PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The MEDEA randomized intervention study protocol in Cyprus, Greece and Israel for mitigation of desert dust health effects in adults with atrial fibrillation
AUTHORS	Anagnostopoulou, Pinelopi; Kouis, Panayiotis; Papatheodorou, Stefania; Middleton, Nicos; Papasavvas, Ilias; Avraamides, Panayiotis; Simantirakis, Emmanuel; Anastasiou, Ioannis; Novack, Victor; Stamatelatos, Gerasimos; Revvas, Efstathios; Kaniklides, Christos; Tymvios, Filippos; Savvides, Chrysanthos; Koutrakis, Petros; Yiallouros, Panayiotis

VERSION 1 – REVIEW

REVIEWER	Ma, Tszshana Emory University
REVIEW RETURNED	26-Dec-2022

GENERAL COMMENTS	Thank you for the opportunity to review this research protocol. As a whole, the protocol reads well. The authors clearly articulate why this research question is of importance and lay out a comprehensive plan for their study. A few minor comments: - It is not clear whether exposure (air pollution reduction) across intervention groups are considered as outcomes for evaluation. Maybe to clarify in the statistical analysis section. - In statistical analysis, it is not clear how personal physical activity measurements as compliance would be taken into account for assessing the exposure changes and related health outcomes across groups. This study highlights the importance of individual-level compliance measure to reduce exposure misclassification. It is important to clarify how this data will be utlized, will it be assessed as one of the outcome, or would it be adjusted as a confounders when the study tries to evaluate the reduction in AD burden attributable to air pollution exposure reduction? - It is a concern that all DDS events are treated equal. Would it be a concern if the severity of DDS events are different? - It is a concern would compliance percentage affects sample size calculation.

REVIEWER	Mazzone, Patrizio Ospedale San Raffaele
REVIEW RETURNED	15-Jan-2023

GENERAL COMMENTS	In their research project, the authors propose a randomized clinical trial in order to evaluate the effectiveness of recommendations aimed at reducing exposure to desert dust storms and consequently their effect on the rising of arrhythmic phenomena in patients with a

	history of paroxysmal AF and PM or dual-chamber ICD. The study design is well described and the three comparison groups with the planned interventions for each group are well reported. However, there are some points to be clarified: - All patients enrolled in the study have a history of paroxysmal AF and the primary outcome is identified in the assessment of a 20 per cent reduction in arrhythmic events. With reference to this figure, we ask why you did not consider a control group of PM or dual-chamber ICD patients without a history of AF in order to assess the incidence of arrhythmic episodes in the 3 groups under investigation. - Population selection: please specify the characteristics of the population admitted to the study (e.g. age considered) and how the presence of one or more cardiovascular risk factors and/or comorbidities has been taken into consideration in patient selection. - In the project, the measures implemented to reduce dust exposure in and outside home are reported and described, but it is necessary to deepen how to check the fair adherence to the prescriptions of patients in groups 2 and 3. - In the study it would be appreciated a clarification regarding how we can distinguish the effects of the desert dust storms from the anthropogenic particulate pollution.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Tszshana Ma, Emory University
Comments to the Author:
Thank you for the opportunity to review this research protocol. As a whole, the protocol reads well. The authors clearly articulate why this research question is of importance and lay out a comprehensive plan for their study.

A few minor comments:
- It is not clear whether exposure (air pollution reduction) across intervention groups are considered as outcomes for evaluation. Maybe to clarify in the statistical analysis section.

Thank you for this important comment. Indeed, the exposure reduction across intervention groups is an additional outcome. The description of outcomes and the statistical analysis parts have been revised accordingly. The Methods and Analysis section now reads as follows.

Page 11, Line 8:

“Other health outcomes include the presence or absence of arrhythmia symptoms in the prior 4-week period, heart rate variability, arrhythmia medication use and unscheduled hospital visits for heart arrhythmias. Apart from the health outcomes, the exposure reduction across the intervention groups will be assessed as an outcome of this study, estimating directly the compliance and the effectiveness of the recommendations.”

Page 11, Line 24:

“The statistical analysis plan for the impact of intervention on exposure will include the estimation of the fraction of outdoor particles that penetrate indoors and remain suspended using the infiltration factor approach as described previously [30] and will employ multiple linear regression models to quantify the effect of intervention measures on indoor PM levels.”

Relevant References

Diapouli, E., Chaloulakou, A., & Koutrakis, P. (2013). Estimating the concentration of indoor particles of outdoor origin: A review. Journal of the Air & Waste Management Association, 63(10), 1113-1129.

- In statistical analysis, it is not clear how personal physical activity measurements as compliance would be taken into account for assessing the exposure changes and related health outcomes across groups. This study highlights the importance of individual-level compliance measure to reduce exposure misclassification. It is important to clarify how this data will be utlized, will it be assessed as one of the outcome, or would it be adjusted as a confounders when the study tries to evaluate the reduction in AD burden attributable to air pollution exposure reduction?

Thank you for raising this very important point and we would like to clarify that, according to the study protocol, individual level compliance will be assessed as an additional outcome and will not be used as a confounder in the relationship between intervention group and AF burden. This approach is consistent with an intention to treat analysis which estimates the effect of a treatment assignment rather than the treatment effect to those that complied with the treatment. However, we acknowledge that in randomized trials, complete compliance to treatments is not always possible or feasible and this can affect the estimation of the effectiveness of an intervention. Therefore, accurate data on compliance are important to prevent biased conclusions, especially in the case of large or moderate treatment effects (Ye C 2014). A per protocol analysis is commonly used to understand the effects of non-compliance on the treatment effects and this approach compares outcomes only in the fully compliant population. The issue is that the benefits of randomization are lost in such per protocol analysis and these results are also prone to bias (Ranganathan P, 2016). Nevertheless, considering the reviewers’ point, a secondary analysis can be carried out that will utilize appropriate causal inference methods such as the instrumental variable approach (G Dunn, 2005) and complier average causal effect (J S. Gruber 2014) to take into account compliance data in the estimation of health effects.

Relevant references:

Ye, C., Beyene, J., Browne, G., & Thabane, L. (2014). Estimating treatment effects in randomised controlled trials with non-compliance: a simulation study. BMJ open, 4(6), e005362.

Ranganathan, P., Pramesh, C. S., & Aggarwal, R. (2016). Common pitfalls in statistical analysis: Intention-to-treat versus per-protocol analysis. Perspectives in clinical research, 7(3), 144.

Dunn, G., Maracy, M., & Tomenson, B. (2005). Estimating treatment effects from randomized clinical trials with noncompliance and loss to follow-up: the role of instrumental variable methods. Statistical methods in medical research, 14(4), 369-395.

Gruber, J. S., Arnold, B. F., Reygadas, F., Hubbard, A. E., & Colford Jr, J. M. (2014). Estimation of treatment efficacy with complier average causal effects (CACE) in a randomized stepped wedge trial. American journal of epidemiology, 179(9), 1134-1142.

- It is a concern that all DDS events are treated equal. Would it be a concern if the severity of DDS events are different?

We agree with the reviewer that the severity might differ among DDS events and we acknowledge that some events may be characterised by greater levels of PM10 and/or longer duration compared to other events. However, there are currently no well-established cut-offs for identifying a “severe” DDS event. In addition, the origin and path of each DDS event may also influence the chemical composition of the transported particles thus making the characterisation of DDS event as “severe” even more difficult and arbitrary to a certain extent. Nevertheless, apart from the above facts it is important to highlight that all intervention groups are followed in parallel and as a result exposed to the same DDS event at the same time and thus severity of the event shouldn’t be a confounding factor in the analysis. As a response to the reviewer’s comment, we further clarify this point in the Methods and Analysis section.

Page 8, Line 18:

Of note, so far there is no well-established classification system for DDS severity, thus the forecasting models and alert algorithms treat all DDS events equally [27].

Relevant References

Benedetti, A., Reid, J. S., Knippertz, P., Marsham, J. H., Di Giuseppe, F., Remy, S., ... & Terradellas, E. (2018). Status and future of numerical atmospheric aerosol prediction with a focus on data requirements. Atmospheric Chemistry and Physics, 18(14), 10615-10643.

- It is a concern would compliance percentage affects sample size calculation.

Compliance is an important factor that determines the success of this study protocol. For this reason, we are targeting participants that fit and willing to comply with the basic requirements of the study in terms of data collection (wearing the smartwatch daily). To support data collection and ensure that compliance is well monitored, an extended support system has been established which includes initial training, a user manual, a helpline, and on-site visits. However, given that an intention-to-treat approach will be followed for our primary analysis, the compliance percentage is not expected to affect sample size calculation. The Methods and Analysis section has been modified accordingly to reflect the efforts carried out to secure successful monitoring of compliance.

Page 9, Line 23:

“The recordings of wearable GPS and activity sensors will be coupled with the measurements collected from the air pollution samplers and the questionnaires to provide a much higher spatiotemporal accuracy for personal air pollution exposure, and an estimate of the compliance to the intervention. To ensure minimal technical problems with the wearables and devices, as well as to facilitate data collection compliance of the participants, we maintain an extended support system characterized by frequent communication with participants and their families and implement simple and cost-effective setting adjustments to the device to ensure systematic activation of the data collection application at regular time intervals, increase battery duration and facilitate uninterrupted operation of smartwatch background process as described elsewhere [28].”

Relevant References

Michanikou, A., Kouis, P., Karanicolas, K., Yiallouros, P. K. Setup of Consumer Wearable Devices for Exposure and Health Monitoring in Population Studies. J. Vis. Exp. (192), e63275.

Reviewer: 2

Dr. Patrizio Mazzone, Ospedale San Raffaele
Comments to the Author:
In their research project, the authors propose a randomized clinical trial in order to evaluate the effectiveness of recommendations aimed at reducing exposure to desert dust storms and consequently their effect on the rising of arrhythmic phenomena in patients with a history of paroxysmal AF and PM or dual-chamber ICD. The study design is well described and the three comparison groups with the planned interventions for each group are well reported. However, there are some points to be clarified:

- **All patients enrolled in the study have a history of paroxysmal AF and the primary outcome is identified in the assessment of a 20 per cent reduction in arrhythmic events. With reference to this figure, we ask why you did not consider a control group of PM or dual-chamber ICD patients without a history of AF in order to assess the incidence of arrhythmic episodes in the 3 groups under investigation.**

We agree that the inclusion of a control group without AF history would be necessary in an observational study that assesses the impact of DDS events on AF burden. However, due to the interventional nature of the present study, the scope is to measure the change (reduction) in AF burden under behavioural interventions, as compared to patients with AF history, who follow the 'business as usual' scenario during DDS events, and are considered to be the controls.

- **Population selection: please specify the characteristics of the population admitted to the study (e.g. age considered) and how the presence of one or more cardiovascular risk factors and/or comorbidities has been taken into consideration in patient selection.**

Thank you for raising this important issue, which was one of our concerns during the design of the study. Usage of smart devices requires a certain degree of technological literacy, which is challenging, especially in the older population of the AF patients. The age itself has not been used as a limiting factor for the participation in the study, but the inability to understand and use study tools (smartphones, software applications), due to age, intellectual disability, etc. Also, patients on terminal illness, bed-bound patients and/or patients with impaired physical mobility are excluded from the study, due to the limited outdoor exposure. The patients' recruitment has been facilitated by the medical staff of cardiology clinics, who are aware of the medical history (e.g. permanent AF, other reversible causes of AF), the comorbidities (e.g. visual impairment, hearing impairment), the lifestyle habits (e.g. active smoking, regular change of household) and the readiness of each patient to participate in the study and comply with the basic requirements.

This information has been added to the supplementary material under the "*Details of recruiting AF patients"* section which now reads as follows:

Supplementary material, Page 1, Line 10:

"The medical/symptom and medication history and downloads from patients' pacemakers or ICDs are obtained and examined in order to assess whether the candidate for enrolment fulfils the eligibility criteria. The age itself has not been used as a limiting factor for the participation in the study, but the inability to understand and use study tools (smartphones, software applications), due to age, intellectual disability, etc. Also, patients on terminal illness, bed-bound patients and/or patients with impaired physical mobility are excluded from the study, due to the limited outdoor exposure. The patients' recruitment has been facilitated by the medical staff of cardiology clinics, who are aware of the medical history (e.g. permanent AF, other reversible causes of AF), the comorbidities (e.g. visual impairment, hearing impairment), the lifestyle habits (e.g. active smoking, regular change of household) and the readiness of each patient to participate in the study and comply with the basic requirements."

- In the project, the measures implemented to reduce dust exposure in and outside home are reported and described, but it is necessary to deepen how to check the fair adherence to the prescriptions of patients in groups 2 and 3.

Thank you for this comment. We have included more details on the monitoring of the implemented measures, including the regular coupling of the sensor recordings with the samplers measurements and the questionnaires, as well as the frequent contact with the participants to ensure the compliance to the measures and to exclude technical problems with the devices. We have modified the Methods and Analysis section to reflect the efforts carried out to secure successful monitoring of compliance (adherence).

Page 9, Line 23:

"The recordings of wearable GPS and activity sensors will be coupled with the measurements collected from the air pollution samplers and the questionnaires to provide a much higher spatiotemporal accuracy for personal air pollution exposure, and an estimate of the compliance to the intervention. To ensure minimal technical problems with the wearables and devices, as well as to facilitate data collection compliance of the participants, we maintain an extended support system characterized by frequent communication with participants and their families and implement simple and cost-effective setting adjustments to the device to ensure systematic activation of the data collection application at regular time intervals, increase battery duration and ensure uninterrupted operation of smartwatch background process as described elsewhere [28]."

Relevant References

Michanikou, A., Kouis, P., Karanicolas, K., Yiallouros, P. K. Setup of Consumer Wearable Devices for Exposure and Health Monitoring in Population Studies. J. Vis. Exp. (192), e63275.

- In the study it would be appreciated a clarification regarding how we can distinguish the effects of the desert dust storms from the anthropogenic particulate pollution.

Technically, travelling desert dust is always mixed with the locally emitted particulate matter (PM) in a given area. Thus, an increase in PM concentration, as captured by the forecasting models, is the combination of desert dust, anthropogenic and natural PM. Forecasting modes rely on the transport scheme of the desert dust, the proximity of the given area to the desert source and other factors (Querol, X 2019). This information is taken into consideration and based on increased PM concentration on the ground, an alert is issued to the participants. Based on this information, PM concentration levels on the ground cannot distinguish between anthropogenic and DDS particles, and this is an issue that any intervention study aiming to reduce the health impact of desert dust has to face. Nevertheless, in our study, the main scientific question is to demonstrate that AF burden can be reduced using exposure reduction approaches, during the high DDS season in Cyprus, Crete and Israel. As a result, the proposed behavioural changes (interventions) do not target specifically the DDS-produced particles, but they intend to reduce the high PM exposures encountered during the DDS events. In response to the reviewer's comment, we have updated the Abstract, Methods and Analysis section to further clarify these points.

Abstract, Page 3, Line 12:

"The study is performed in three heavily exposed to desert dust regions of the Eastern Mediterranean: Cyprus, Israel, and Crete-Greece. Adults with paroxysmal AF and implanted pacemaker are recruited and randomized to three parallel groups: a) no intervention, b) interventions to reduce outdoor

exposure to desert dust, c) interventions to reduce both outdoor and indoor exposure to particulate matter during desert dust episodes."

Page 8, Line 13:

"The forecasting models for desert dust rely on the transport scheme of the desert dust, the proximity of the given area to the desert source and other factors [25]. The study personnel takes into account these forecasts for DDS and issues alerts to participants based on increased PM concentrations (including both particles of desert dust and anthropogenic origin) compared to site-specific background levels as described previously [26]."

Relevant References:

Querol, X., Tobías, A., Pérez, N., Karanasiou, A., Amato, F., Stafoggia, M., ... & Alastuey, A. (2019). Monitoring the impact of desert dust outbreaks for air quality for health studies. Environment international, 130, 104867.

Kouis, P., Papatheodorou, S. I., Kakkoura, M. G., Middleton, N., Galanakis, E., Michaelidi, E., ... & Yiallouros, P. K. (2021). The MEDEA childhood asthma study design for mitigation of desert dust health effects: implementation of novel methods for assessment of air pollution exposure and lessons learned. BMC pediatrics, 21(1), 1-9.

VERSION 2 – REVIEW

REVIEWER	Ma, Tszshana Emory University
REVIEW RETURNED	08-Mar-2023

GENERAL COMMENTS	Thank you for the thoughtful revision of your protocol. All of my prior comments have been addressed.

REVIEWER	Mazzone, Patrizio Ospedale San Raffaele
REVIEW RETURNED	24-Feb-2023

GENERAL COMMENTS	Dear Authors, is possible to accept with the corrections.