The HELlenic Thoracic Society Initiative for COPD and CVD (HELICOPD): Rationale and study design

Paschalis Steiropoulos[1], Georgios Hillas[2], Konstantinos Kostikas[3], Panos Stafylas[4], Stelios Loukides[2], on behalf of HELICOPD study investigators

ABSTRACT

Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVDs) frequently coexist. Patients with COPD are at a higher risk of developing myocardial infarction, stroke, heart failure and atrial fibrillation, and vice versa; patients with CVD have more frequently COPD, compared with age-matched general population individuals. In patients with comorbid COPD and CVD higher rates of morbidity, hospitalization, worsening quality of life (QoL), and mortality are observed, compared to those with either disease. Lung hyperinflation, systemic inflammation, and arterial stiffness, as well as sharing common risk factors, e.g. smoking, are some of the suggested pathophysiological links between the two diseases. Despite the improvement in understanding the underlying mechanisms of the coexistence and the recent evidence suggesting that a better management of COPD may have beneficial cardiovascular effects, patients with COPD and CVD remain underdiagnosed, and thus undertreated. COPD is one of the most common respiratory diseases in Greece, and maybe more than half a million Greek citizens suffer both from COPD and CVD; however, their characteristics and management remain unknown. HELICOPD is a national, multicenter, prospective, non-interventional study designed to contribute to the better understanding and depicting the demographic and clinical characteristics of this population, the COPD- and CVD-related adverse events in a two-years period, their quality of life and the healthcare resources use. The study is initiated and coordinated by the Hellenic Thoracic Society.

CLINICAL TRIAL REGISTRATION: The study is registered on the official website of ClinicalTrials.gov
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AFFILIATION
1 Department of Respiratory Medicine, University General Hospital of Alexandroupolis, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece
2 2nd Respiratory Department, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
3 Department of Respiratory Medicine, School of Medicine, University of Ioannina, Ioannina, Greece
4 HEALTHINK, Thessaloniki, Greece

CORRESPONDENCE TO
Paschalis Steiropoulos. Department of Respiratory Medicine, University General Hospital of Alexandroupolis, School of Medicine, Democritus University of Thrace, Dragana 68100 Alexandroupolis, Greece
E-mail: steiropoulos@yahoo.com
ORCID iD: https://orcid.org/0000-0001-7121-6253

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a condition often associated with comorbidities such as cardiovascular diseases (CVD)[1-3], stroke, osteoporosis, depression, lung cancer and diabetes mellitus (DM)[2]. Population-based studies investigating the prevalence of CVD, stroke, DM, and arterial hypertension in the COPD population conclude that these conditions are more likely to coexist with COPD compared to the general population[2,4]. Moreover, evidence has shown that among a long list of comorbidities observed in individuals with COPD, cardiovascular comorbidities are generally considered the most significant[5].

COPD and CVD share a significant pathophysiological association including lung hyperinflation, ventilatory failure, systemic inflammation, and arterial stiffness[6]. Compared with the non-COPD population, patients with COPD are more likely to be diagnosed with CVD, with a two- to five-fold higher risk of ischemic heart disease, cardiac arrhythmia, heart failure, and pulmonary hypertension. Indeed, the evidence shows that the increased risk of myocardial infarction (MI) or stroke, is significantly associated with COPD exacerbations[2,7]. Finally, patients with COPD more often report arterial hypertension, DM and smoking as risk factors[8].

Cardiovascular diseases not only rank among the most common comorbidities in COPD but are also associated with an increased mortality risk. It has been demonstrated that a typical patient with COPD has an equal likelihood of mortality from cardiovascular causes as from respiratory ones[5]. Moreover, existing data showing that patients with stable COPD exhibit a prothrombotic state that predisposes them to an increased risk of cardiovascular events[9]. Patients with COPD and CVD, in addition to high mortality rates, present increased morbidity rates, worse quality of life (QoL) and a higher risk of hospitalization[2,7]. However, comorbidities in patients with COPD, such as CVD, apart from their direct and significant impact on the disease's clinical course by increasing the risks of hospitalization, mortality[2,4,10] and care expenses[2,11,12], are often underdiagnosed and undertreated[2,13,14].

COPD is one of the most common respiratory diseases[15].

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While COPD is a disease that can be effectively managed and prevented[2], it remains globally the leading cause of disability and death among respiratory diseases. In fact, in 2019, there were 212.3 million cases and 3.3 million deaths, worldwide[15]. In Greece, the prevalence has been estimated to be between 8.4% and 10.6%, even higher among elderly patients and residents of rural areas[16,17]. The estimated prevalence is expected to increase due to high smoking rates, air pollution and the aging population[17]. It should be noted that the prevalence of certain comorbidities, associated with COPD, varies widely between different studies[18].

COPD medication, apart from preventing lung hyperinflation, systemic inflammation, and COPD exacerbations, may have beneficial cardiovascular effects, which are associated associated with a decrease in the risk of subsequent acute CV events and improvements in arterial wall stiffness, pulmonary vasoconstriction, and cardiac function. However, further research is needed to demonstrate these cardiovascular benefits and understand the potential relationship between COPD, CVD, and their management approaches[2].

The HELlenic Thoracic Society Initiative for COPD and CVD (HELICOPD) study is designed to improve the understanding and management of COPD patients with cardiovascular comorbidities in Greece, since real-world data (RWD) about this population are not widely available. The primary objective of HELICOPD study is to outline the demographic and clinical characteristics of patients with COPD and cardiovascular comorbidities and their management. Secondary objectives are the assessment of exacerbation rates in prespecified subgroups, the identification of any correlation of specific phenotypes and COPD treatments with cardiovascular events and other clinical outcomes. Moreover, HELICOPD will assess the QoL of the target population, their work productivity, and the healthcare resource utilization, to identify the main determinants for the latter outcomes.

METHODS

Study design

HELICOPD is a national, multicenter, prospective, non-interventional study of patients with COPD and cardiovascular comorbidities in Greece, initiated and coordinated by the Hellenic Thoracic Society. The study will be conducted in collaboration with selected clinical centers in Greece with representative geographical distribution, covering both the public and private sector, providing primary, secondary, and tertiary care. All these centers have a confirmed expertise in managing patients with COPD and cardiovascular comorbidities.

A representative sample of the Greek population will be enrolled in the study. The investigators will assess the eligibility of their patients, and they will inform them about the aims and the procedures of the study. If the eligible patients agree to participate, they will sign an informed consent form and then enrolled. The duration of the study is 2 years, with a follow-up period for each patient of 6–24 months.

Patients will be monitored according to standard clinical practice for most participating centers (one visit every 6 months). Data collection will take place during the initial visit (patient enrolment), final visit (last 6 months of study) and at least every 6 months (interim visits, during scheduled routine center visits). Baseline demographic and clinical characteristics, medical history, comorbidities, and risk factors will be collected during the initial visit by the recruiting investigator. Information regarding patient follow-up (current treatment, clinical outcomes, etc.) will be collected at the remaining visits as part of routine care and in accordance with standard clinical practice. According to the observational study design, no additional visits, laboratory or imaging tests, or therapeutic interventions other than those performed as part of routine patient care, are required.

The study is designed and will be conducted in accordance with the Declaration of Helsinki, the Guidelines for Good Pharmacoepidemiology Practice of the International Society for Pharmacoepidemiology, the STROBE guidelines where applicable, the EU General Data Protection Regulation, and the national rules and regulations. HELICOPD study has been registered in clinicaltrials.gov [NCT06595784].

Eligibility criteria

Eligible patients are adults aged ≥35 years, who will provide informed consent, with a diagnosis of COPD and at least one of the following cardiovascular comorbidities: 1) heart failure; 2) atherosclerotic cardiovascular disease; 3) atrial fibrillation; or 4) severe valvular disease. At least 30% of the participants from each center will have a new diagnosis of COPD or CVD on the day of recruitment or in the last month before the recruitment.

The diagnosis of COPD was established in accordance with the criteria outlined by the Global Initiative for Obstructive Lung Disease (GOLD). Specifically, COPD was diagnosed by the presence of persistent airflow limitation, defined as a post-bronchodilator FEV_1/FVC of less than 0.7, in conjunction with relevant clinical symptoms such as dyspnea, chronic cough, and/or recurrent exacerbations. A history of exposure to tobacco smoke or other noxious gases and particulate matter further supported the diagnosis.

All participants responded to the following questions regarding the history of COPD: 1) Year of first diagnosis of COPD; 2) Number of moderate COPD exacerbations during the past 12 months; 3) Number of severe COPD exacerbations during the past 12 months; and 4) Family history of COPD.

Diagnosis of heart failure, atherosclerotic cardiovascular disease, atrial fibrillation and severe valvular disease was based on patient reports and/or hospital records. Additional testing, namely electrocardiogram and transthoracic echocardiogram, were optional and used to further support the above diagnoses.

Patients will be excluded from the study if they fulfil any of the following criteria: 1) medical history of lung cancer; 2) other active malignancy and undergoing treatment (chemotherapy/radiotherapy/immunotherapy); 3) any thoracic or abdominal surgery planned during study follow-up period; and 4) participation in any COPD-related interventional study during the recruitment and the follow-up period.

A pre-set list of comorbidities with 'yes/no' response was used in the study. Cardiovascular comorbidities included: cardiac failure, myocardial infarction, coronary artery disease without myocardial infarction, stroke, carotid artery disease, peripheral artery disease, abdominal or thoracic aortic aneurysm, atrial fibrillation, severe valvular heart disease. Other comorbidities included: arterial hypertension, hyperlipidemia, diabetes, obesity, chronic renal failure, and neuro-degenerative diseases. Comorbidities were diagnosed based on patient reports and/or hospital records when available.

The following laboratory tests were optionally performed: hemoglobin, white blood cells count, number and percentage of circulating eosinophils, α1 antitrypsin, serum creatinine, total cholesterol-, low- and high-density cholesterol, triglycerides, glucose, hemoglobin A1C, and NT-proBNP (N-terminal prohormone of brain natriuretic peptide).

Sample size

To accurately calculate the required sample size for this prospective observational study, key parameters were derived from the existing literature. These parameters were selected to ensure the study's findings would be sufficiently robust to meet the reliability standards necessary for informing health policy and decision-making[19]. In Greece, the prevalence of COPD has been estimated between 8.4% and 10.6%[16,17]. Additionally, 75.6% of patients with COPD have at least one cardiovascular comorbidity, resulting in an overall prevalence of 8.01% for COPD with cardiovascular comorbidities[20]. Based on published epidemiological data and considering an anticipated attrition rate of 10–20%, it was determined that a sample of approximately 777–883 patients diagnosed with COPD and at least one cardiovascular comorbidity is needed. This sample will be drawn from a representative selection of centers across Greece, allowing for reliable conclusions regarding the demographic and clinical characteristics of these patients and the management of their conditions (Table 1). Based on this assessment, we have set a target population of 900 eligible patients to ensure that a deviation of up to 20% from the target will not affect the statistical power of the analysis, the reliability and representativeness of the study results.

Table 1. Sample size estimation

Parameter	%
Prevalence of COPD [a]	10.60
Cardiovascular comorbidities [b]	75.60
Prevalence of COPD with coexisting cardiovascular comorbidities	8.01
Level of confidence intervals	95
Precision	2.0
	n
Estimate sample size range based on an attrition rate of 10–20%	777–883

COPD: chronic obstructive pulmonary disease. Sources: **a** Tzanakis et al.[16], Kourlaba et al.[17], Tzanakis et al.[8]. **b** Perlikos et al.[19].

Patient enrolment, study monitoring and interruption processes

Eligible patients will be enrolled in the study during their scheduled visit to the center where, after being informed about the study and agreeing to participate, they will sign the consent form, which will be kept at the center.

The subsequent step entails the completion of the electronic CRF of the initial visit. In addition, patients will be monitored during scheduled center visits, at least every 6 months, where electronic CRF of each visit will be completed. The study will conclude with the patient's final visit in the last 6 months of the study (June – November 2025), during which the electronic CRF of the final visit will be completed.

In case the patient does not schedule a visit during this period and does not present to the center for the final visit, a phone call will be made by the attending physician, to either remind/schedule the review or close the electronic CRF with adding basic information deriving from the telephone communication, e.g. health status.

As patient participation is voluntary, patients retain the right to withdraw their consent to participate in the study, or their consent regarding the use of their health data for research purposes, at any time. In this case, there will be no impact on the medical care they receive and their treatment (the clinical monitoring of the patients will continue), while the data that have already been collected can (in anonymous form) be used to draw scientific conclusions in the context of research purposes.

If patient follow-up period is discontinued without knowing the reason for discontinuation, a telephone contact will be made to identify and record the reason for discontinuation in the electronic CRF of the final visit (e.g. withdrawal of consent, death, change of address/contact information, other reason). All information already collected as part of the study will be retained for analysis in anonymous form and may be used to draw scientific conclusions for research purposes.

Data collection

Patient follow-up and data collection begin after the patient has signed the consent form and has been informed about the content of the study. The duration of the study is 2

years, with a follow-up period of 6–24 months for each patient, including at least two visits (initial and final), and in addition an interim visit at least every 6 months, as part of the regular clinical follow-up of the patient. Data collection will be conducted using an electronic CRF. The flow chart of the study and the questionnaires that will be used to collect data in each visit are presented in Table 2. Based on the study protocol, no visit is mandatory. Data collection at these predefined time points will only take place if the patient visits the hospital or doctor's office as part of routine care and in accordance with standard clinical practice. Researchers should collect data from the most recent visit occurring within the designed time intervals. Data will be inserted into an electronic CRF. The database includes anonymized data regarding patient demographics, disease characteristics, individual patient history and risk factors, disease management, and clinical outcomes.

Study outcomes

The demographic and clinical characteristics of the study population, and the main clinical outcomes will be presented by gender, age group, and region. The main clinical outcomes recorded are related to either COPD or CVD, including: 1) COPD exacerbations, moderate (requiring outpatient use of antibiotics and/or corticosteroids) or severe (requiring hospitalization); 2) cardiovascular complications/outcomes (acute coronary syndrome, stroke, pulmonary embolism, percutaneous coronary intervention or coronary artery bypass grafting, heart failure exacerbation, other event requiring hospitalization in a cardiology department); 3) unscheduled hospital admissions (due to any other reason); and 4) death (related to COPD, CVD or other cause).

Moreover, the quality of life, the impact on work productivity and activity impairment[21] and the healthcare resource utilization are included in study outcomes. The management of the target population requires significant healthcare resources; however, this burden remains unknown. HELICOPD study will assess the use of the following resources to approximate the economic burden for the healthcare system and to identify the main determinants of this burden: 1) physician visits; 2) emergency department visits; 3) hospitalizations; 4) imaging tests; and 5) medications.

Statistical analysis

Data will be analyzed using descriptive and inferential statistical analysis[22]. All qualitative variables will be presented as percentages and absolute values. Chi-squared or Fisher's

Table 2. Flow chart of visits and data collection

Parameter	Initial visit	2nd visit	3rd visit	Final visit
Consent form	X			
Inclusion/exclusion criteria	X			
Demographic characteristics	X			
History of COPD	X			
Medical history/comorbidities	X			
COPD exacerbations and CV events		X	X	X
Smoking	X	X	X	X
Vaccinations	X			X
COPD medications	X	X	X	X
Other medications	(X)			(X)
Oxygen therapy/non-invasive ventilation	X	X	X	X
Modified Medical Research Council Dyspnea Scale (mMRC)[32]	X	X	X	X
COPD Assessment Test® (CAT)[33]	X	X	X	X
Clinical examination/spirometry	X	X	X	X
Cardiac examination	(X)			(X)
Laboratory test	(X)			(X)
Quality of Life based on EQ5D[34]		(X)		
Healthcare resource utilization		(X)		
Work Productivity and Activity Impairment Questionnaire (WPAI)[21]		(X)		

X: mandatory data collection. (X): optional data collection. COPD: chronic obstructive pulmonary disease. CV: cardiovascular.

test will be used to examine any statistically significant differences between subgroups of patients with COPD (e.g. men vs women) on categorical variables[23]. All quantitative variables will be presented as mean and standard deviation (SD) or median and interquartile range (IQR) if they are normally or skewed distributed, respectively. To test the normality of a continuous variable a Q-Q plot and histogram will be used. In addition, the Kolmogorov–Smirnov test[24] will be used when the number of observations is greater or equal to 50 and alternatively the Shapiro-Wilk test[25], when the number of observations is less than 50. Student's t-test[26] or the non-parametric Mann-Whitney test will be performed to investigate any potentially statistically significant differences between subgroups of patients with COPD (e.g. male vs female) on continuous normally or skewed distributed variables, respectively. One-way analysis of variance (ANOVA)[27] will be used to compare the mean of two or more samples, followed by Tukey *post hoc* analysis[28] to determine which means are different, if the data are normally distributed, and homogeneity of variances exist. Otherwise, the non-parametric Kruskal-Wallis test[29] will be used with the Bonferroni correction[30] to determine whether there is a difference between the mean of all possible pairs. The proportion of missing data will be reported for each measured variable in the study. Where appropriate, full or available data analysis will be performed, or missing data will be presented as a separate category. All tests will be two-tailed and considered to be statistically significant at a 0.05 level. Data management and statistical analysis will be performed using the R statistical software.

Data protection and safety

This is a non-interventional study, which does not concern specific pharmacotherapy, conducted by the Hellenic Thoracic Society, with the aim of collecting and analyzing anonymized data to reliably record the demographic and clinical characteristics of patients with COPD and cardiovascular comorbidities in Greece and their management.

The Hellenic Thoracic Society ensures data security with the following measures: 1) Token-based authentication with 256-bit encryption (HS256) is used for user access to the platform's Application Programming Interface (API) resources; 2) The patient data in the system database are anonymous, as no contact or other identification information of any kind is kept. The identification of a patient becomes possible only through an alphanumeric, unique per patient record, which will be owned exclusively by the investigator – treating physician; 3) Each user has limited access to the data of the patients of the institution he belongs. An exception is anonymous aggregate statistical data; 4) New users can only be registered by the system administrator (HTS staff); 5) Users' communication with the system will be encrypted via Secure Sockets Layer (SSL) protocol; and 6) Database will be backed up daily. The electronic CRF will be hosted on a certified cloud service provider, ensuring compliance with General Data Protection Regulation (GDPR) and other national data protection regulations. The infrastructure is designed for fault tolerance and high uptime, backed by Service Level Agreements (SLAs), and is compliant with industry-leading certifications.

DISCUSSION

HELICOPD aims to provide crucial insights into the clinical and demographic characteristics of patients with COPD and coexisting cardiovascular comorbidities and to investigate the management strategies followed for the Greek population but also for specific predefined patient groups (based on their age, gender, severity of the disease)[8]. In addition, the rationale behind this study design is to provide a comprehensive snapshot of exacerbation rates among the different study subgroups to facilitate future analyses. Apart from that, HELICOPD will try to explore potential correlations of specific phenotypes of the two coexisting diseases and treatment pathways with the different clinical outcomes. Finally, the quality of life and health care resources use will be assessed to identify the impact of these chronic diseases on these aspects[31].

HELICOPD will allow the in-depth understanding of COPD with CVD comorbidities in the general population in Greece, as it is designed to include assessments based on functional tests and questionnaires that have been designed to identify major features of COPD and to establish comparability with known data. For this reason, the study will utilize the modified Medical Research Council (mMRC)[32] and the COPD assessment test (CAT)[33] scores to evaluate the symptom status and generate reproducible and comparable to other studies results. In addition, CAT and mMRC scores are strongly correlated and should be assessed together to prevent the misclassification rates of patients with COPD. Moreover, HELICOPD will follow a patient-centric approach focusing on the impact of coexisting COPD and CVD morbidity on patients' quality of life and work productivity using valid instruments such as EuroQol-5 Dimension (EQ-5D)[34] and Work Productivity and Activity Impairment (WPAI)[21]. Thus, this multidimensional collection of data could contribute to improve the management strategies and potentially inform the development of local guidelines for patients with COPD and concurrent comorbidities.

The HELICOPD study is designed not only to enhance prior knowledge, but also to integrate data from previous studies, such as a previous study of Tzanakis et al.[16], which was a population-based, multiregional, cross-sectional study providing valuable evidence regarding the prevalence of patients with COPD in Greece. Moreover, based on other COPD cohorts, cardiovascular comorbidities were frequent in the study populations and functional and clinical baseline characteristics were typically derived from large COPD studies[35]. Thus, the HELICOPD study, which will include a representative sample of approximately 900 patients, seems appropriate for examining the clinical characteristics and the

disease management of patients with CVD as concurrent comorbidity. Population-based studies have already provided evidence for the association of COPD with CVD as comorbidity, although these studies either did not specifically target patients with COPD and comorbidities or collected more limited data regarding the clinical and demographic characteristics, the management of patients with COPD and CVD, the impact on their quality of life, work productivity and the required healthcare resources utilization[36].

Limitations

It should be mentioned that there are some limitations attributed to the study design. First, in this observational study, there is a risk associated with patient selection bias and the inherent dangers of self-reporting bias. To reduce the impact of these types of bias, we will use a consecutive sampling process, validated and standardized instruments involving short recall periods, and specific timing for QoL completion. The study design does not allow for control over exposure levels, and there may be unmeasured confounders that can affect the outcomes. Another foreseen limitation of HELICOPD could concern a significant decrease in the sample size, but based on the study design it has already been estimated an anticipated loss of more than 20%.

CONCLUSIONS

HELICOPD is the first national, multicenter, non-interventional study investigating in such an extend the patients with COPD and CVD comorbidities in Greece. During this study, the investigators working either in the public or private sector, providing primary, secondary or tertiary care, will collect a significant amount of real-world data to generate useful evidence about the target population characteristics and the most efficient management of this sensitive target population in the Greek setting. Moreover, the study will allow the Hellenic Thoracic Society to identify potential gaps in diagnosis and management, contributing to the elimination of these gaps.

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CONFLICTS OF INTERESTS

The authors have each completed and submitted an ICMJE form for Disclosure of Potential Conflicts of Interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. P. Steiropoulos reports consultancy fees from Guidotti and grants or honoraria from Guidotti and Pfizer, and support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, Chiesi, Menarini and Pfizer. G. Hillas reports consulting fees from Boehringer Ingelheim, Innovis, Guidotti and honoraria from Boehringer Ingelheim, Innovis, Gilead, Guidotti, Pharmathen, Pfizer, Sanofi, Specialty Therapeutics, and UCB, and support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, Chiesi, Elpen, Innovis, GSK, Guidotti, Menarini, Novartis, Pharmathen, Pfizer, Sanofi, and Specialty Therapeutics. K. Kostikas reports consulting fees and honoraria from Guidotti and support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, Chiesi, Menarini, Pfizer, and Sanofi. Participation on a Data Safety Monitoring Board or Advisory Board of Chiesi. Leadership or fiduciary role as Member of GOLD Assembly. Other financial or non-financial interests: AstraZeneca as an employee from 2 September to 29 November 2024. P. Stafylas is the Scientific Director of HealThink. S. Loukides has received honoraria for presentations and consultancy fees from Pfizer, Guidotti and MSD, and support for attending meetings and/or travel from Boehringer Ingelheim and Elpen. Participation on a Data Safety Monitoring Board or Advisory Board of Astrazeneca, GSK, Chiesi, Menarini, Elpen, Guidotti, and Pfizer.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Institutional Review Board of the University General Hospital of Alexandroupolis, Greece (Approval number: 9836; Date: 20 February 2024). All participants must provide written informed consent to participate in the study.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created.

AUTHORS' CONTRIBUTIONS

PS and KK: primary investigators of the study, playing pivotal roles in both the study design and overall coordination. PStaf: major contribution to the study design and to drafting the initial version of the study protocol and manuscript. SL: major contribution to the conceptualization and design of the study. All authors critically reviewed, read and approved the final version of the manuscript.

PROVENANCE AND PEER REVIEW

Commissioned; externally peer reviewed.

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