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Aerosolized Red-Tide Toxins (Brevetoxins) and Asthma

Lora E. Fleming, MD, PhD, MPH, MSc, Barbara Kirkpatrick, EdD, Lorraine C. Backer, PhD, MPH, Judy A. Bean, PhD, Adam Wanner, MD, FCCP, Andrew Reich, MS, Julia Zaias, DVM, PhD, Yung Sung Cheng, PhD, Richard Pierce, PhD, Jerome Naar, PhD, William M. Abraham, PhD, and Daniel G. Baden, PhD

National Institute of Environmental Health Sciences Marine and Freshwater Biomedical Sciences Center (Drs. Fleming, Zaias, and Abraham), Rosenstiel School of Marine and Atmospheric Sciences, and School of Medicine (Dr. Wanner), University of Miami, Miami, FL; Mote Marine Laboratory (Drs. Kirkpatrick and Pierce), Sarasota, FL; National Center for Environmental Health (Dr. Backer), Centers for Disease Control and Prevention, Atlanta, GA; Children's Hospital Medical Center and University of Cincinnati (Dr. Bean), Cincinnati, OH; Florida Department of Health (Mr. Reich), Tallahassee, FL; Lovelace Respiratory Research Institute (Dr. Cheng), Albuquerque, NM; and the Center for Marine Science Research (Drs. Naar and Baden), University of North Carolina at Wilmington, Wilmington, NC

Abstract

Background—With the increasing incidence of asthma, there is increasing concern over environmental exposures that may trigger asthma exacerbations. Blooms of the marine microalgae, *Karenia brevis*, cause red tides (or *harmful algal blooms*) annually throughout the Gulf of Mexico. *K brevis* produces highly potent natural polyether toxins, called *brevetoxins*, which are sodium channel blockers, and possibly histamine activators. In experimental animals, brevetoxins cause significant bronchoconstriction. In humans, a significant increase in self-reported respiratory symptoms has been described after recreational and occupational exposures to Florida red-tide aerosols, particularly among individuals with asthma.

Methods—Before and after 1 h spent on beaches with and without an active *K brevis* red-tide exposure, 97 persons \geq 12 years of age with physician-diagnosed asthma were evaluated by questionnaire and spirometry. Concomitant environmental monitoring, water and air sampling, and personal monitoring for brevetoxins were performed.

Results—Participants were significantly more likely to report respiratory symptoms after *K brevis* red-tide aerosol exposure than before exposure. Participants demonstrated small, but statistically significant, decreases in FEV₁, midexpiratory phase of forced expiratory flow, and peak expiratory flow after exposure, particularly among those participants regularly using asthma medications. No significant differences were detected when there was no Florida red tide (*ie*, during nonexposure periods).

Conclusions—This study demonstrated objectively measurable adverse changes in lung function from exposure to aerosolized Florida red-tide toxins in asthmatic subjects, particularly among those requiring regular therapy with asthma medications. Future studies will assess these susceptible subpopulations in more depth, as well as the possible long-term effects of these toxins.

Correspondence to: Lora E. Fleming, MD, PhD, MPH, MSc, c/o Department of Epidemiology & Public Health, University of Miami School of Medicine, 1801 NW Ninth Ave, Highland Professional Building, Suite 200 (R 669), Miami, FL 33136; e-mail: lfleming@med.miami.edu.

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Keywords

asthma; brevetoxins; harmful algal blooms; *Karenia brevis*; red tides; sensitive populations; spirometry

Asthma in the United States affects 10.6% of noninstitutionalized adults and 12.5% of children.¹ Asthma is a major health disorder causing asthmatic children to miss 14 million school days per year.² In 2002, asthma health-care costs totaled \$14 billion (in US dollars).³ A range of environmental exposures (from air pollution to cockroach antigen) is associated with this asthma epidemic.^{2,4} Frequent Florida red-tide events in the Gulf of Mexico present a unique environmental exposure for persons with asthma who live or work near the shore. Our research in animals and humans suggests that persons with asthma (including children) may be more sensitive to the aerosols of these red tides.^{5–8}

Red tides, an annual events in the heavily populated Gulf of Mexico, are blooms of the marine dinoflagellate *Karenia brevis*.^{9,10} The blooms, often lasting for months, can span the Florida coastline, and have been reported in Mexico and on the North Carolina coast. The highly potent natural polyether toxins of *K brevis*, known as *brevetoxins*, activate voltage-sensitive sodium channels and possibly act as histamine activators. More than 12 brevetoxins have been identified. Studies^{7,8,11,12} in experimental animals have shown that brevetoxins can cause respiratory irritation and bronchoconstriction. In humans, brevetoxins produced during *K brevis* red tides can cause both neurotoxic shellfish poisoning, which is an acute gastroenteritis with neurologic symptoms occurring after the ingestion of contaminated shellfish, and upper respiratory distress after the inhalation of the red-tide brevetoxin aerosols.^{5,6,12–22} Persons with asthma may be particularly sensitive to adverse health effects from these aerosolized toxins.^{5,6,10,23}

Respiratory effects from exposure to aerosolized *K brevis* red tides and from pure brevetoxins have been reported in experimental animals.^{7,8,11} In an experimental asthma sheep model, inhalation challenge with aerosolized red tide (as well as pure brevetoxins) at doses less than or equal to those experienced by humans inhaling *K brevis* red-tide aerosols on beaches caused a significant and rapid increase in airway resistance.^{7,8} This brevetoxin-induced bronchospasm was effectively blocked by atropine, the mast cell-stabilizing agent cromolyn, the histamine H₁ antagonist chlorpheniramine, and the β_2 -agonist albuterol.^{7,8} Furthermore, although the acute bronchoconstrictor effects of inhaled brevetoxins can be seen in both asthmatic and normal sheep, the response is more severe in the asthmatic subgroup with previously inflamed lungs due to a recently induced asthma exacerbation.⁷

Human exposure to aerosolized Florida red-tide toxins occurs on or near beaches during an active *K brevis* bloom with onshore winds and surf, which breaks up the cells and releases toxins into the water, creating onshore aerosols.²⁴ Brevetoxin concentrations in the aerosols ranging from < 0.5 to 108 ng/m³ have been measured during *K brevis* red-tide episodes associated with reported respiratory symptoms in humans.^{5,6,20,21,25–27} With a mass median aerodynamic diameter of 7 to 9 μm , > 90% of the particulate is believed to be deposited in the nose; however, very fine respirable particulates of red-tide brevetoxin aerosol < 2.5 μm in size have been measured.

In humans, the inhalation of aerosolized *K brevis* red-tide toxins results in conjunctival irritation, rhinorrhea, nonproductive cough, and wheezing.^{10,12,15,19,22,28} In the population of healthy individuals, there is reportedly rapid reversal of these symptoms by leaving beach areas or entering an air-conditioned area.^{9,19,20,29} Asthmatic persons appear to be more susceptible to *K brevis* red-tide aerosols.^{5,6} This study further evaluated the exposures and

effects of aerosolized red-tide brevetoxins in 97 asthmatic subjects after 1-h exposure to *K brevis* red tides and after 1-h nonexposure at the beach.

Materials and Methods

This study was part of the ongoing evaluation of aerosolized *K brevis* red-tide brevetoxin exposure, and the possible acute and chronic adverse health effects of brevetoxins in humans and animals by an interdisciplinary team of researchers from federal, state, private, and local organizations.⁵ These studies have been approved by the participating institutional review boards. The study location was Siesta Beach (Sarasota, FL), where prolonged Florida red tides lasting months have become an almost annual event.

Asthmatic participants were defined as follows: (1) self-reported diagnosis by a physician; (2) age ≥ 12 years; (3) smoking history of ≤ 10 years; (4) ability to walk for ≥ 30 min continually on the beach; and (5) resident of the Sarasota area for ≥ 6 months. They were asked to spend ≥ 1 h at the beach in areas with ongoing environmental monitoring; they could return at any time from the beach if they felt symptomatic, and all participants were encouraged to use any personal medications as needed throughout the study period.⁶

Each asthmatic subject participated in at least one evaluation during an active *K brevis* bloom (*ie*, the exposure period), and in one evaluation during a period when there was not a bloom (*ie*, the nonexposure period). Both evaluations included the following before and after the beach visit: questionnaires, nasal swab sampling, and spirometry. Study participants were asked to carry a personal air monitor while at the beach. Detailed baseline information was collected for all subjects (including their medical history and possible confounders) in a baseline questionnaire, while a questionnaire administered before and after beach visits collected information on recent medical history and medication use as well as symptoms and possible confounders (*eg*, smoking).⁶

Since active *K brevis* bloom aerosols have been measured ≥ 1 mile inshore from the coast,²³ coastal residence was defined as residence on a barrier island or along Sarasota Bay. The use of asthma medications within 12 h before going to the beach was used as a surrogate for increased asthma severity.

Study personnel who were trained according to National Institute of Occupational Safety and Health standards administered spirometry portable 10-L dry rolling seal volume spirometer (OMI2000; Occupational Marketing, Inc; Houston, TX) before and after a 1-h beach exposure.³⁰ The spirometry values measured were FEV₁, midexpiratory phase of forced expiratory flow, peak expiratory flow, and FVC. Only data conforming to the standard guidelines for the collection and interpretation of spirometry measurements were accepted, and all study participants had three or more reproducible spirograms before and after visiting the beach.³¹

Environmental Monitoring

As described previously,^{22,25–27} a portable, self-contained weather station was used near high-volume impactor and environmental air sampling locations to monitor the air temperature, relative humidity, wind speed, and direction. Water samples were collected twice daily in 1-L glass bottles from the surf zone adjacent to the high-volume air sampler locations. The water samples were analyzed for *K brevis* cell counts and for brevetoxin analyses, using both the new brevetoxin enzyme-linked immunosorbent assay (ELISA) and liquid chromatography mass spectroscopy analysis.^{6,21,32} The limit of detection (LOD) for brevetoxins in seawater was 0.03 $\mu\text{g/L}$.^{22,25–27}

Air samples for toxin and particulate size were collected using the following three different samplers: high-volume air; high-volume air impactors equipped to capture aerosol particles by size; and personal breathing zone.^{6,22} Two 4-h air filter samples and one 8-h aerosol particle sample were collected each day. The 1-h personal exposure of each participant was measured using an individual personal sampler that was placed near the breathing zone. The sampling flow rate was 2 L/m during 2003 to 2004 study period, then, with the use of improved technology, 12 L/min for the 2005 study period.^{22,25–27} Brevetoxins associated with marine aerosols were recovered using liquid chromatography mass spectroscopy throughout the study, and using ELISA in the 2005 study period.^{5,6,21,22,25,26} The LOD for the analysis of impactor samples was 0.01 ng/m³; the ELISA LOD for all brevetoxins was 0.6 ng per sample.

Statistical Analysis

A study database was created (ACCESS; Microsoft; Redmond, WA) with direct entry during participant interviews. Descriptive and other statistical analyses were performed using a statistical software package (SAS, version 9.1; SAS Institute; Cary, NC). Statistical hypothesis testing was performed utilizing paired *t* tests for continuous data and the McNemar test for categorical data to compare pre-beach visit and post-beach visit data.³³ The number of persons not reporting a symptom before going on the beach but reporting the particular symptom after exposure was compared to the number who reported no symptom before and after their beach walk. Each participant served as their own spirometry control subject (*ie*, pre-beach walk and post-beach walk). The mean difference of the individual preexposure minus postexposure spirometry values is presented; therefore, a positive mean difference indicated that there had been a decrease in lung function in the postexposure spirometry value (Tables 3–5).

Results

The environmental monitoring results for the exposed periods (March 2003 and March 2005) and the unexposed periods (January 2003, May 2004, and October 2004) are reported in Table 1. The exposed periods were characterized by high levels of *K brevis* cells and brevetoxins in the water, with onshore winds leading to low-to-moderate brevetoxin levels in the aerosols; the unexposed periods were characterized as being without *K brevis* cells and brevetoxins in the water and brevetoxins in the aerosols, regardless of wind direction. Temperatures varied throughout the study periods, including significant cold temperatures during January 2003 and February 2005.

Ninety-seven asthmatic subjects participated in at least one evaluation during an active *K brevis* bloom and one evaluation during a nonexposure period. Their mean (\pm SD) age was 38.2 ± 18.6 years (range, 12.0 to 69.0 years) [Table 2]. They were predominantly white non-Hispanic, and female (58%). At the baseline interview, participants had first received a diagnosis of asthma a mean time 21.8 ± 19.4 years before; 42 participants (50%) reported regularly using asthma medications, and 16 participants (16.5%) reported being hospitalized at least once for respiratory causes in the past year. Only 9 participants (9.3%) were current smokers, and 71 participants (84.5%) reported having experienced respiratory symptoms with exposure to Florida red-tide blooms prior to participating in the study.

During active *K brevis* bloom exposure periods, significant differences were found for all participants between pre-beach visit and post-beach visit reports of symptoms and pre-beach visit and post-beach visit spirometry (Table 3). In particular, the mean spirometry values after 1 h of Florida red-tide exposure were uniformly decreased. In contrast, no significant differences were observed between pre-beach visit and post-beach visit reports of symptoms and pre-beach visit and post-beach visit spirometry testing during the nonexposure period, although the numerical difference between the mean FEV₁ values for the exposed and unexposed periods was not large (*ie*, 36.4 ± 107.9 mL vs 26.1 ± 141.5 mL).

The participants were examined separately in subpopulations by medication use within 12 h prior to the study period and by their geographic location of residence (Table 4). Symptoms (predominantly chest tightness) for both the medication and residence groups were statistically different during exposure period, whereas, no significant differences during a nonexposure period (data not shown) were found. Although both medication and nonmedication subgroups had significant differences in their pre-beach visit and post-beach visit spirometry values during an exposure period, the 50 participants with more severe asthma demonstrated more uniform and greater differences in spirometry values and started with lower preexposure baseline values. Both the inland and coastal subpopulations had similar and significant differences in their pre-beach visit and post-beach visit spirometry values. There were no significant differences in spirometry in any of the subpopulations during the unexposed periods (data not shown).

The subpopulations in which medication and residence were combined (*ie*, inland/medication; coastal/medication; coastal/no medication; and inland/no medication) were evaluated (Table 5). Inland residents in the current study population were significantly more likely to have severe asthma ($p = 0.04$). No group demonstrated any significant differences in reported symptoms or spirometry measurements during the nonexposure period (data not shown). Only inland and coastal residents who did not use medication had significant differences in their reported pre-beach visit and post-beach visit exposure symptoms (predominantly chest tightness) during the exposed period (data not shown). In the pre-beach visit and post-beach visit exposure spirometry measurements, only the 39 inland resident subjects with more severe asthma had statistically significant differences in the exposed period; however, these differences were numerically similar to those of the coastal residents without medication use and those of the inland residents with medication use, although they were not statistically significant (Table 5). Of interest, the inland residents without medication use had higher preexposure baseline spirometry values than the other three subpopulations.

Discussion

This study expanded earlier work^{5,6,19,20,22,25,26} demonstrating that aerosolized brevetoxins from Florida red tides could cause symptoms in recreational beachgoers and occupationally exposed life-guards and persons with asthma, as well as significant differences in reported symptoms and respiratory function in persons with asthma. This study confirmed that, in a larger group of asthmatic subjects, certain environmental conditions were associated with increased respiratory symptoms and decreased respiratory function after only 1 h of beach exposure to toxins from a Florida red tide, which is an annual and prolonged event throughout the Gulf of Mexico. Furthermore, 1 h of unexposed beach exposure in an area without an active *K brevis* bloom did not result in significant changes in symptoms or respiratory function, despite variable temperature conditions.³⁴

Persons with more severe asthma had more significant reported symptoms and decreases in their respiratory function after *K brevis* red-tide aerosol exposure. In the allergic sheep model, Abraham and colleagues^{7,8} demonstrated that pretreatment with commonly used asthma medications could minimize the effects of both brevetoxins and *K brevis* bloom aerosols on respiratory function. This suggests that without the prior preventive use of these asthma and brevetoxin-blocking medications, the effects of aerosolized red-tide brevetoxins among the participants with more severe asthma might have been even greater.

It is possible that persons living inland may be less exposed on a regular basis to the aerosols of an active *K brevis* bloom, even though these aerosols have been measured ≥ 1 mile inshore from the coast.²³ Although in this study population there were significantly more persons with severe asthma among the inland residents, the average preexposure baseline spirometry values

were higher among inland asthmatic subjects (particularly those with less severe asthma) compared with coastal residents. This suggests that it is possible that coastal residents with asthma actually had already been affected by *K brevis* red-tide brevetoxin aerosols through residential environmental exposure even prior to the study exposure, thus reacting less to the 1-h beach exposure.

Although this study only examined 1 h of short-term exposure, another study by the investigators²³ has indicated additional evidence for the negative impact of long-term exposure to *K brevis* red-tide brevetoxin aerosols on coastal residents. During active *K brevis* red-tide blooms, there was an increased rate of respiratory emergency department admissions (for upper airways disease, asthma, pneumonia, and bronchitis), particularly for coastal residents, compared to the rate for a similar unexposed period.²³

Study Limitations and Strengths

Exposure to the aerosols of an active *K brevis* bloom is a natural event with significant variation over time and space. The exact constituents of these aerosols, and their individual and combined effects on humans and other animals, need further evaluation. For example, *K brevis* produces a natural inhibitor of brevetoxin (including blocking bronchoconstriction in the allergic sheep model), known as *brevenol*. Brevenol was measured on the environmental air samplers in varying concentrations during all of the exposed study periods.^{7,8,22,25–27,35}

The study site is located in an area with prolonged and almost annual *K brevis* red-tide brevetoxin aerosol exposures. Therefore, the participants (even those living inland) may have experienced intermittent *K brevis* red-tide brevetoxin aerosol exposure that had gone unmeasured by investigators before, after, and during the study periods. Furthermore, the average decreases in spirometry values between the exposed and unexposed periods was not large, suggesting a possible independent “beach effect.” Further studies conducted at different aerosolized brevetoxin levels with larger subject numbers are needed to explore this and other issues.

As used in occupational and environmental air pollution studies,^{36–38} in addition to the objective effect measure of spirometry, this study used a methodology in which each subject served as their own control subject, before and after 1 h of beach exposure during exposed and unexposed periods of an active *K brevis* bloom. Finally, this study integrated extensive environmental and exposure assessment with the evaluation of adverse acute human health effects in sensitive subpopulations.

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Abbreviations

ELISA	enzyme-linked immunosorbent assay
LOD	limit of detection

Table 1
 Environmental Conditions and Concentrations of Brevetoxins in Water and Air Samples During the Unexposed and Exposed Sampling Periods*

Date	Temperature, °C	Humidity, %	Average Wind Speed, KPH	Wind Direction	<i>K. brevis</i> Concentration in Water, Cells/L	Water Toxin Concentration, [†] µm/L	Environmental Air Toxin Concentration, [‡] ng/ m ³	Personal Air Toxin Concentration, ^{§§} ng/ m ³
Unexposed periods								
January 2003	3.9–14.5	37–84	0–32	Off shore	< 1,000–6,000	< 0.01–0.20	< 0.01–0.20	< LOD
May 2004	23.1–26.6	70–95	6–27	Onshore	< 1,000	< 0.01	< 0.01	< LOD
October 2004	16.0–27.7	35–91	0–18	Offshore to onshore	< 1,000–2,000	< 0.01	< 0.01	< LOD
Exposed periods								
March 2003	10.7–24.6	15–95	3–34	Offshore to onshore	14,000–182,000	0.50–29.20	0.02–76.6	12.0 ± 20.7
March 2005	16.7–21.0	14–98	0–19	Onshore	59,000–200,000	2.25–11.95	7.10–69.00	30.4 ± 27.7
Potential exposed period								
February 2005	8.9–23.9	40–97	0–24	Offshore	1,051,000–4,630,000	13.36–128.02	< 0.01–0.14	< LOD

* KPH = kilometers per hour.

[†] Measured by liquid chromatography mass spectroscopy.

[‡] Measured by brevetoxin ELISA.

^{§§} Values are given as the time-weighted mean ± SD.

Table 2
Demographics of 97 Physician-Diagnosed Asthmatic Study Participants at Time of Study Enrollment*

Variables	Data
Participants, No.	97
Age, yr	38.2 ± 18.6 (12.0–69.0)
Female gender	56 (57.7)
Race	
White	94 (96.9)
Hispanic	3 (3.1)
Time of diagnosis, yr	21.8 ± 19.4
Using asthma medications currently [†]	42 (50.6)
History of Florida red tide symptoms with exposure	71 (84.5)
Current smoker	9 (9.3)
Hospitalized > 1 time in past year due to respiratory causes	16 (16.5)

* Data are given as No. (%), mean ± SD (range), or mean ± SD unless otherwise indicated.

[†] Predominantly β₂-agonists.

Table 3
Self-Reported Symptoms and Spirometry Results for 97 Study Participants Before and After Beach Walk During Exposed and Unexposed Periods to Florida Red Tide*

Variables	Unexposed Period			Exposed Period			
	Pre-Beach Walk-No/Post-Beach Walk-Yes	Pre-Beach Walk	Difference After Beach Walk [‡]	Pre-Beach Walk vs Post-Beach Walk Difference Significance [†]	Pre-Beach Walk	Difference After Beach Walk [‡]	p Value [§]
Reported symptoms							
Respiratory							
Cough	15			1.00			
Wheezing	7			0.25			
Shortness of breath	13			0.28			
Chest tightness	19			0.03			
Other							
Throat irritation	8			0.28			
Nasal congestion	11			0.82			
Eye irritation	8			0.79			
Headache	9			0.16			
Itchy skin	2			0.65			
Diarrhea	0			0			
Spirometry [¶]							
FEV ₁		2.86 ± 0.87 L	26.1 ± 141.5 mL		2.90 ± 0.87 L	36.4 ± 107.9 mL	0.01
FVC		3.88 ± 1.09 L	-0.5 ± 160.7 mL		3.91 ± 1.07 L	28.5 ± 150.9 mL	0.07
FEF ₂₅₋₇₅		2.40 ± 2.15 L/s	46.1 ± 312.9 mL/s		2.42 ± 1.21 L/s	87.1 ± 271.4 mL/s	0.002
PEF		7.31 ± 2.15 L/s	103.9 ± 228.4 mL/s		7.41 ± 2.03 L/s	76.1 ± 502.4 mL/s	0.14

* FEF₂₅₋₇₅ = midexpiratory phase of forced expiratory flow; PEF = peak expiratory flow.

[†] McNemar test.

[‡] Difference = individual preexposure values – individual values after 1 h of beach exposure (*ie*, positive value represents a decrease in the postexposure spirometry values).

§ Paired *t* test.

// Values are given as the mean \pm SD, unless otherwise indicated.

Table 4

Spirometry Results for Study Participants Preexposure and Postexposure to Beach by Medication Use and by Residence Subpopulations During Exposure Period (n = 96)*

Spirometry Values	Asthma Medications Before Beach Walk (n = 50)			No Asthma Medications Before Beach Walk (n = 46)			Inland Residence (n = 66)			Coastal Residence (n = 31)		
	Before Beach Walk	Difference After Beach Walk	p Value [†]	Before Beach Walk	Difference After Beach Walk	p Value [†]	Before Beach Walk	Difference After Beach Walk	p Value [†]	Before Beach Walk	Difference After Beach Walk	p Value [†]
FEV ₁	2.79 ± 0.87 L	40.8 ± 99.7 mL	0.006	3.03 ± 0.88 L	32.6 ± 118.0 mL	0.07	2.95 ± 0.92 L	36.1 ± 111.8 mL	0.01	2.79 ± 0.79 L	37.1 ± 100.9 mL	0.05
FVC	3.81 ± 1.06 L	36.0 ± 147.2 mL	0.09	4.02 ± 1.12 L	21.1 ± 157.7 mL	0.37	3.97 ± 1.16 L	20.3 ± 159.2 mL	0.30	3.77 ± 0.87 L	94.4 ± 132.4 mL	0.06
FEF ₂₅₋₇₅	2.19 ± 1.16 L/s	84.6 ± 246.9 mL/s	0.02	2.68 ± 1.24 L/s	92.0 ± 300.8 mL/s	0.04	2.46 ± 1.20 L/s	102.3 ± 238.1 mL/s	0.0009	2.35 ± 1.26 L/s	54.8 ± 333.5 mL/s	0.37
PEF	7.30 ± 1.94 L/s	143.8 ± 501.6 mL/s	0.05	7.53 ± 2.17 L/s	5.0 ± 504.0 mL/s	0.95	7.42 ± 2.14 L/s	34.8 ± 523.2 mL/s	0.59	7.39 ± 1.83 L/s	163.9 ± 450.5 mL/s	0.05

* Values are given as the mean ± SD, unless otherwise indicated. See Table 3 for abbreviations not used in the text. There is one missing data point each for asthma medication and residence values.

[†] Paired *t* test.

Table 5

Spirometry Results for Study Participants Preexposure and Postexposure to Beach by Combined Asthma Medications and Residence Subpopulations During Exposure Period (n = 96)*

Spirometry Values	Asthma Medications Before Beach and Coastal Residence (n = 11)			Asthma Medications Before Beach Walk and Inland Residence (n = 39)			No Medications and Inland Residence (n = 27)			No Asthma Medications and Coastal Residence (n = 19)		
	After Beach Walk	Difference After Beach Walk	p Value [†]	After Beach Walk	Difference After Beach Walk	p Value [†]	After Beach Walk	Difference After Beach Walk	p Value [†]	After Beach Walk	Difference After Beach Walk	p Value [†]
FEV ₁	2.84 ± 0.99 L	38.2 ± 80.8 mL	0.15	2.77 ± 0.85 L	41.5 ± 105.4 mL	0.02	3.22 ± 0.96 L	28.1 ± 122.1 mL	0.24	2.76 ± 0.70 L	38.9 ± 114.9 mL	0.16
FVC	3.89 ± 1.16 L	21.8 ± 89.1 mL	0.44	3.79 ± 1.05 L	40.0 ± 160.5 mL	0.12	4.23 ± 1.29 L	- 8.3 ± 155.8 mL	0.79	3.70 ± 0.70 L	62.6 ± 154.9 mL	0.09
FEF ₂₅₋₇₅	2.15 ± 1.54 L/s	6.0 ± 197.6 mL/s	0.92	2.21 ± 1.06 L/s	110.3 ± 255.4 mL/s	0.01	2.82 ± 1.32 L/s	90.7 ± 214.8 mL/s	0.04	2.35 ± 1.28 mL/s	93.7 ± 399.5 mL/s	0.32
PEF	7.69 ± 1.79 L/s	24.9 ± 574.0 mL/s	0.18	7.19 ± 1.98 L/s	114.1 ± 483.3 mL/s	0.15	7.75 ± 2.34 L/s	80.0 ± 556.6 mL/s	0.47	7.38 ± 1.86 L/s	125.3 ± 383.2 mL/s	0.17

* Values are given as the mean ± SD, unless otherwise indicated. See Table 3 for abbreviations and explanations not given in the text. There is one missing data point each for asthma medication and residence values.

[†] Paired *t* test.