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Effects of home air purifiers in the quality of life of patients with chronic obstructive pulmonary disease in Mexico City: a phase III, single-center, triple-blinded, randomized controlled trial (GREAT-COPD).

L. Otalvaro Acosta[1], C. Raggio[2], M. Younis[3], R. Motta[4], J. Espinoza[5], J. Szaszdi[6], P. López[7], M. Fernandez[8], L. Rocha[9], D. Schoene[10], S. Abu Jamra[11], E. Saldanha[12], J. Guajardo[13], K. Ariza[14], J. Li[15], K. Loss[16]

**Corresponding author: Laura Otalvaro Acosta, MD. Research fellow Boston Medical Center. Email: lotalvaroa@unal.edu.co*

Rest of author's affiliation at the end of the manuscript.

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Abstract:

Background: *Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. Air pollution is associated with a decrease in lung function and an increase in inflammatory biomarkers, respiratory symptoms, and hospital admissions due to several causes, including COPD exacerbations. Nevertheless, uncertainty exists on whether indoor air quality improvement could lead to a reduction in morbidity associated with COPD. Therefore, we aim to prove the efficacy of High-Efficiency Particulate Air (HEPA) filters to reduce respiratory symptoms related to COPD exacerbations.*

Methods: *We propose a single-center, parallel, controlled, randomized with a 1:1 allocation, double-blinded, phase III trial that will be performed on patients 45 years and older with moderate to severe COPD in Mexico city, comparing the use of HEPA filters with carbon air filters vs. sham devices. The main outcome will be the average change of the COPD Assessment Test (CAT) score between baseline and 4-month follow-up comparing intervention and control groups. Secondary outcomes will include CAT score measurements at 8 and 12 months, distance measured by a 6-minute walk test, Forced Expiratory Volume in 1 second, and number of and time to exacerbations measured at 4, 8, and 12 months.*

Discussion: *With this intervention, we expect to reduce symptoms associated with COPD, therefore observing a reduction in emergency department visits, hospital admissions, and economic burden. The results of this study could potentially help assess future guidelines, economic analysis, and healthcare policies on the implementation of air cleaning strategies and healthcare policies, directing resources towards air quality improvement.*

Keywords: *Chronic Obstructive Pulmonary Disease, Air Filters, Pollution, Exacerbations, Randomized Clinical Trial, COPD Assessment Test.*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, and the World Health Organization estimates it caused around 3.23 million deaths during 2019 (WHO, 2021). Although smoking has been identified as the leading cause of COPD, environmental pollution has also been associated with lung function reduction (D. M. Halpin et al., 2017). Indoor air pollution is closely related to an increased

risk of emergency department visits in patients with COPD (Ko et al., 2016). Several studies suggest an increased probability of exacerbations, defined by the American Thoracic Society as "acute episode characterized by worsening of the patient's respiratory symptoms", after short-term exposure to air pollutants (Eisner et al., 2010, Li et al., 2016; Viniol & Vogelmeier, 2018). Air pollution leads to worsening of symptoms linked to exacerbations, increased hospitalization, and mortality rates (Rui-Rui Duan et al., 2020)

Air pollutants comprise particulate matter (PM), a complex mixture of solid particles, liquid, and gases with different chemical compositions and molecular sizes. These particles can absorb many toxic substances from the environment and deposit them within the respiratory tract (Fiordelisi et al., 2017). Furthermore, PM less than 2.5 micrometers are of great concern since once inhaled, they can reach deeper into the alveoli and be absorbed into the bloodstream, causing local and systemic damage (Hadley et al., 2018).

Portable air cleaners have been suggested as a practical solution to remove indoor air pollutants, decreasing the risk for respiratory diseases. HEPA filters remove 99.997% of particles below 0.3 microns via inertial impaction, diffusion, interception, and sieving, whereas carbon filters use adsorption by trapping particles in their pored structure. Chen et al. (2015) explored the impact of air purifiers use on different outcomes such as circulating biomarkers, lung function parameters, blood pressure, and respiratory inflammation, demonstrating short-term improvement in examined blood markers and a beneficial effect on respiratory health.

However, there is currently insufficient evidence to support the use of air filters as environment modifiers in patients with COPD to reduce exacerbations, respiratory symptoms and improve healthcare outcomes (Hansel et al., 2021). We hypothesize that better indoor air quality will result in a reduction of COPD exacerbations and better health outcomes. Therefore, we aim to prove the efficacy of High-Efficiency Particulate Air (HEPA) filters to reduce respiratory symptoms as measured by the COPD Assessment Test (CAT) score compared to sham devices in patients with COPD at a 4-month follow-up.

METHODS

Study Design

The GREAT-COPD trial is a single-center, parallel, block randomized using a 1:1 allocation ratio, sham-controlled, triple-blinded, phase III trial. It is intended to last 24 months, from the enrollment process until the end of the statistical analysis and final results. To evaluate the effectiveness of HEPA filters in reducing respiratory symptoms, we will expose COPD patients to the effects of either true or sham devices for 12 months and compare clinical and surrogate outcomes achieved by the two groups during the intervention.

Study Setting

As the largest metropolis in North America with 22 million inhabitants (United Nations, 2018), Mexico City is widely recognized for its high levels of air pollution. In the 2022 World Air Quality Index, Mexico City showed a PM 2.5 level of 31.1μg/m3, 6.2 times above the WHO annual air quality guideline value (World Air Quality, 2022). Considering a prevalence of COPD of around 7.8% mainly associated with biomass exposure (Menezes et al., 2017), we acknowledge this city as optimal for the trial. Our study will recruit participants from the COPD clinic of the Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas (INER). One of the biggest respiratory disease centers in the city. With 1.546 COPD patients treated during 2019, this institute is likely to provide the desired sample size (Secretaría de Salud, 2021). This protocol will be submitted to the INER Science, Bioethics and Research Committee and IRB approval will be requested.

Participants

Inclusion Criteria

- Patients aged 45 years or older (Holm et al., 2014) with a confirmed diagnosis of COPD by a physician (based on spirometric values (FEV1/FVC < 0.70) diagnosis (D. M. G. Halpin et al., 2021) with disease stage based in Global Initiative for COPD (GOLD) categories ranging from B to D (Based on the risk of exacerbation and symptoms as measured by CAT and mMRC: Group B: Low risk, more symptoms. Group C: High risk, fewer symptoms, Group D: High risk, more symptoms).
- Ability to respond to questionnaires and perform spirometry and 6-minute walk tests (6MWT).
- Willingness and ability to maintain a 1-year follow-up at the study site.

Exclusion Criteria

- Patients without the capacity to consent, altered mental status, or inability to complete the questionnaires.

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- Presence of important comorbidities (decompensated heart failure, active cancer, alpha-1-antitrypsin deficiency, asthma, asthma-COPD overlap, tuberculosis)
- Regular use of HEPA filters at home at the time of enrollment
- Pregnant and nursing persons
- Chronic systemic corticosteroid use (>3 months in the past 12 months)
- Previous lung resection or lung reduction surgery
- Exacerbation in the last 6 weeks
- Current smokers (however, we will include former smokers defined as those who have smoked more than 100 cigarettes in their lifetime, but who have not smoked in the past 30 days, Choi K. et al, 2013).
- Patients diagnosed with COVID-19 infection in the last 3 months.

Interventions

Patients will be randomized to either control or intervention arms. All eligible participants will receive 2 SmartAir HEPA filters with incorporated carbon filters, which will be installed in their bedroom and one common area. The filter used is medical grade H13 HEPA with a capacity to filter 99.9% of particles down to 0.1 microns with a capacity to replace 100% air in a 1500sq ft space every hour (Mechanisms of filtration, 2018). Each device will be equipped with a built-in electronic sensor that will transmit data to a centralized program. Data collected will provide a real-time official EPA Air Quality Index Score and operating time.

Under the control arm, all eligible participants will receive 2 sham devices that will be installed in their bedroom and one common area. The sham device will be the same used in the intervention arm (SmartAir™) without HEPA and carbon filters.

True and sham devices will have the same functionality, appearance, and noise and will operate 24 hours per day. The device should be on for a minimum of 18 hours daily to consider adherence to the protocol. Self-report on the number of hours indoors per day will be recorded and a smart device that will record the hours spent in the residency will be provided to each participant.

The main concerns about HEPA filters are related to noise and the potential proliferation of microorganisms if maintenance is inadequate. The noise produced can range between 46 and 66 dB according to manufacturer technical specifications. Our study will follow the recommendations provided by the manufacturer concerning the maintenance of these devices, which will guarantee optimal performance. Patients that withdraw their consent due to adverse events will be properly recorded.

Sample Size

For the primary outcome, CAT is a questionnaire designed to measure the impact of COPD on a person's life and to assess if there are changes over time or after an intervention. The CAT has a scoring range of 0-40. The minimum important difference was found to be in the range of 2 to 4 points and is a reliable estimate of clinical improvement when assessing interventions in research studies using the CAT score. Based on these data, we determined a mean difference of 2 points and a standard deviation of 6 for our sample size calculation, using a power of 80% and a significance level of 0.05 (García-Sidro et al., 2015; Kon et al., 2014; Zhou et al., 2017). The results showed that 143 subjects will be needed in each study arm, 286 in total. Assuming a dropout rate of 20% according to previous literature (Hansel et al. 2021), we will need to recruit 358 subjects as our final study population.

Recruitment

All INER clinic patients will be screened and potentially eligible participants will be identified. Potential participants will be assessed by research assistants who will obtain the informed consent after a complete explanation of the trial procedures. Once the signed paperwork is obtained, we will continue the recruitment process until 358 patients are included. Recruitment is expected to be completed within 12 months.

Randomization

We will implement a block randomization method with randomly selected block sizes using a computer-generated 1:1 Random Allocation Software (Saghaei, 2004). Research assistants in charge of the distribution of the devices will be involved in the process of randomization and will have access to the allocation. All the other parts of the trial will only have access to case-identifying sequential numbers.

Blinding

We will implement a triple-blinded strategy. All participants, health care providers, research assistants, outcome assessors, and statisticians will be blinded.

The intervention used in this study is a well-documented safe procedure; to our knowledge, there is

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no previous evidence of harm caused by its use. However, an emergency unblinding protocol would be implemented in life-threatening circumstances including unexpected severe respiratory infections conditions that would lead to inpatient management. Patients will receive standard care treatment for their adverse events. In these cases, an assigned investigator will record the event and proceed to contact the maintenance staff in charge of the devices and will be encouraged to maintain blinding as far as possible. The remaining research staff will be kept blinded. In case of device malfunctioning, it should be turned off and removed to prevent any permanent damage to the performance of the study while the event is evaluated. We expect that these events will be negligible and if deemed feasible after analysis of the event, the device will be cautiously reintroduced following the previous allocation to avoid unblinding.

Adherence

A run-in period of 15 days will be implemented to detect those participants at high risk of non-compliance and test the potential drop-out rate. During this time participants' questions will be addressed and proper use of the device will be evaluated daily. Adherence will be monitored every week for the first month and then every month by checking the built-in electronic sensor. Contacts will be performed via phone calls. Every 4 months the maintenance team will evaluate signs of usage of the filters and change them if necessary. We will remind participants of the importance of following the protocol and detect possible reasons for non-adherence and reinforce strategies that increase compliance. If patients find that their sleep or quality of life is being jeopardized by the devices' sounds, investigators will offer earplugs to reduce noise during sleep hours and try to relocate the device inside the rooms to decrease any nuisance. If the patient decides to leave the trial, the devices will be collected from the participant's residency.

Timeline

Enrollment will require approximately 12 months, including 15 days of run-in evaluation (**Figure 1**). Either

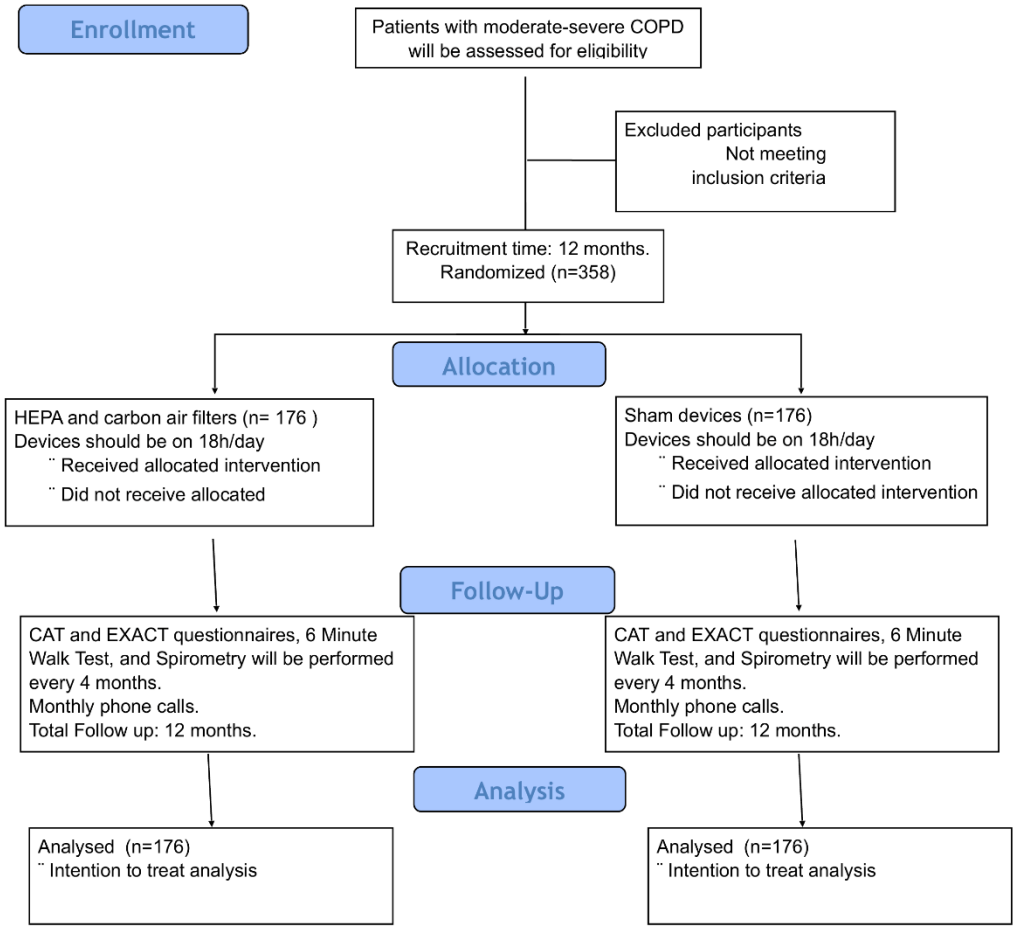

Figure 1. Timeline

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air filters or sham devices will be used for a year with follow-up visits every 4 months to record the CAT and EXACT scores, spirometry, and a 6MWT.

Outcomes

Primary outcome measures

The primary outcome is the CAT average difference in means between baseline and 4-month measurements. Additionally, the CAT score will be measured at 8 and 12 months as secondary endpoints.

The difference between the two treatment arms will be considered a success if a decrease of 2 points in CAT score is measured (Kon et al., 2014). Since the CAT score is a continuous variable, the mean will be used as a method of aggregation and for comparison between the results of the two study arms.

Secondary outcome measures

- 6MWT will be performed at baseline and every 4 months. As a continuous variable, a mean will be reported for each arm (Celli et al., 2016).
- Number of exacerbations will be evaluated by the EXACT, which defines exacerbation as a 12-point increase above baseline for two consecutive days or a nine-point increase for 3 days (Perez-Padilla & Menezes, 2019, n.d.). We will report this outcome as a discrete variable at 4, 8, and 12 months.
- Time-to-event for exacerbations will be evaluated using EXACT definition over 12 months of follow-up.
- Spirometry will be performed at baseline and every 4 months until completion of 1 year of follow-up. FEV1 will be reported as a continuous outcome for each case and the difference of means at each time point will be used for the analysis.

Data Management

All endpoints will be collected by a trained research assistant and stored electronically in a centralized computer and original questionnaires and forms will be kept at INER. Sociodemographic characteristics including age, sex, body mass index, controller medications, Charlson comorbidity index, time spent indoors, time since smoking cessation, and pack-years, as well as outcome measurements (CAT, EXACT, FEV1, 6MWT) will be stored in a password protected dataset with restricted access. Personal identifiers will be stored in a different password-protected file, only those listed as co-investigators will have access to the dataset, and will only be used for logistic purposes. Data integrity will be ensured through checks at data entry and before input into the database. A data manual will be created and used to unify data collection. A person from the Data Monitoring Committee will send weekly email reports on missing data to the INER.

The data will be stored in a cloud and a backup will be saved weekly. The data will be destroyed after 3 years or after the termination of the study. A Data User Agreement will be developed establishing the protocol for sharing information with any eventual collaborators.

Data Monitoring Committee

A Data Monitoring Committee (DMC), including a clinician, a statistician, and a technician expert on air filters, independent from the principal investigator will be established. This Committee aims to ensure the ethical and safety interests of the subjects (Schöffski et al., 2021). For this purpose, the DMC will periodically review cumulative data on efficacy and adverse events. The latter may include but are not limited to allergies, headaches, and an increase in respiratory infections. There are insufficient reports of adverse events related to HEPA and carbon air filters, and the available evidence only reports them as ecological niches for indoor bacteria (Guo et al., 2020) which may represent a potential source of harm from the devices.

Based on its independent activities, the DMC will notify the investigators of its recommendations regarding the continuation, modification, or termination of the study.

Statistical Analysis

Absolute frequencies and percentages will be used to describe the categorical variables. Measurements of central tendency and dispersion, mean and standard deviation, or median and interquartile range, will be used to summarize and describe continuous variables. The primary outcome is the 4-month difference in CAT score and will be presented as the difference between two means of control and intervention groups. Intention to treat and per-protocol analyses will be performed. Student t-test will be used for comparison under the assumption of normality, which will be evaluated using a Shapiro-Wilk test. If normality assumption is not satisfied, a Mann-Whitney U test will be used instead. The analysis of secondary outcomes, mean number of exacerbations, distances from 6MWT and FEV1 will be compared using t-test. Survival analysis will be performed for the time-to-event, in this case, COPD exacerbations. As we will recruit patients with different disease severity, we will perform a subgroup analysis to assess any differences that may arise between different

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disease stages, as well as gender, age, and smoking history. STATA- BE 17.0 will be used as a software platform for all statistical analysis. A difference was determined to be significant in all tests with a p-value <0.05.

Missing data

Strategies will be implemented to prevent missing data, simple and accessible guidelines will be provided to both outcome assessors and research staff. Patients will receive a thorough explanation and will have access to a research assistant that will solve their questions to decrease the rates of drop-out. All data will be analyzed by intention to treat. A per-protocol analysis will also be conducted to assess the confidence in the results. Multiple imputation methods and a sensitivity analysis will be used for missing data (Jakobsen et al., 2017).

DISCUSSION

This study tests the efficacy of a novel intervention that may reduce costs in the care of patients with COPD and would have a significant impact on health and quality of life. Its strengths include a larger sample than prior studies that evaluate the efficacy of this intervention, which will provide sufficient power to detect a small but clinically significant effect. The INER will facilitate recruitment since it is a large referral center for COPD patients, ensuring an adequate recruitment rate and achieving the expected sample size. We aim to include only moderate to severe COPD patients, which decreases heterogeneity and increases the likelihood to detect a significant effect of the intervention. The use of HEPA filters has proved to be safe, with few side effects described in the literature; this feature would likely decrease the number of people refusing to participate, dropouts, or emergency unblinding scenarios. Protocol adherence will be measured with electronic sensors, which may provide an objective estimation for adherence to protocol. Randomization ensures a balance for significant covariates and our follow-up will be longer than previous studies that only evaluated the effect of the intervention after 6 months (Hansel et al., 2021).

Nevertheless, this study has several limitations such as poor control over outdoor exposure to pollutants. The subjects included in our target population present moderate and severe COPD from a reference center, which may lead to selection bias and limited generalizability. The above limitations may have implications for the interpretation of our findings.

If our study rejects the null hypothesis, a large population with this condition may be able to access a device that may have a positive impact on their health outcomes. If we fail to reject the null, we can still expect it to contribute to the existing evidence on interventions to modify air quality in respiratory diseases. Finally, the GREAT-COPD trial results can potentially lead to the creation of guidelines, reduction of COPD economic and quality of life burden, and the creation of healthcare policies to direct resources towards air quality improvement.

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Author affiliations

1 Boston Medical Center, Boston, USA
2 Garrahan Hospital, Buenos Aires, Argentina.
3 MBA Northwestern University, IL, USA
4 Hospital Universitário, Federal University of Juiz de Fora, Brazil
5 Jackson Memorial Hospital, Miami, USA
6 Institute of Nutrition of Central America and Panama (INCAP), Ciudad de Guatemala, Guatemala
7 School of Medicine and Health Sciences, Tecnológico de Monterrey Guadalajara Campus, Mexico.
8 Universidad del Norte, Barranquilla, Colombia.
9 Hospitais Rede D'Or São Luiz, Brasília, Brazil
10 Department of Neurology, University Hospital Carl Gustav Carus, Dresden, Germany
11 Hospital das Clinicas de Ribeirao Preto, University of Sao Paulo (USP), Brazil
12 A.C. Camargo Cancer Center, Sao Paulo, Brazil
13 Facultad de Medicina Clinica Alemana UDD Santiago, Chile
14 Colegio Mayor Nuestra Señora del Rosario, Bogotá, Colombia
15 Bristol Myers Squibb, Cambridge, MA, USA
16 Children's Hospital Los Angeles (CHLA), USA

Conflict of interest

None.

REFERENCES

Annual Self-Assessment Report of The General Director from the National Institute of Respiratory Diseases Ismael Cosío Villegas. (2021). Secretaría de Salud. Retrieved from: http://iner.salud.gob.mx/descargas/informelabores/2020.pdf

Celli, B., Tetzlaff, K., Criner, G., Polkey, M. I., Sciurba, F., Casaburi, R., Tal-Singer, R., Kawata, A., Merrill, D., & Rennard, S. (2016). The 6-Minute-Walk Distance Test as a Chronic Obstructive Pulmonary Disease Stratification Tool. Insights from the COPD Biomarker Qualification Consortium. American Journal of Respiratory and Critical Care Medicine, 194(12), 1483–1493. https://doi.org/10.1164/rccm.201508-1653OC

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Chen, R., Zhao, A., Chen, H., Zhao, Z., Cai, J., Wang, C., Yang, C., Li, H., Xu, X., Ha, S., Li, T., & Kan, H. (2015). Cardiopulmonary Benefits of Reducing Indoor Particles of Outdoor Origin. Journal of the American College of Cardiology, 65(21), 2279–2287. https://doi.org/10.1016/j.jacc.2015.03.553

Choi K., Forster J. Characteristics associated with awareness, perceptions, and use of electronic nicotine delivery systems among young US Midwestern adults. Am. J. Public Health. 2013;103:556–561. doi: 10.2105/AJPH.2012.300947

Chronic Obstructive Pulmonary Disease. (2021, June 21). Chronic Obstructive Pulmonary Disease. Retrieved August 10, 2021, from https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)

Eisner, M. D., Anthonisen, N., Coultas, D., Kuenzli, N., Perez-Padilla, R., Postma, D., Romieu, I., Silverman, E. K., & Balmes, J. R. (2010). An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine, 182(5), 693–718. https://doi.org/10.1164/rccm.200811-1757ST

Fiordelisi, A., Piscitelli, P., Trimarco, B., Coscioni, E., Iaccarino, G., & Sorriento, D. (2017). The mechanisms of air pollution and particulate matter in cardiovascular diseases. Heart Failure Reviews, 22(3), 337–347. https://doi.org/10.1007/s10741-017-9606-7

García-Sidro, P., Naval, E., Martinez Rivera, C., Bonnin-Vilaplana, M., Garcia-Rivero, J. L., Herrejón, A., Malo de Molina, R., Marcos, P. J., Mayoralas-Alises, S., Ros, J. A., Valle, M., Esquinas, C., Barrecheguren, M., & Miravitlles, M. (2015). The CAT (COPD Assessment Test) questionnaire as a predictor of the evolution of severe COPD exacerbations. Respiratory Medicine, 109(12), 1546–1552. https://doi.org/10.1016/j.rmed.2015.10.011

Guo, J., Xiong, Y., Kang, T. et al. Bacterial community analysis of floor dust and HEPA filters in air purifiers used in office rooms in ILAS, Beijing. Sci Rep 10, 6417 (2020). https://doi.org/10.1038/s41598-020-63543-1

Hadley, M. B., Baumgartner, J., & Vedanthan, R. (2018). Developing a Clinical Approach to Air Pollution and Cardiovascular Health. Circulation, 137(7), 725–742. https://doi.org/10.1161/CIRCULATIONAHA.117.030377

Halpin, D. M. G., Criner, G. J., Papi, A., Singh, D., Anzueto, A., Martinez, F. J., Agusti, A. A., & Vogelmeier, C. F. (2021). Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine, 203(1), 24–36. https://doi.org/10.1164/rccm.202009-3533SO

Halpin, D. M., Miravitlles, M., Metzdorf, N., & Celli, B. (2017). Impact and prevention of severe exacerbations of COPD: A review of the evidence. International Journal of Chronic Obstructive Pulmonary Disease, Volume 12, 2891–2908. https://doi.org/10.2147/COPD.S139470

Hansel, N. N., Putcha, N., Woo, H., Peng, R., Diette, G. B., Fawzy, A., Wise, R. A., Romero, K., Davis, M. F., Rule, A. M., Eakin, M. N., Breysse, P. N., McCormack, M. C., & Koehler, K. (2021). Randomized Clinical Trial of Air Cleaners to Improve Indoor Air Quality and COPD Health: Results of the CLEAN AIR STUDY. American Journal of Respiratory and Critical Care Medicine, rccm.202103-0604OC. https://doi.org/10.1164/rccm.202103-0604OC

Holm, K. E., Plaufcan, M. R., Ford, D. W., Sandhaus, R. A., Strand, M., Strange, C., & Wamboldt, F. S. (2014). The impact of age on outcomes in chronic obstructive pulmonary disease differs by relationship status. Journal of behavioral medicine, 37(4), 654–663. https://doi.org/10.1007/s10865-013-9516-7

Jakobsen, J. C., Gluud, C., Wetterslev, J., & Winkel, P. (2017). When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Medical Research Methodology, 17(1), 162. https://doi.org/10.1186/s12874-017-0442-1

Ko, F. W., Chan, K. P., Hui, D. S., Goddard, J. R., Shaw, J. G., Reid, D. W., & Yang, I. A. (2016). Acute exacerbation of COPD: Hot topics on acute exacerbation of COPD. Respirology, 21(7), 1152–1165. https://doi.org/10.1111/resp.12780

Kon, S. S. C., Canavan, J. L., Jones, S. E., Nolan, C. M., Clark, A. L., Dickson, M. J., Haselden, B. M., Polkey, M. I., & Man, W. D.-C. (2014). Minimum clinically important difference for the COPD Assessment Test: A prospective analysis. The Lancet Respiratory Medicine, 2(3), 195–203. https://doi.org/10.1016/S2213-2600(14)70001-3

Li, J., Sun, S., Tang, R., Qiu, H., Huang, Q., Mason, T., & Tian, L. (2016). Major air pollutants and risk of COPD exacerbations: A systematic review and meta-analysis. International Journal of Chronic Obstructive Pulmonary Disease, Volume 11, 3079–3091. https://doi.org/10.2147/COPD.S122282

Mechanisms Of Filtration. (2018, May 30). Mechanisms Of Filtration. Retrieved August 1, 2021, from https://www.air-quality-eng.com/air-cleaners/filtration-mechanisms/

Menezes, A., Wehrmeister, F., Perez-Padilla, R., Viana, K., Soares, C., Müllerova, H., Valdivia, G., Jardim, J. R., & Montes de Oca, M. (2017). The PLATINO study: Description of the distribution, stability, and mortality according to the Global Initiative for Chronic Obstructive Lung Disease classification from 2007 to 2017. International Journal of Chronic Obstructive Pulmonary Disease, Volume 12, 1491–1501. https://doi.org/10.2147/COPD.S136023

Perez-Padilla, R., & Menezes, A. M. B. (2019). Chronic Obstructive Pulmonary Disease in Latin America. Annals of Global Health, 85(1), 7. https://doi.org/10.5334/aogh.2418

Schöffski P. Importance and role of independent data monitoring committees (IDMCs) in oncology clinical trials. BMJ Open. 2021;11(10):e047294. Published 2021 Oct 25. doi:10.1136/bmjopen-2020-047294

United Nations, Department of Economic and Social Affairs, Population Division (2019). World Urbanization Prospects: The 2018 Revision (ST/ESA/SER.A/420). New York: United Nations.

Viniol, C., & Vogelmeier, C. F. (2018). Exacerbations of COPD. European Respiratory Review, 27(147), 170103. https://doi.org/10.1183/16000617.0103-2017

World Air Quality. (2022). Air quality in Mexico City. Retrieved from: https://www.iqair.com/mexico/mexico-city

Yang, D., Yang, X., Deng, F., & Guo, X. (2017). Ambient Air Pollution and Biomarkers of Health Effect. In G.-H. Dong (Ed.), Ambient Air Pollution and Health Impact in China (Vol. 1017, pp. 59–102). Springer Singapore. https://doi.org/10.1007/978-981-10-5657-4_4

Zhou, Z., Zhou, A., Zhao, Y., & Chen, P. (2017). Evaluating the Clinical COPD Questionnaire: A systematic review: The CCQ: A systematic review. Respirology, 22(2), 251–262. https://doi.org/10.1111/resp.12970

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