq.gov/.

ORCID
Neha Solanki http://orcid.org/0000-0002-9078-2952

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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