

**Mitigating the Health Effects of Desert Dust
Storms Using Exposure-Reduction
Approaches
(MEDEA) project**

**ACTION C.7: Assessment of health outcomes
in children with asthma during desert dust
storm (DDS) events (with vs without
intervention measures)**

Public Health Interventional Study

**Protocol Template
(April 2018)**

**MITIGATING THE HEALTH EFFECTS OF DESERT DUST STORMS
USING EXPOSURE-REDUCTION APPROACHES
(MEDEA) PROJECT**

**ACTION C.7: ASSESSMENT OF HEALTH OUTCOMES IN CHILDREN
WITH ASTHMA DURING DESERT DUST STORM (DDS) EVENTS
(WITH VS WITHOUT INTERVENTION MEASURES)**

Principal Investigator and Action Leader:

Name: Dr. Panayiotis Yiallourous

Position: Professor of Paediatrics

Department: Medical School

University: University of Cyprus

Supported by:

LIFE+ 2016

The MEDEA project is funded by the European LIFE+ 2016 Climate Change Adaptation programme

(LIFE16 CCA/CY/000041)

**Version 1
April, 2018**

TABLE OF CONTENTS

	<u>Page</u>
TABLE OF CONTENTS	2
STUDY TEAM ROSTER.....	4
Local Study Coordinator: Dr. Panayiotis Yiallourous	4
Summary.....	5
Study Title.....	5
Objectives	5
Design, Interventions and Outcomes	5
Duration	6
Study Population.....	7
1 STUDY OBJECTIVES.....	8
1.1 Primary Objective	8
1.2 Secondary Objectives.....	8
2 BACKGROUND AND RATIONALE	8
2.1 Background on Condition, Disease, or Other Primary Study Focus	8
2.2 Study Rationale.....	9
3 STUDY DESIGN.....	10
4 SELECTION AND ENROLLMENT OF PARTICIPANTS	11
4.1 Inclusion Criteria	11
4.2 Exclusion Criteria	12
4.3 Study Enrollment Procedures	12
5 STUDY INTERVENTIONS	12
5.1 Interventions, Administration, and Duration	12
5.2 Handling of Study Interventions.....	14
5.3 Adherence Assessment	15
6 STUDY PROCEDURES	16
6.1 Schedule of Evaluations.....	16

6.2	Description of Evaluations.....	17
6.2.1	Screening and Enrollment Evaluation	17
6.2.2	Baseline, and/or Randomization	17
6.2.3	Follow-up Assessments	18
6.2.4	Completion/Final Evaluation	19
7	ASSESSMENTS OF ADVERSE EVENTS	19
8	INTERVENTION DISCONTINUATION.....	19
9	DATA COLLECTION	20
9.1	Data Collection Forms	20
9.2	Data Management	20
10	PARTICIPANT RIGHTS AND CONFIDENTIALITY	21
10.1	Informed Consent Forms	21
10.2	Participant Confidentiality	21
11	ETHICAL CONSIDERATIONS.....	22
12	COMMITTEES.....	23
13	REFERENCES.....	23
14	SUPPLEMENTS/APPENDICES	24

I. Informed Consent Form Templates

STUDY TEAM ROSTER

Cyprus

Local Study Coordinator: Dr. Panayiotis Yiallourous

Address: Medical School
University of Cyprus
215/6 Palaios dromos, Nicosia-Limassol
2029 Aglantzia
Nicosia, Cyprus
Telephone: 22895212
Fax: 22895396
e-mail address: yiallourous.panayiotis@ucy.ac.cy

Cyprus team members:

Panayiotis Kouis, PhD
Maria Kakkoura, PhD
Paraskevi Kinni
Margarita Kaliva

Greece

Local Study Coordinator: Dr. Emmanouel Galanakis

Address: School of Medicine,
University of Crete,
Voutes Campus,
Heraklion, Crete,
GR-71003, Greece

Greece team members

Dr Eleni Michailidi
Dr Chrysoula Perdikogianni
Dr Lena Dimitriou
Julieta Pérez

SUMMARY

Study Title

Mitigating the Health Effects of Desert Dust Storms Using Exposure-Reduction Approaches
(LIFE+ MEDEA)

Objectives

The primary objective of this panel study will be to quantify the vulnerability of children with asthma during desert dust storm (DDS) outbreaks and provide evidence-based estimates demonstrating which interventions/recommendations work best in mitigating adverse health effects in this group of patients (primary outcome: difference of 3 points in the Asthma Control Test (ACT) questionnaire score) after randomization to three parallel intervention groups:

- a) No intervention for DDS
- b) Intervention for outdoor exposure reduction, and
- c) Interventions for both outdoor and indoor exposure reduction

The secondary objectives of the study are to:

1. Demonstrate which of the recommendations are effective in reducing outdoor and indoor exposures to DDS in a panel of children with asthma.
2. Assess secondary health outcomes, such as the presence or absence of asthma symptoms in the prior 4 week period and unscheduled visits for asthma.

Design, Interventions and Outcomes

Type of study: Public Health Intervention Study

Intervention: Children with asthma will be recruited and will be randomized during the high DDS outbreaks season (Spring 2019 and 2020) with 1:1:1 ratio into three parallel groups to receive:

- a) No intervention for DDS.
- b) Intervention for outdoor exposure reduction, by reducing the time spend outdoors and by avoiding physical activity.
- c) Interventions for outdoor (as above) and indoor exposure reduction (by minimizing home ventilation and filtering indoor air).

Disease-related adverse health outcomes will be assessed in the three parallel arms of the study.

Approaches for delivering the intervention:

- A bidirectional, patient-centered e-Platform will be developed in order to facilitate prompt communication with the participants and provide early warnings regarding forecasted upcoming DDS events through text messaging and smartphone applications. Furthermore, the same IT platform and mobile application will be utilised for the dissemination of the

exposure reduction guidelines that the participants will follow.

Assessment of adherence to intervention:

- Monitor compliance to exposure-reduction guidelines using remote sensors. The intervention for outdoor exposure reduction, entailing reduction of the time spend outdoors and avoidance of physical activity, will be assessed with the use of smart wristwatches that will be equipped with Global Positioning System (GPS) and an accelerometer.
- The intervention for indoor exposure reduction, entailing minimization of home ventilation and filtering of indoor air, will be assessed with the use of particle samplers that will be placed outside and inside of houses and school classrooms.

Assessment of health outcomes:

- Phone interviews at baseline and then at every 1 month throughout the high DDS period recording information on asthma medication use and unscheduled visits to health professional for asthma.
- Frequency of respiratory symptoms will be assessed via caregiver and child's responses to questions on daytime and night-time symptoms in the past 4 weeks, with the help of a validated Greek version of the ACT.
- Specific aeroallergen sensitivities will be assessed at baseline and Lung function, FeNO at baseline, middle and end of high DDS season.

Primary health outcome will be a change of 3 points in the ACT questionnaire score. For the primary analysis we will compare the combined effect in the two intervention groups versus the control group. Next, we will compare between each of the intervention groups and control group and between the intervention groups.

Secondary health outcomes will be the presence or absence of asthma symptoms in the prior 4-week period, asthma medication use, unscheduled visits for asthma, forced expiratory volume in 1 second, peak expiratory flow, and FeNO.

Duration

Duration of the study: A feasibility (pilot) trial aiming to the refinement of protocols and tools will be performed during the high DDS outbreaks season of 2018. During the fall 2018 and 2019, with the onset of academic year, screening survey questionnaires (International Study of Asthma and Allergies in Children, ISAAC) will be addressed to the parents of all children in 18-20 primary schools in Nicosia by the MEDEA personnel to detect and enrol eligible asthmatic children (recruitment procedure) for the two main study periods (high DDS outbreaks season of February to May 2019 and 2020). Data collection, data cleaning and statistical analysis will take place in 2020.

Study Population

Study population, sample size and location: Children with mild to moderate persistent asthma, aged 6-11 years, will be recruited from primary schools in Nicosia-Cyprus (n=150) in academic years 2018-2019 and 2019-2020. In order to facilitate recruitment, schools principals will be contacted individually at the beginning of each academic year and details of the study will be explained. Relations with the Administrative and Nursing staff of the Schools and Parents Associations will be established with the aim to facilitate field work. During fall 2018 and 2019, MEDEA personnel will start recruitment efforts to detect eligible children with asthma for participation in the study in the high DDS periods of February-May 2019 and 2020. The same number of children will be recruited at the second study site of Heraklion-Crete.

With an average number of 250 students per school, a childhood asthma prevalence of 9-10% and an estimated response of 60%, in 18-20 primary schools we expect to detect 300 students with reported asthma. We expect that 50% of the children with reported asthma will meet eligibility criteria giving us for randomization 150 subjects in Nicosia. We estimate a dropout rate of 30%, which will eventually give us 105 asthmatic children in total to analyze.

The feasibility of protocols to assess health outcomes with and without implementation of exposure reduction guidelines will be tested in a pilot study during the high DDS period of 2018 at both study sites in a small number of patients (6 children with asthma per study site).

1 STUDY OBJECTIVES

1.1 Primary Objective

The primary objective of this panel study will be to quantify the vulnerability of children with asthma during DDS outbreaks and provide evidence-based estimates demonstrating which interventions/recommendations work best in mitigating adverse health effects in this group of patients after randomization to three parallel intervention groups:

- a) No intervention for DDS
- b) Intervention for outdoor exposure reduction, and
- c) Interventions for both outdoor and indoor exposure reduction

The primary health outcome will be a change of 3 points in the Asthma Control Test (ACT) questionnaire score. For the primary analysis we will compare the combined effect in the two intervention groups versus the control group. Next, we will compare between each of the intervention groups and control group and between the intervention groups.

1.2 Secondary Objectives

The secondary objectives of the study are to:

1. Demonstrate which of the recommendations are effective in reducing outdoor and indoor exposures to DD in a panel of asthmatic children.
2. Assess secondary health outcomes including the presence or absence of asthma symptoms in the prior 4-week period, asthma medication use, unscheduled visits for asthma, forced expiratory volume in 1 second, peak expiratory flow, and FeNO.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

The MEDEA project is envisioned to provide the field-based evidence for the adoption of a strategic plan for mitigating the health effects of DDS events in South-Eastern Europe. Over the past decade, several studies have demonstrated that DDS in Mediterranean countries, originating mostly from the Sahara and Arabian Peninsula deserts, have been increasing in number and magnitude and linked it to desertification, climatic variability and global warming. EU legislation considers DDS impossible to prevent, implicitly harmless and discounts their contribution to daily and annual air quality standards of particulate matter up to 10 microns (PM10).

However, there is increasing evidence from epidemiological studies which correlates exposure to PM₁₀ during DDS with a significant increase in mortality and hospital admissions from cardiovascular and respiratory causes. Therefore, there is a pressing need for EU policies to reduce population exposures and increase individual, population and institutional resilience to the growing frequency and intensity of DDS.

MEDEA ultimate goal is to demonstrate the feasibility and effectiveness of an adaptation strategy to DDS and better inform EU policy making.

2.2 Study Rationale

Desert dust storm events across Southern Europe

A dust storm is a phenomenon common to arid and semi-arid regions. In the EU, the term “Desert Dust Storms (DDS)” is used in the context of sandstorms originating primarily from the Sahara desert but also from the Arabian–Negev desert. The term DDS refers to the condition created when finer sand particulate matter (PM) from the desert surface is transported over a long distance. DDS pose a major risk to populations residing in affected areas, such as in Mediterranean countries belonging to the global dust belt, extending from West Africa to the Arabian Peninsula (Querol et al., 2009). During DDS events, which can last for several days, PM₁₀ levels are considerably higher than the 2005 EU daily limit value of 50 µg/m³ (Achilleos et al, 2014). Dust PM is mostly composed of rock-forming and clay minerals and they may carry microbial agents, such as bacteria, fungi and viruses (Griffin et al, 2007), and mix with anthropogenic atmospheric pollutants during transport.

Associations of DDS with mortality and hospital admissions

Historically, DDS were not considered harmful to humans due to their natural origin and crustal composition; however, in recent years, a large number of studies worldwide and in particular from Cyprus (Middleton et al., 2008; Neophytou et al., 2013), Greece (Samoli et al., 2011), Italy (Mallone et al., 2011) and Israel (Vodanos et al., 2014) have reported associations of PM₁₀ during DDS outbreaks with increased hospital admissions for asthma, chronic obstructive pulmonary disease, cardiovascular disease and increased mortality. The pathogenic effect of PM inhalation has been attributed to direct physical and toxic action of particles on human airway epithelium and systemic inflammatory responses triggering endothelial dysfunction or dysfunction of the autonomic nervous system (Leski et al., 2011). Increased hospital admissions and mortality are only two of a much larger number of adverse outcomes of exposure to DDS PM. Beyond these serious complications, patients suffer symptomatic exacerbations of pre-existing conditions, require unscheduled hospital visits, use excessive medications, and lose their sense of well-being, often with days off work or school. These relatively less studied consequences are more common, but largely unquantified and un-investigated. Finally, DDS PM exposure is associated with sub clinical effects on the general population, from mild discomfort, eye and skin irritation to substantial effects on biological processes and quality of life.

Framework for designing, implementing and testing an adaptability strategy

Our knowledge of the health risks associated with exposures to DDS PM in southern Europe comes mostly from small-scale local or national studies. Despite their limited scope, these investigations have provided sufficient evidence of a real human health risk affecting a large proportion of the EU population. Reversing the unfavourable climate trends that are exacerbating the effect of DDS in the region is a daunting task, and the benefits of global climate change policies will take decades to realize.

At the moment, the EU national competent authorities and mass media in the DDS-exposed regions, during some of the events, issue not-standardised recommendations to the public/vulnerable groups, most commonly advising them to stay indoors, and reduce outdoor activities. To date, no scientific evidence exists on the effectiveness of any of these recommendations in either reducing the exposure to DDS PM or mitigating related health effects. The EU needs to develop evidence-based policies that increase individual, population, and institutional resilience to the growing frequency and intensity of DDS. We propose in three of the most heavily DDS-affected Mediterranean regions (Cyprus, Crete, and Israel) to apply, test and demonstrate the efficacy of patient-specific and population-wide public health interventions to reduce personal exposures to DDS as a means of adaptation.

This study will address a significant knowledge gap in the health effects of personal exposures to desert dust particles, and establish vulnerability assessments in groups such as adults with AF and children with asthma, driven by our findings on the impact of the interventions on exposure, measures of health, and morbidity, thus enabling participant countries to build adaptation strategies and evidence-based policies. During and after the end of the project, this information and knowledge will be used to fine-tune tools for informed decision-making and strategic planning both at national (individual country stakeholders) and cross national levels and will be disseminated to facilitate an exchange of best practices and raise awareness within the population on their vulnerability to DDS pollutants as set out in EU policy priorities.

3 STUDY DESIGN

Type of study: Public Health Intervention Study

Children with asthma will be recruited during DDS outbreaks and will be randomized into three parallel groups to receive:

- a) No intervention for DDS,
- b) Intervention for outdoor exposure reduction, and
- c) Interventions for both outdoor and indoor exposure reduction.

Disease-related adverse health outcomes will be assessed in all the parallel arms of the study.

Previous publications of the MEDEA partners (Achilleos et al, 2014; Gerasopoulos et al, 2006; Krasnov et al, 2014), indicated that 2/3 of each year's DDS events in the Eastern Mediterranean region appear during February-May, with 10-15% of the days during this period being "DDS days". Thus, we will perform this panel study during February–May of 2019 and 2020.

Study population and location: Children with mild to moderate persistent asthma, aged 6-11 years, will be recruited from primary schools in Nicosia-Cyprus (n=200), in academic years 2018-2019 and 2019-2020. Each child will have assessment of health outcomes during only one high DDS period.

Duration of the study: A feasibility trial and refinement of protocols and tools will be performed in the high DDS period of 2018. In fall 2018 and 2019, with the onset of academic year, screening survey questionnaires (International Study of Asthma and Allergies in Children, ISAAC) will be addressed to the parents of all children in 18-20 primary schools in Nicosia by the MEDEA personnel to detect eligible asthmatic children for participation in the study during the upcoming high DDS periods of February-May 2019 and 2020.

Assessment of health outcomes:

- Phone interviews at baseline and then at every 1 month throughout the high DDS period will be carried out, recording information on asthma medication use and unscheduled visits to health professionals for asthma.
- Frequency of respiratory symptoms will be assessed via caregiver and child's responses to questions on daytime and night-time symptoms in the past 4 weeks, with the help of a validated Greek version of the ACT.
- Lung function, FeNO and specific aeroallergen sensitivities will be assessed at baseline, middle and end of high DDS season

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

The inclusion criteria for this panel study will be children with physician-diagnosed asthma for at least one year and with at least one of the following:

- Anti-asthma medication in the past year,
- Wheezing in the past year, or

- An unscheduled medical visit for asthma in the past year.

4.2 Exclusion Criteria

Exclusion criteria will be:

- Lung disease other than asthma
- Cardiovascular disease
- Not living at least 5 days per week in the household

4.3 Study Enrollment Procedures

Children with mild to moderate persistent asthma, aged 6-11 years, will be recruited at primary schools in Nicosia-Cyprus (n=150) in academic years 2018-2019 and 2019-2020. In order to facilitate recruitment, schools' principals will be contacted individually at the beginning of each academic year and details of the study will be explained. Relations with the Administrative and Nursing staff of the Schools and Parents Associations will be established with the aim to facilitate field work. With the use of screening questionnaires (ISAAC questionnaires, see Appendices), parents will, after giving written consent (EKBK03, consent form 1, see Appendices), report their child's respiratory health information. Then the parents of children with asthmatic symptoms will be invited to participate in the MEDEA program after they give their written consent (EKBK03, consent form 2, see Appendices). For children participating in the program, consent to their participation will be given by their parents/guardians. Parents will be asked by the study personnel to read the respective consent forms for the survey and the study, and will be given the opportunity to ask any clarification questions for their child's participation.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Following the eligibility assessment, we will randomize participating schools (and their students with asthma) with a 1:1:1 ratio to three parallel groups to receive:

- a) no intervention for DDS
- b) intervention for outdoor exposure reduction, by reducing the time spend outdoors and by avoiding physical activity
- c) interventions for outdoor (as above) and indoor exposure reduction (by minimizing home ventilation and filtering indoor air).

In the indoor intervention arm of the study, exposure reduction measures will be applied in the asthmatic child's classroom/school and bedroom/household settings.

After randomization, the children, their parents and schoolteachers will be trained in the tools and procedures to be followed.

Prior to the high DDS season, each eligible child will have at the school:

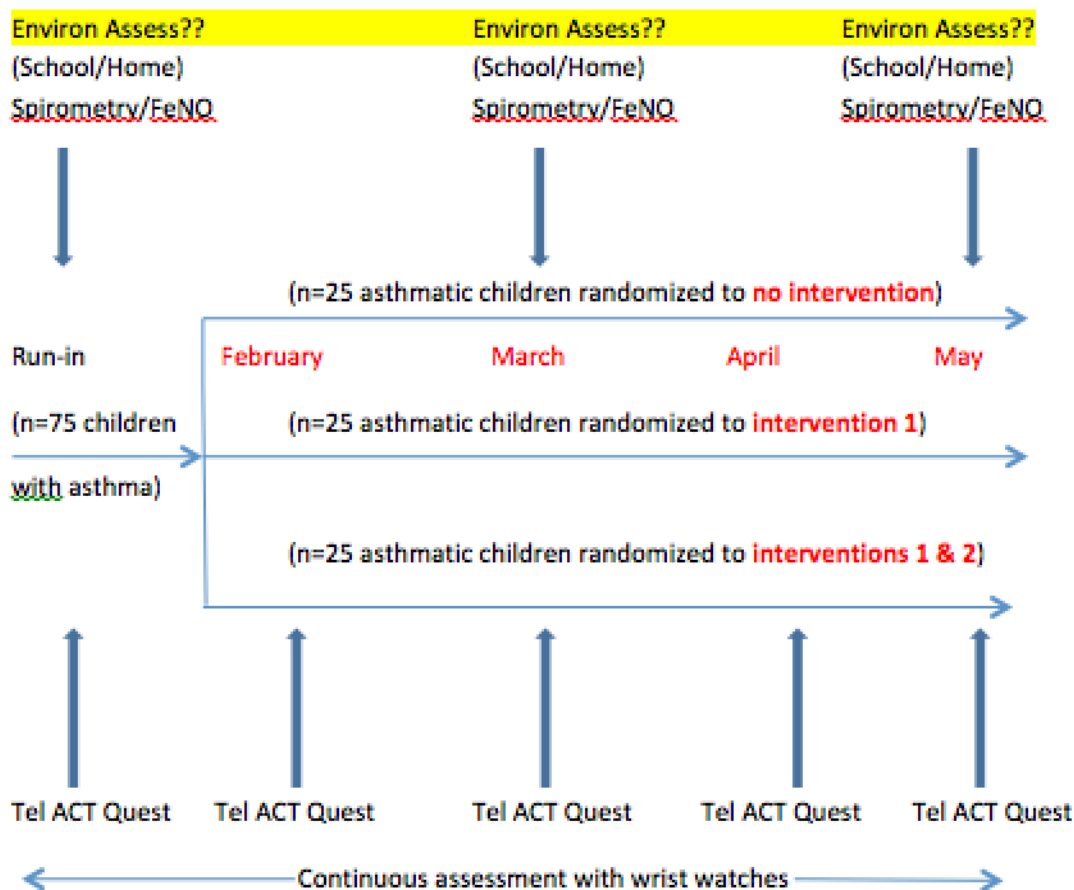
- baseline demographic, medical, and symptom survey, and
- assessments of lung function (Spirometry), fractional exhaled nitric oxide (FeNO), and specific aero-allergen sensitivities.

The study design offers also the opportunity to assess:

- outdoor exposures to PM,
- indoor exposures to PM and
- related health outcomes in three parallel groups during the same DDS events with and without intervention measures (Figure C7.1).

Figure C7.1. Study Year 1 (February-May 2019) - 75 asthmatic children in each study site (Nicosia-Cyprus & Heraklion-Crete) to be randomized to three levels of intervention

(to be repeated in Study Year 2, February-May 2020)



5.2 Handling of Study Interventions

A bidirectional, patient-centered e-Platform will be created to:

- Communicate promptly forecast alerts to individuals about upcoming DDS events through smartphone applications and text messaging
- Disseminate exposure reduction guidelines

In particular, in the group where there will be intervention for outdoor exposure reduction, the intervention will be carried out by:

- Informing the participant and the parent for upcoming desert dust storm episodes.
- Simultaneous transmission of instructions to a smartphone to reduce outdoor

exposure during the episode (stay indoors, avoid intense physical activity outdoors, avoid competitive sports, avoid unnecessary walks).

In the group where there will be interventions for outdoor and indoor exposure reduction, the intervention will be carried out by:

- Informing the participant and the parent for upcoming desert dust storm episodes.
- Simultaneous transmission of instructions to a smartphone to reduce:
 - a) Outdoor exposure during the episode (stay indoors, avoid intense physical activity outdoors, avoid competitive sports, avoid unnecessary walks) and
 - b) Indoor, home and classroom exposure (closed windows and doors, sealing possible cracks around windows and doors in order to minimize home ventilation, and using an air cleaner in order to filter indoor air).

5.3 Adherence Assessment

The compliance to exposure-reduction guidelines will be monitored with the use of remote sensors. The intervention for outdoor exposure reduction, (by reducing the time spend outdoors and by avoiding physical activity) will be assessed with the use of smart wristwatches that will be equipped with Global Positioning System (GPS) and accelerometer. The intervention for indoor exposure reduction (by minimizing home ventilation and by filtering indoor air) will be assessed with the use of particle samplers that will be placed outside and inside of houses and school classrooms.

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening and Enrollment	Baseline Assessment, and Randomization March 2019/2020	Intervention mid-point assessment April 2019/2020	Intervention end-point assessment May 2019/2020
Informed Consent Form	X			
Demographics	X	X		
Medical History	X	X		
House Assessment		X		
Current Medications	X	X	X	X
Intervention Discontinuation		X	X	X
Tel ACT Questionnaire		X	X	X
Lung function assessment		X	X	X
FeNO assessment		X	X	X
Specific aero-allergen sensitivities assessment		X		
Adverse Events		X	X	X

6.2 Description of Evaluations

6.2.1 Screening and Enrollment Evaluation

These evaluations will be performed to determine if the candidate is eligible for the study.

Consenting Procedure

Before any screening procedure is performed, informed consent must be obtained. There will be two consenting processes, one regarding the participation to the screening process and the final one which will regard full study enrollment.

The survey consent form that describes the screening procedure will be given by classroom's teachers to the children to take to their parents at home, whereas the second consent form for enrollment to the study will be handed by the study personnel to children's parents directly.

With the use of screening questionnaires (ISAAC questionnaires, see Appendices), parents upon written consent (EKBK03, consent form 1, see Appendices) will report their child's respiratory health data. Then parents of children with asthmatic symptoms will be invited to participate in the MEDEA program after they have given their written consent (EKBK03, consent form 2, see Appendices). Parents will be asked by the study personnel to read the consent form carefully and will be given the opportunity to ask clarification questions regarding the study and their child's participation. Following a discussion with the parents, they will be asked to give their signed approval. The explanations given to the children will be in comprehensible non-technical terminology.

Screening and Enrollment

The screening procedure with the use of ISSAC questionnaires, will take place during fall 2018 and 2019. The ISSAC questionnaire will allow for the collection of demographic, medical, medication and symptom data. The enrollment date is day the child participant has met all the screening criteria (both inclusion and exclusion criteria) and the parent signs the second informed consent form.

6.2.2 Baseline, and/or Randomization

Baseline Assessments

Participants who have been successfully screened for eligibility and are enrolled into the study, baseline assessments will be performed during January-February of each study year. Prior to the high DDS season, each eligible child at school will:

- a) Answer a questionnaire regarding socio-demographic characteristics
- b) Provide detailed medical and medication history (frequency of respiratory symptoms will be assessed via caregiver and child's responses to questions on daytime and nighttime symptoms in the past 4 weeks, with the help of a validated Greek version of ACT, asthma medication use, unscheduled visits to health professionals for asthma)
- c) Have household characteristics assessments
- d) Have assessments of lung function (Spirometry), fractional exhaled nitric oxide (FeNO), and specific aero-allergen sensitivities.

Randomization

Following the eligibility assessment and prior to the baseline visit, participating schools (and their students with asthma) will be randomized using standard computer software (Microsoft Excel) that allows for random number generation. Randomization will be carried out with a 1:1:1 ratio to three parallel groups:

- a) Control group A: No intervention for DDS,
- b) Intervention group B: Intervention for outdoor exposure reduction, and
- c) Intervention group C: Interventions for outdoor and indoor exposure reduction (asthmatic child's classroom/school and household/bedroom settings).

6.2.3 Follow-up Assessments

- Intervention mid-point assessment April 2019/2020:
 - Current medications
 - Intervention discontinuation
 - Telephone ACT questionnaire (monthly)
 - Lung function assessment
 - FeNO assessment
 - Specific aero-allergen sensitivities
 - Adverse events

6.2.4 Completion/Final Evaluation

- Intervention end-point assessment May 2019/2020:
 - Current medications
 - Intervention discontinuation
 - Telephone ACT questionnaire (monthly)
 - Lung function assessment
 - FeNO assessment
 - Specific aero-allergen sensitivities
 - Adverse events

7 **ASSESSMENTS OF ADVERSE EVENTS**

Since, the intervention under study is behavioral/lifestyle intervention, it does not involve any specific drug administration nor any change in ongoing medication regimen. Furthermore, it does not include any invasive procedure and all the health outcomes are assessed using non-invasive methods (smart-watches, phone interviews) and questionnaires. Hence, there are no specific safety parameters to quantify adverse health events related to interventions.

At any point during the study, patients will have the opportunity to bring any information or issue (e.g. health issue) that concerns them to the attention of the primary investigator, Dr Panayiotis Yiallourous, whose contact information will be given to all participants during the enrollment phase, and will also be available on the program's website.

8 **INTERVENTION DISCONTINUATION**

Subjects may withdraw voluntarily from the study at any time and for any reason.

Parents or guardians of asthmatic children can make oral complaints to members of the research team as well as to the principal investigators of each site.

The criteria for discontinuation of intervention will be:

- Non-adherence to the intervention
- Moving to a different house than the reported initial one
- Moving to a different school

- Significant change in health status

9 DATA COLLECTION

9.1 Data Collection Forms

Health assessment data:

- The baseline demographic (gender, age, city), medical, medication and symptom data will be obtained using surveys/questionnaires (ISAAC).
- The lung function will be assessed using portable spirometers.
- The fractional exhaled nitric oxide (FeNO) will be assessed using handheld fractional exhaled nitric oxide analyzers (NIOX VERO).
- Specific aero-allergen sensitivities will be assessed with skin prick testing.
- Frequency of respiratory symptoms will be assessed via caregiver and child's responses to questions on daytime and nighttime symptoms in the past 4 weeks, with the help of a validated Greek version of the ACT.
- Information will also be obtained on asthma medication use and unscheduled visits to health professionals for asthma via phone interviews.

Exposure data:

- Household characteristics will be assessed with the help of a questionnaire at the onset of the study.
- Real time location data will be assessed using personal smartphones application for The Global Positioning System (GPS), satellite-based navigation system installed in every smartphone.
- Real time location data from the GPS will be coupled with accelerometer data from smart wristwatches.
- Hourly central data on air pollutants, including; ambient concentrations of PM₁₀, PM_{2.5}, as well as meteorological factors (temperature and relative humidity).
- Outdoor and indoor PM and chemicals at participants' households and school will be assessed with outdoor and indoor samplers.

9.2 Data Management

The study will be overseen and managed by the Medical School, University of Cyprus, under the supervision of the LIFE+ MEDEA principal investigator, Professor Panayiotis Yiallourous.

All collected data, will be analyzed and discussed between LIFE+ MEDEA partners only by using codes to ensure that the anonymity of the participants is fully preserved.

10 PARTICIPANT RIGHTS AND CONFIDENTIALITY

Patients and their parents/guardians will be informed about the program and the data to be acquired through the information material that will be provided with the consent form.

During the study, patients will have the opportunity to get any additional information on any subject that concerns them from the study personnel and/or the principal investigator (project coordinator) Prof. Panayiotis Yiallourous whose contact information will be given to all participants during the recruitment process and will also be available on the program's website.

Also, relevant conclusions resulting from the collected data analysis will be communicated to patients at the end of the program. This information will concern the better monitoring and forecasting of dust storms and the results of the interventions in order to reduce exposure of the population to DDS events.

10.1 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record.

10.2 Participant Confidentiality

Administrative safeguards:

Data will be completely anonymized and encrypted prior to sending to the central database. The full record of Cypriot asthmatic children with names, addresses, and other personal information will be kept by the principal investigator Prof. Panayiotis Yiallourous at the Medical School of the University of Cyprus and only authorized personnel will have access to this data (Panayiotis Kouis). All data to be collected, will be analyzed and discussed between program partners only by using codes (a participant identification number (Participant ID, PID) to ensure that the anonymity of the participants is fully preserved and to maintain confidentiality.

Technical safeguards:

Electronic access to Cypriot patient data will require a user name and password that will only be held by authorized personnel. All computer entry and networking programs will be done using PIDs only. In addition, the Microsoft Azure storage platform that will be used for the purpose of data storage and backup, is Health Insurance Portability and Accountability Act (HIPAA) compliant, that establishes requirements for the use, disclosure, and safeguarding of individually identifiable health information.

The University of Cyprus has a policy that requires computer users not to leave computers unattended and not to exchange entry codes between them. Still, it is worth mentioning that after a few hours of non-use, the computer automatically turns off and locks again, requiring the use of the input code again.

In the event that a computer containing personal data is no longer used, the University of Cyprus will ensure that the data will either be transferred or destroyed.

Physical safeguards:

The Medical School of the University of Cyprus is housed in the Shakolio Educational Center, a safe building on Nicosia-Limassol Old Road, in Aglantzia, Nicosia.

The building is protected internally and with the supervision of the surrounding area, on a daily basis with a 24-hour security guard. The guard checks all incoming people in the building.

Data that may be in print will be kept in a closet in the office of the Project Coordinator so that no unauthorized person has access to them.

All records will be kept in a locked file cabinet.

11 ETHICAL CONSIDERATIONS

The study has already obtained permission from the Cyprus National Bioethics Committee. The intervention under study meets the criteria of the Helsinki declaration and follows the ICH/GCP and EC rules of good clinical practice. Data from individual countries will be completely anonymized and encrypted prior to sending to the central database.

There are no significant ethical considerations, since all necessary safeguards will be taken so that all participants do not face any risk and their personal data are protected. Participation will be on a voluntary basis and all participants will be able to withdraw at any point in the program.

12 COMMITTEES

Steering Committee:

The Steering Committee will scrutinize the quality of the project performance and will act as a supervisory body to ensure that the work described in individual actions is carried out. The members of the steering committee will include the Project Coordinator, Project Manager, and the Leaders of all other project partners (Soroqa Clinical Research Center, University of Crete, Cyprus University of Technology, E.n.A. Consulting, Department of Labor Inspection, Cyprus Broadcasting Corporation, Cyprus Department of Meteorology). The Steering Committees will be responsible for the:

- Decisions on technical roadmaps for the project and monitoring implementation;
- Provision of data for preparation of reports and deliverables to the Commission.

External Advisory Committee:

The external advisory committee will be responsible to counsel the project and to help transform our results to policies. The advisory committee will consist of relevant regulatory authorities and interested social stakeholders. There will be in total 30 members from all participating sites, i.e. ~10 members from each site.

13 REFERENCES

- Achilleos S, et al. PM10 concentration levels at an urban and background site in Cyprus: the impact of urban sources and dust storms. *J Air Waste Manag Assoc* 2014; 64:1352-60.
- Gerasopoulos E, et al. Origin and variability of particulate matter (PM10) mass concentrations over the Eastern Mediterranean. *Atmos Environ* 2006; 40:4679-4690.
- Griffin D. Atmospheric movement of microorganisms in clouds of desert dust and implications for human health. *Clin Microbiol Rev.* 2007; 20:459-77.
- Krasnov H, et al. Contribution of dust storms to PM10 levels in an urban arid environment. *J Air Waste Manag Assoc* 2014; 64:89-94.
- Leski T, et al. Application of a broad-range resequencing array for detection of pathogens in desert dust samples from Kuwait and Iraq. *Appl Environ Microbiol* 2011;77:4285-92.
- Mallone S, et al. Saharan dust and associations between particulate matter and daily mortality in Rome, Italy. *Environ Health Persp* 2011; 119:1409–1414.
- Middleton N, et al. A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effect of short-term changes in air pollution and dust storms. *Environ Health* 2008; 22;7:39.
- Neophytou A, et al. Particulate matter concentrations during desert dust outbreaks and daily mortality in Nicosia, Cyprus. *J Expo Sci Environ Epidemiol.* 2013; 23:275-80.
- Querol X, et al. African dust contributions to mean ambient PM10 mass-levels across the Mediterranean, Basin. *Atmos Environ* 2009; 43:4266-4277.

- Samoli E, et al. Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification. *Environ Res* 2011;111:418-24.
- Vodonos A, et al. The impact of desert dust exposures on hospitalizations due to exacerbation of chronic obstructive pulmonary disease. *Air Qual Atmos Health* 2014; 7:433–439.

14 SUPPLEMENTS/APPENDICES

I. Informed Consent Form Templates

A. Informed Consent Form Templates – Consent Form 1 (screening)

B. Informed Consent Form Templates – Consent Form 2 (enrolment)

