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DOCTORAL DISSERTATION

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

Prevention, diagnosis and treatment of chronic respiratory diseases in Primary Health Care settings: the FRESH AIR project. A focus on Crete.

Πρόληψη, διάγνωση και θεραπεία χρόνιων αναπνευστικών νοσημάτων στην Πρωτοβάθμια Φροντίδα Υγείας: Το πρόγραμμα FRESH AIR.
Εστίαση στην Κρήτη.

by
από

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FRESH AIR
global action for healthy lungs

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Dedications

To my family

To my mentors

To all the people of FRESH AIR

‘Love responsibility. Say: it is my duty, and mine alone, to save the earth. If it is not saved, then I alone am to blame.’

(Nikos Kazantzakis)

Contents

Abbreviations

ACOS	Asthma-COPD overlap syndrome
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CI	Confidence Interval
CO	Carbon monoxide
COM-B	Capability, opportunity, motivation - behaviour
COPD	Chronic Obstructive Pulmonary Disease
CRD	Chronic Respiratory Disease
CRF	Case Report Form
DALYs	Disability-Adjusted Life-Years
EQ-5D	EuroQol Group's 5 Dimension Questionnaire
EU	European Union
FRESH AIR	Free Respiratory Evaluation and Smoke exposure reduction by primary Health cAre Integrated gRoups
GP	General practitioner
HAP	Household Air Pollution
ICS	Inhaled Corticosteroids
ICU	Interquartile Range
IQR	Interquartile Range
ISWT	Incremental Shuttle and Walking Test
LABA	long-acting beta-agonist
LAMA	long-acting muscarinic antagonist
LMICs	Low- and Middle- Income Countries
MCID	Minimum Clinically Important Difference
mMRC	modified Medical Reaserch Council dyspnea scale
MRC	Medical Reaserch Council dyspnea scale
NCSCT	National Center for Smoking Cessation and Training
OR	Odds Ration
PHC	Primary Health Care
PHQ-9	Patient Health Questionnaire-9
PM2.5	Particulate Matter smaller than 2.5 μg
PR	Pulmonary Rehabilitation
QoL	Quality of Life
SABA	Short-acting beta-agonist
SAMA	Short-acting muscarinic antagonist
SD	Standard Deviation
SGRQ	Saint George Respiratory Questionnaire
UK	United Kingdom
USA	United States of America
VBA	Very Brief Advice
VIF	Variance Inflation Factor
WHO	World Health Organisation
WPAI	Work Productivity and Impairement questionnaire

Definitions

The following definitions have been adapted by the original FRESH AIR protocol, as relevant for this PhD thesis.

Asthma	An inflammatory disorder with hyper-reactive airways resulting in narrowing of the bronchial tree, airflow obstruction and production of overt mucus. Asthma symptoms include long-term cough or/and wheeze and breathing difficulties or attacks of severe cough and breathing difficulties in absence of a viral infection.
COPD	A chronic lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing
Chronic cough	Cough lasting more than 8 weeks, or repetitive periods of daily cough lasting more than 2 weeks
Chronic respiratory diseases	Diseases of the airways and other structures of the lung. Some of the most common are chronic obstructive pulmonary disease (COPD) and asthma, occupational lung diseases and pulmonary hypertension. In this thesis, the term refers to asthma and/or COPD, unless otherwise stated.
Direct costs of CRD	Costs that are associated with healthcare expenditure for CRD management and include pharmaceutical and medical treatments, hospitalizations, admissions to intensive care units, laboratory tests and functional or imaging examinations.
Healthcare professional	Any person involved in healthcare with direct patient contact, including but not be limited to doctors, trained nurses, primary care physicians and pharmacists.
Illness perception	The organized cognitive representations that patients have about their illness.
Indirect costs of CRD	Costs that refer to non-medical expenditure (e.g. cost of patients' time) and relate to lost productivity because of the disease (e.g. cost of work loss days, impaired activity at work, impairement of daily activities, costs of non-paid caregivers' time).

Low-resource setting	Settings characterized by a lack of funds to cover health care costs, on individual or societal basis, which may lead to limited access to medication, equipment, supplies and devices, less-developed infrastructure, fewer or less-trained personnel, limited access to maintenance and parts and limited availability of equipment, supplies and medication.
Respiratory symptom	The organised cognitive representations or beliefs that patients have about their respiratory signs
Rural	Areas with a population density less than 2500 residents per square mile

Abstract

Introduction

Chronic respiratory diseases (CRDs) constitute a significant public health problem globally. According to the World Health Organization (WHO), chronic obstructive pulmonary disease (COPD) ranks as the third cause of death worldwide, while about 262 million people suffer from asthma. The greatest burden is observed in low-resource settings, with over 90% of COPD deaths and 80% of asthma deaths occurring in low-and-middle income countries. In Greece, COPD and asthma prevalence is substantial, estimated at 8.4% and 9% respectively. Evidence suggests that the situation has worsened during the recent economic crisis which significantly affected population health and risk behaviours. In particular, due to the increases in prices of conventional fuel oils, increases were observed to the use of traditional biomass-burning fireplaces for domestic heating purposes, exposing more and more people to the adverse respiratory effects of household air pollution (HAP). At the same time, the tobacco epidemic is a major issue in Greece, since the country exhibits the highest rate of smoking in the European Union (42%). Additionally, COPD and asthma place substantial financial burden on patients and the healthcare system, with the annual management costs being estimated at €4,730 and €2,281.8 per patient respectively. The economic crisis has further impacted healthcare provision in multiple ways, with low-resource rural populations, mainly served by primary health care (PHC), being disproportionally affected.

Aim and objectives

As part of the European (Horizon 2020) FRESH AIR project, the overall aim of the present thesis was to contribute to the improvement of prevention, diagnosis and treatment of CRDs in low-resource PHC settings on the island of Crete, Greece. The specific objectives of this thesis were:

1. To assess the clinical and economic burden of asthma/COPD, illustrating the local health-economic impact of CRDs.
2. To explore context-specific community beliefs and perceptions towards CRDs and examine how these are related to risk behaviours.
3. To measure levels of HAP, as a risk factor related to the recent economic crisis and examine exposure in parallel to respiratory health outcomes.
4. To assess the impact of a ‘Very Brief Advice (VBA) on Smoking’ educational module on general practitioners’ (GPs) knowledge, self-efficacy and self-reported practice
5. To assess the applicability of a remote spirometry training and feedback program (Spirometry 360) among local GPs.

6. To adapt a pulmonary rehabilitation (PR) programme and examine its applicability and impact on health outcomes of patients with CRDs.

Methods

Objective 1: Secondary data on the socioeconomic burden of CRDs in Greece were firstly collected through a scoping literature review. Additionally, primary data were collected through an observational study of 100 patients with asthma and/or COPD, consecutively visiting 10 purposively selected PHC services. Data on clinical status, healthcare expenditure and productivity losses were collected using the Work Productivity and Impairment (WPAI) questionnaire. Primary data were analyzed using descriptive statistics.

Objective 2: An observational study was conducted among 200 community members from 20 randomly selected villages. Data on beliefs, perceptions and behaviours towards CRD were collected through a questionnaire based on the SETTING tool. The questionnaire introduced a vignette describing typical symptoms of CRDs which was reflected upon and used to answer the questions. Data were analyzed descriptively, while binary logistic regression was used to examine how perceptions affected risk behaviors (smoking and solid fuel use).

Objective 3: An observational study with repeated design was conducted. HAP levels (PM2.5 and CO) were measured in 32 purposively selected rural households at two periods reflecting lesser (baseline) versus extensive (follow-up) domestic heating. Respiratory symptoms and clinical outcomes of household residents were assessed using questionnaires. Data were analysed descriptively. McNemar's and Wilcoxon Signed Rank tests were used to explore differences in outcomes between measurements.

Objective 4: An observational study with repeated design was conducted. The VBA on Smoking training was delivered to purposively selected general practitioners (GPs). Their knowledge, self-efficacy and self-reported practice were assessed before, after and one moth following the training. Changes in categorical outcomes were explored through Cochranes' Q tests with post-hoc McNemar's test. Changes in quantitative outcomes were explored through Friedman's tests and post-hoc Wilcoxon Signed Rank tests.

Objective 5: A qualitative study was conducted among 5 GPs who had completed the Spirometry360 training and feedback programme. GPs participated in a focus group discussion which was guided by an interview guide developed on the basis of the Chronic Care Model. Applicability of the Spirometry360 training and feedback programme was accessed in terms of reception, attendance, comprehensiveness, usefulness and added value. Data were analysed using thematic analysis.

Objective 6: An observational implementation science study with repeated design and qualitative interviews with patients and stakeholders was conducted. In a rural primary healthcare centre, patients

with COPD and/or asthma were referred to a locally adapted PR programme. The programme comprised of 6 weeks of exercise and education sessions, supervised by a multidisciplinary team of physiotherapists, nurse and general practitioner. Patient outcomes [Medical Research Council (MRC) breathlessness scale, Clinical COPD Questionnaire (CCQ), COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), Patient Health Questionnaire-9 (PHQ-9), Incremental Shuttle Walking Test (ISWT)] were collected before and after the programme. Changes in categorical outcomes were explored with Fisher's exact test. Changes in continuous outcomes were interpreted based on minimum clinically important differences of (MCID). Qualitative outcomes (feasibility, acceptability) were analysed using thematic analysis.

Results

Objective 1: A total of 100 patients participated in the study [60.0% men, median (IQR) age: 72.5 (15) years]. Participants reported a median (IQR) of 1 (2) visit to the GP the last three months (reimbursed 93% of the time) and 0 (1) visits to the pulmonologist (reimbursed 61.0% of the time). In case of no reimbursement, the median (IQR) co-payments were 35 (14) euros for GP and 32.5 (20) euros for pulmonologist visits. Diagnostic tests and medications performed during the last year were reimbursed 78.9% and 76.5% of the time respectively. If not reimbursed, the median (IQR) out-of-pocket payments were 45 (28) and 20 (10) euros respectively. If all reported healthcare expenditure is annualized, visits to the pulmonologist represent the highest out-of-pocket payments [median (IQR) of 150 (80) euros], accounting for a raw 2.5% of annual income of patients. Among employed participants (n=15), the median (IQR) of working hours missed due to CRD during the past week was 2 (6). Overall, the median (IQR) degree of activity impairment due to CRD in the past week was 4 (5) (scored in 0-10-point Likert scale).

Objective 2: Overall, 200 community members [46.5% men, median (IQR) age: 60 (31) years] were recruited. In terms of perceived identity, about half of participants (51.5%) linked respiratory symptoms presented in the vignette to a respiratory condition. While 67.5% strongly agreed that smoking causes respiratory symptoms, the respective percentage for HAP was 8.5%. In terms of susceptibility, 36% of participants reported that they were fairly likely to develop respiratory symptoms. About half (50.5%) would be fairly concerned about such symptoms and 55.5% mentioned that such a condition would affect their lives fairly much. Overall, 73.5% of the sample were smokers, while 61.0% were using biomass fuels. Smoking behaviour was inversely associated with the opinion of peoples' social environment on the importance of seeking medical help (Odds Ratio - OR=0.628, 95%Confidence Interval - CI: 0.401-0.985) and perceived duration of disease (OR=0.742, 95%CI: 0.545, 1.010) and positively associated with perceived susceptibility (OR=2.225, 95%CI: 1.401-3.534) and presence of previous CRD diagnosis (OR=2.992, 95%CI: 1.135-7.887). Biomass fuel use was associated only with perceived control over the disease (OR=1.537, 95%CI: 1.106-2.137).

Objective 3: In the 32 participating households, mean PM2.5 were not significantly different between measurements (36.34 μg/m^3 vs. 54.38 μg/m^3, p-value=0.60) but exceeded the WHO air quality guidelines (25 μg/m^3 for 24 hours mean). Mean CO levels were found at 0.56 ppm at baseline versus 0.34 ppm at follow-up (p-value=0.414), while maximal CO levels reached 26.1 ppm at baseline versus 9.72 ppm at follow-up (p-value=0.007). These values were below the WHO cut-off points (26.6 ppm for 1 hour and 6.1 ppm for 24 hours mean). In total, 90.6% of households were using wood burning stoves or fireplaces for heating, but half of them also owned clean fuel devices. The differences between devices that were owned versus those that were used were attributed to financial reasons. In both assessments, the most frequent respiratory symptoms reported by household residents [N=42, 72.7% women, mean (SD) age: 66.8 (14.9) years] were phlegm (27.3% versus 15.2%; p-value=0.34) and cough (24.2% versus 12.1%; p-value=0.22). Less than half of participants (48.5%) knew that indoor biomass burning for heating could harm their health.

Objective 4: Overall, 29 GPs attended the training [62.1% men, median (IQR) age: 44.5 (5.8) years]. A knowledge gap seemed to exist regarding their patients' reaction to smoking cessation advice, since this question was answered correctly only by 31.0% of participants at baseline. Statistically significant increases were found in GPs' self-efficacy in advising patients on the best methods of quitting [median (IQR) score: 3 (1) pre-training, 5 (2) post-training and 4 (2) at follow-up; p-value=0.002] and acting on patients' decision [median (IQR) score: 3 (0) pre-training, 4 (2) post-training and 4 (1) at follow-up; p-value=0.030]. Increases documented in GPs' self-reported delivery of VBA elements (ASK, ADVICE, ACT) were not statistically significant.

Objective 5: GPs indicated that the training increased their confidence in performing spirometry and interpreting results, pointing out its usefulness in enabling timely referral to specialized care. According to GPs, their training and practice had a direct impact on patients, as it provided the opportunity to those lacking direct access to diagnostic testing to be monitored or referred accordingly. Busy working schedules and lack of equipment were reported barriers to training attendance and subsequent practice. The on-demand and time-effective nature of the training were mentioned as facilitators to attendance, while the trust of patients to their family doctors was reported as a facilitator of continuing spirometry performance in clinical practice.

Objective 6: Thirty-one patients with COPD and/or chronic asthma completed the 6-week PR programme (55.0% women, mean age of 67.2 years). Mean MRC dyspnoea scale was reduced by 1.03 points, reaching the MCID of 1. The mean sit-to-stand time was reduced by 2.41 seconds, a change close to the MCID of 2.3 seconds. The mean ISWT increased by 87.39 meters, greatly exceeding the MCID of 47.5 meters. The mean CCQ total score was reduced by 0.53 units, a difference above the MCID of 0.4. Mean CAT score dropped by almost 6 units, exceeding the MCID of 2. The mean SGRQ total score decreased by 23 units, a difference higher than the MCID of 4. The mean Karnofsky score

was improved by 9.67 units. PHQ-9 scores were low already from baseline, yet a reduction of 1.10 points was observed. The direct PR benefits and the necessity of implementing similar initiatives in remote areas were highlighted.

Conclusions

Starting with assessing the socioeconomic burden of CRDs in Greece (objective 1), the findings of this thesis suggested that relieving the indirect burden of CRDs, including activity impairment, seems to be an important area to be targeted by health interventions.

Considering the factors that may influence implementation and adoption of health interventions (objective 2), the opinion of the social environment and perceived disease severity were context-specific predictors of smoking behaviour and this may be useful to consider when respective actions are designed.

Levels of HAP exceeding the air quality guidelines were documented (objective 3), confirming the return to harmful practices during Greece's austerity. This result indicates that strategies and policies to advocate for fuel poverty, raise awareness and empower communities may be of particular importance during austerity periods.

In terms of addressing exposure to risk factors, there seemed to be space for raising public awareness regarding HAP (objectives 2 and 3). However, more drastic actions seem to be needed for smoking, as despite presence of awareness, rates were high in all thesis studies. The VBA training (objective 4) appeared to influence GPs self-efficacy in advising patients on smoking cessation, suggesting that, in a period following austerity, GPs' training in providing effective smoking cessation support during their daily practice may be further examined as a strategy for addressing tobacco use and contributing to CRDs' prevention.

In terms of improving CRD diagnosis (objective 5), it was suggested that, for rural populations who may lack direct access to diagnostic options, training GPs in lung function testing may be helpful for improving under- or mis-diagnosis and facilitating proper monitoring and timely referral to specialized care.

The function of a PR programme (objective 6) for the first time in the rural periphery and Greek PHC suggested that such low-cost, patient-centered and empowering approaches may be a feasible, beneficial and acceptable option for the treatment of CRD in low-resource settings.

Lastly, performed studies are limited by their designs and small samples and further research is required to confirm results.

Περίληψη

Εισαγωγή

Τα χρόνια αναπνευστικά νοσήματα (ΧΑΝ) αποτελούν σημαντικό πρόβλημα δημόσιας υγείας παγκοσμίως. Σύμφωνα με τον Παγκόσμιο Οργανισμό Υγείας (ΠΟΥ), η χρόνια αποφρακτική πνευμονοπάθεια (ΧΑΠ) κατατάσσεται ως τρίτη αιτία θανάτου στον κόσμο, ενώ περίπου 262 εκατομμύρια άνθρωποι έχουν άσθμα. Το μεγαλύτερο φορτίο παρατηρείται σε περιοχές χαμηλών οικονομικών πόρων, με το 90% των θανάτων από ΧΑΠ και το 80% των θανάτων από άσθμα να εντοπίζονται σε χώρες χαμηλού και μεσαίου εισοδήματος. Στην Ελλάδα, οι επιπολασμοί της ΧΑΠ και του άσθματος είναι σημαντικοί και εκτιμώνται στο 8,4% και 9% αντίστοιχα. Οι ενδείξεις συνιστούν ότι η κατάσταση επιδεινώθηκε κατά την περίοδο της πρόσφατης οικονομικής κρίσης, η οποία επηρέασε σημαντικά τόσο την υγεία του πληθυσμού, όσο και τις συμπεριφορές που σχετίζονται με μεγαλύτερο κίνδυνο για την υγεία. Συγκεκριμένα, λόγω της αύξησης στην τιμή των συμβατικών καυσίμων, παρατηρήθηκαν αυξήσεις στη χρήση των παραδοσιακών τζακιών καύσης βιομάζας για λόγους οικιακής θέρμανσης, εκθέτοντας όλο και περισσότερους ανθρώπους στις δυσμενείς επιπτώσεις της ρύπανσης του ενδο-οικιακού αέρα. Ταυτόχρονα, η επιδημία του καπνίσματος αποτελεί μείζον θέμα στην Ελλάδα, καθώς η χώρα παρουσιάζει το μεγαλύτερο ποσοστό καπνίσματος στην Ευρωπαϊκή Ένωση (42%). Επιπλέον, η ΧΑΠ και το άσθμα επιφέρουν ένα σημαντικό οικονομικό βάρος στους ασθενείς και το σύστημα υγείας, με τα ετήσια κόστη διαχείρισης να εκτιμώνται στα 4.730 και 2.228,8 ευρώ ανά ασθενή αντίστοιχα. Η οικονομική κρίση επηρέασε την παροχή υπηρεσιών υγείας με πολλαπλούς τρόπους, με τους αγροτικούς πληθυσμούς χαμηλών οικονομικών πόρων, οι οποίοι εξυπηρετούνται κυρίως από την Πρωτοβάθμια Φροντίδα Υγείας (ΠΦΥ), να πλήττονται δυσανάλογα.

Σκοπός και επιμέρους στόχοι

Ως μέρος του Ευρωπαϊκού (Horizon 2020) προγράμματος FRESH AIR, ο γενικός σκοπός της παρούσας διατριβής ήταν να συμβάλει στη βελτίωση της πρόληψης, της διάγνωσης και της θεραπείας των ΧΑΝ σε περιοχές ΠΦΥ με χαμηλούς πόρους, στο νησί της Κρήτης. Οι επιμέρους στόχοι της διατριβής ήταν:

1. Να διερευνήσει το κλινικό και οικονομικό φορτίο του άσθματος και της ΧΑΠ, ως ένδειξη της κλινικό-οικονομικής επίδρασης των ΧΑΝ.
2. Να εξετάσει τις τοπικές αντιλήψεις και πεποιθήσεις γύρω από τα ΧΑΝ και να διερευνήσει πώς αυτές σχετίζονται με συμπεριφορές υψηλού κινδύνου για την υγεία.
3. Να μετρήσει τα επίπεδα της ρύπανσης του ενδο-οικιακού αέρα ως παράγοντα κινδύνου που σχετίζεται με την οικονομική κρίση και να εξετάσει την έκθεση αυτή παράλληλα με δείκτες αναπνευστικής υγείας.

4. Να αξιολογήσει την επίδραση της εκπαίδευσης στην «Πολύ Σύντομη Συμβουλή για το Κάπνισμα» στις γνώσεις, την αυτό-αποτελεσματικότητα και την αυτό-αναφερόμενη κλινική πρακτική γενικών/οικογενειακών ιατρών (ΓΙ).
5. Να εξετάσει τη δυνατότητα εφαρμογής ενός διαδικτυακού προγράμματος εκπαίδευσης και ανατροφοδότησης στη σπιρομέτρηση (Spirometry360) μεταξύ ΓΙ.
6. Να προσαρμόσει ένα πρόγραμμα πνευμονικής αποκατάστασης (ΠΑ) και να διερευνήσει τη δυνατότητα εφαρμογής και την επίδρασή του στις κλινικές εκβάσεις ασθενών με ΧΑΝ.

Μέθοδοι

Στόχος 1: Αρχικά, συλλέχθηκαν δευτερογενή δεδομένα για το κοινωνικό-οικονομικό φορτίο των ΧΑΝ στην Ελλάδα μέσω βιβλιογραφικής ανασκόπησης. Επιπλέον, πρωτογενή δεδομένα συλλέχθηκαν από 100 ασθενείς με άσθμα ή/και ΧΑΠ, οι οποίοι προσέρχονταν διαδοχικά σε 10 δομές ΠΦΥ που είχαν επιλεγεί μέσω κατευθυνόμενης δειγματοληψίας. Δεδομένα σχετικά με την κλινική κατάσταση, τις δαπάνες υγείας και τις απώλειες στην παραγωγικότητα των ασθενών συλλέχθηκαν μέσω του ερωτηματολογίου Εργασιακής Παραγωγικότητας και Αναπηρίας (Work Productivity and Impairment - WPAI). Η ανάλυση των πρωτογενών δεδομένων έγινε με χρήση περιγραφικής στατιστικής.

Στόχος 2: Μια μελέτη παρατήρησης πραγματοποιήθηκε μεταξύ 200 κατοίκων από 20 τυχαία επιλεγμένα χωριά. Δεδομένα σχετικά με τις αντιλήψεις, τις πεποιθήσεις και τις συμπεριφορές γύρω από τα ΧΑΝ συλλέχθηκαν μέσω ενός ερωτηματολογίου, βασισμένου στο εργαλείο SETTING. Το ερωτηματολόγιο ξεκινούσε εισάγοντας την ιστορία ενός ατόμου με τυπικά συμπτώματα ΧΑΝ, βάσει της οποίας οι συμμετέχοντες απαντούσαν τις ερωτήσεις. Η ανάλυση των δεδομένων έγινε με χρήση περιγραφικής στατιστικής, ενώ πραγματοποιήθηκε λογιστική παλινδρόμηση για τη διερεύνηση της συσχέτισης μεταξύ πεποιθήσεων και συμπεριφορών υψηλού κινδύνου (κάπνισμα και χρήση καυσίμων βιομάζας).

Στόχος 3: Πραγματοποιήθηκε μελέτη παρατήρησης με επαναλαμβανόμενες μετρήσεις. Τα επίπεδα της ρύπανσης του ενδο-οικιακού αέρα (PM2.5 και CO) μετρήθηκαν σε 32 νοικοκυριά, τα οποία επιλέχθηκαν μέσω κατευθυνόμενης δειγματοληψίας, σε περιόδους εκτεταμμένης (μέτρηση αναφοράς) έναντι χαμηλής (επαναξιολόγηση) οικιακής θέρμανσης. Τα αναπνευστικά συμπτώματα και οι κλινικές εκβάσεις των ιδιοκτητών αξιολογήθηκαν μέσω ερωτηματολογίων. Τα δεδομένα αναλύθηκαν μέσω περιγραφικής στατιστικής. Έλεγχοι McNemar’s και Wilcoxon Signed Rank χρησιμοποιήθηκαν για τη διερεύνηση διαφορών στις εκβάσεις μεταξύ των δύο μετρήσεων.

Στόχος 4: Πραγματοποιήθηκε μελέτη παρατήρησης με επαναλαμβανόμενες μετρήσεις. Η εκπαίδευση «Πολύ Σύντομη Συμβουλή για το Κάπνισμα» παραδόθηκε σε 29 ΓΙ, οι οποίοι είχαν επιλεγεί με κατευθυνόμενη δειγματοληψία. Οι γνώσεις, η αυτό-αποτελεσματικότητα και η αυτό-αναφερόμενη

κλινική τους πρακτική αξιολογήθηκαν πριν, αμέσως μετά και ένα μήνα μετά την εκπαίδευση. Οι αλλαγές σε κατηγορικά δεδομένα διερευνήθηκαν μέσω ελέγχων Cochranes' Q με post-hoc McNemar's. Οι αλλαγές σε συνεχή δεδομένα διερευνήθηκαν μέσω ελέγχων Friedman's με post-hoc Wilcoxon Signed Rank.

Στόχος 5: Μια ποιοτική μελέτη διενεργήθηκε μεταξύ 5 ΓΙ οι οποίοι είχαν ολοκληρώσει το πρόγραμμα εκπαίδευσης και ανατροφοδότησης Spirometry360. Οι ΓΙ συμμετείχαν σε μια ομάδα εστιασμένης συζήτησης η οποία καθοδηγήθηκε από έναν οδηγό συνέντευξης που αναπτύχθηκε βάσει του θεωρητικού Μοντέλου Χρόνιας Φροντίδας (Chronic Care Model). Η δυνατότητα εφαρμογής του προγράμματος εκπαίδευσης και ανατροφοδότησης Spirometry360 αξιολογήθηκε επί τη βάσει της αποδοχής, της παρακολούθησης, της περιεκτικότητας, της χρησιμότητας και της προστιθέμενης αξίας του προγράμματος. Τα δεδομένα αναλύθηκαν μέσω θεματικής ανάλυσης.

Στόχος 6: Πραγματοποιήθηκε μια εφαρμοσμένης επιστήμης μελέτη παρατήρησης με επαναλαμβανόμενες μετρήσεις και ποιοτικές συνεντεύξεις με ασθενείς και φορείς υλοποίησης. Σε ένα αγροτικό κέντρο υγείας, ασθενείς με ΧΑΠ ή /και χρόνιο άσθμα παραπέμφθηκαν σε ένα τοπικά προσαρμοσμένο πρόγραμμα ΠΑ. Το πρόγραμμα αποτελούνταν από 6 εβδομάδες άσκησης και εκπαιδευτικών συναντήσεων και επιβλέπονταν από μια διεπιστημονική ομάδα φυσιοθεραπευτών, νοσηλευτών και ΓΙ. Δεδομένα για τις εκβάσεις υγείας των ασθενών [κλίμακα δύσπνοιας (Medical Research Council – MRC), Κλινικό Ερωτηματολόγιο για τη ΧΑΠ (Clinical COPD Questionnaire - CCQ), Ερωτηματολόγιο Αξιολόγησης της ΧΑΠ (COPD Assessment Test - CAT), Ερωτηματολόγιο St. George's Respiratory Questionnaire (SGRQ), Ερωτηματολόγιο Υγείας του Ασθενούς (Patient Health Questionnaire - PHQ-9), Τεστ βάδισης Incremental Shuttle Walking Test (ISWT)] συλλέχθηκαν πριν και μετά τη συμμετοχή τους στο πρόγραμμα. Οι αλλαγές σε κατηγορικά δεδομένα διερευνήθηκαν μέσω ελέγχων Fisher's exact. Οι αλλαγές στα συνεχή δεδομένα ερμηνεύτηκαν επί τη βάσει της Ελάχιστης Κλινικά Σημαντικής Διαφοράς (ΕΚΣΔ). Τα ποιοτικά δεδομένα αναλύθηκαν με χρήση θεματικής ανάλυσης.

Αποτελέσματα

Στόχος 1: Συνολικά, 100 ασθενείς συμμετείχαν στη μελέτη [60.0% άνδρες, διάμεση (ενδοτεταρτιμοριακό εύρος- - IQR) ηλικία: 72,5 (15) έτη]. Η διάμεση (IQR) τιμή των αναφερόμενων επισκέψεων σε ΓΙ τους τελευταίους τρεις μήνες ήταν 1 (2) (με κάλυψη στο 93% των επισκέψεων) και των επισκέψεων σε πνευμονολόγους ήταν 0 (1) (με κάλυψη στο 61,0% των επισκέψεων). Σε περίπτωση μηδενικής κάλυψης, η διάμεση (IQR) τιμή της συμμετοχής ήταν 35 (14) ευρώ για την επίσκεψη σε ΓΙ και 32,5 (20) ευρώ για επίσκεψη σε πνευμονολόγο. Οι διαγνωστικοί έλεγχοι και οι φαρμακευτικές αγωγές που πραγματοποιήθηκαν τον τελευταίο χρόνο καλύπτονταν στο 78,9% και 76,5% των

περιπτώσεων αντίστοιχα. Σε περίπτωση μηδενικής κάλυψης, η διάμεση (IQR) τιμή της συμμετοχής ήταν 45 (28) και 20 (10) ευρώ αντίστοιχα. Κατά την αναγωγή των αναφερόμενων δαπανών υγείας σε ετήσια βάση, οι επισκέψεις σε πνευμονολόγο αποτέλεσαν τις υψηλότερες συμμετοχές [διάμεση (IQR) τιμή 150 (80) ευρώ], αντιστοιχώντας σε ένα αδρό 2,5% του ετήσιου εισοδήματος των ασθενών. Μεταξύ των εργαζόμενων συμμετεχόντων (n=15), η διάμεση (IQR) τιμή των ωρών εργασίας που χάθηκαν λόγω ΧΑΝ ήταν 2 (6). Συνολικά, η διάμεση (IQR) τιμή του βαθμού παρεμπόδισης των δραστηριοτήτων λόγω ΧΑΝ κατά την προηγούμενη εβδομάδα ήταν 4 (5) (βαθμολογία σε 0-10-κλίμακα Likert).

Στόχος 2: Συνολικά, 200 κάτοικοι [46,5% άνδρες, διάμεση (IQR) ηλικία: 60 (31) έτη] συμμετείχαν στη μελέτη. Όσον αφορά την αντιλαμβανόμενη ταυτότητα των ΧΑΝ, περίπου οι μισοί συμμετέχοντες (51,5%) συνέδεαν τα αναπνευστικά συμπτώματα με κάποια αναπνευστική νόσο. Ενώ 67,5% των συμμετεχόντων συμφωνούσαν ισχυρά ότι το κάπνισμα προκαλεί αναπνευστικά συμπτώματα, το αντίστοιχο ποσοστό για τη ρύπανση του ενδο-οικιακού αέρα ήταν 8,5%. Αναφορικά με την αντιλαμβανόμενη ευπάθεια, το 36% των συμμετεχόντων ανέφεραν ότι ήταν αρκετά πιθανό να αναπτύξουν αναπνευστικά συμπτώματα. Περίπου οι μισοί (50,5%) θα ανησυχούσαν αρκετά σε περίπτωση τέτοιων συμπτωμάτων και 55,5% ανέφεραν ότι μια τέτοια κατάσταση θα επηρέαζε τη ζωή τους αρκετά. Συνολικά, 73,5% του δείγματος ήταν καπνιστές, ενώ 61,0% χρησιμοποιούσαν καύσιμα βιομάζας. Η καπνιστική συμπεριφορά συσχετίστηκε αντίστροφα με τη γνώμη του κοινωνικού περιβάλλοντος των συμμετεχόντων αναφορικά με τη σημασία της αναζήτησης ιατρικής βοήθειας (Σχετικός Λόγος-ΣΛ=0,628, 95%Διάστημα Εμπιστοσύνης-ΔΕ: 0.401-0.985) και την αντιλαμβανόμενη διάρκεια της νόσου (OR=0.742, 95%CI: 0,545, 1,010), ενώ παρατηρήθηκε θετική συσχέτιση με την αντιλαμβανόμενη ευπάθεια (ΣΛ=2,225, 95%ΔΕ: 1,401-3,534) και την ύπαρξη προηγούμενης διάγνωσης ΧΑΝ (ΣΛ=2,992, 95%ΔΕ: 1,135-7,887). Η χρήση καυσίμων βιομάζας συσχετίστηκε μόνο με τον αντιλαμβανόμενο έλεγχο επί της ασθένειας (ΣΛ=1,537, 95%ΔΕ: 1,106-2,137).

Στόχος 3: Στα 32 νοικοκυριά που συμμετείχαν, η μέση τιμή των επιπέδων PM2.5 δεν ήταν στατιστικά σημαντικά διαφορετική μεταξύ των μετρήσεων (36,34 μg/m^3 vs. 54,38 μg/m^3, p-value=0,60), όμως ξεπερνούσε τις οδηγίες του ΠΟΥ για την ποιότητα του αέρα (25 μg/m^3 για τον 24-ωρο μέσο). Τα μέσα επίπεδα CO βρέθηκαν στα 0.56 ppm κατά τη μέτρηση αναφοράς και στα 0.34 ppm κατά την επαναξιολόγηση (p-value=0,414), ενώ τα μέγιστα επίπεδα CO έφτασαν τα 26,1 ppm στην αρχική μέτρηση και τα 9,72 ppm στην επαναξιολόγηση (p-value=0,007). Αυτές οι τιμές ήταν κάτω από τις οδηγίες του ΠΟΥ (26,6 ppm για μια ώρα και 6,1 ppm για τον 24-ωρο μέσο). Συνολικά, 90,6% των νοικοκυριών χρησιμοποιούσαν ξυλόσομπες ή τζάκια για θέρμανση, αλλά τα μισά από αυτά διέθεταν, επίσης, μοντέρνες συσκευές καθαρών καυσίμων. Όλες οι διαφορές μεταξύ των συσκευών που υπήρχαν έναντι αυτών που χρησιμοποιούνταν στα νοικοκυριά αποδίδονταν από τους ιδιοκτήτες σε οικονομικούς λόγους. Και στις δύο αξιολογήσεις, τα πιο συχνά αναπνευστικά συμπτώματα που αναφέρθηκαν από τους ιδιοκτήτες [N=42, 72,7% γυναίκες, μέση (τυπική απόκλιση) ηλικία: 66,8 (14,9) έτη] ήταν το φλέγμα (27,3% έναντι 15,2%, p-value=0,34) και ο βήχας (24,2% έναντι 12,1%, p-value=0,22).

Λιγότεροι από τους μισούς συμμετέχοντες (48,5%) ήξεραν ότι η καύση βιομάζας σε εσωτερικούς χώρους για λόγους θέρμανσης μπορεί να βλάψει την υγεία.

Στόχος 4: Συνολικά, 29 ΓΙ παρακολούθησαν την εκπαίδευση [62,1% άνδρες, διάμεση (IQR) ηλικία: 44,5 (5,8) έτη]. Ένα κενό στη γνώση των ΓΙ παρατηρήθηκε αναφορικά με την αντίδραση των ασθενών τους στη συμβουλή για διακοπή του καπνίσματος, καθώς αυτή η ερώτηση απαντήθηκε σωστά μόνο από το 31,0% των συμμετεχόντων στην αξιολόγηση αναφοράς. Στατιστικά σημαντικές αυξήσεις παρατηρήθηκαν στην αυτό-αποτελεσματικότητα των ΓΙ να συμβουλεύουν τους ασθενείς τους για τους καλύτερους τρόπους διακοπής [διάμεσο (IQR) σκορ: 3 (1) πριν, 5 (2) αμέσως μετά και 4 (2) ένα μήνα μετά την εκπαίδευση, p-value=0,002] και να δρουν βάσει της απόφασης των ασθενών [διάμεσο (IQR) σκορ: 3 (0) πριν, 4 (2) αμέσως μετά και 4 (1) ένα μήνα μετά την εκπαίδευση, p-value=0,030]. Οι αυξήσεις που καταγράφηκαν στην αυτό-αναφερόμενη παροχή των στοιχείων της «Πολύ Σύντομης Συμβουλής» (ΕΡΩΤΗΣΗ, ΣΥΜΒΟΥΛΗ, ΔΡΑΣΗ) από τους ΓΙ, δεν ήταν στατιστικά σημαντικές.

Στόχος 5: Οι ΓΙ ανέφεραν ότι η εκπαίδευση Spirometry360 αύξησε την αυτοπεποίθησή τους στο να πραγματοποιούν σπιρομέτρηση και να ερμηνεύουν τα αποτελέσματά, σημειώνοντας τη χρησιμότητά της στο να ενεργοποιεί την έγκαιρη παραπομπή σε εξειδικευμένη φροντίδα. Σύμφωνα με τους ΓΙ, η εκπαίδευσή και η πρακτική τους είχαν άμεση επίδραση στους ασθενείς, καθώς έδωσαν την ευκαιρία σε εκείνους που δεν είχαν άμεση πρόσβαση σε διαγνωστικούς ελέγχους να παρακολουθηθούν και να παραπεμφθούν κατάλληλα. Το φορτωμένο εργασιακό πρόγραμμα και η έλλειψη εξοπλισμού αναφέρθηκαν ως εμπόδια στην παρακολούθηση της εκπαίδευσης και την επακόλουθη πρακτική. Ο κατ' απαίτηση και χρονικά αποδοτικός σχεδιασμός της εκπαίδευσης αναφέρθηκαν ως κύριοι παράγοντες διευκόλυνσης της παρακολούθησης, ενώ η εμπιστοσύνη των ασθενών στους ΓΙ αναφέρθηκε ως κύριος παράγοντας διευκόλυνσης της πραγματοποίησης σπιρομέτρησης στην καθημερινή κλινική πράξη.

Στόχος 6: Συνολικά, 31 ασθενείς με ΧΑΠ ή/και χρόνιο άσθμα ολοκλήρωσαν το 6-εβδομάδων πρόγραμμα ΠΑ (55,0% γυναίκες, μέση ηλικία 67,2 έτη). Η μέση τιμή της κλίμακας δύσπνοιας MRC μειώθηκε κατά 1,03 βαθμούς, φτάνοντας την ΕΚΣΔ του 1 βαθμού. Ο μέσος χρόνος καθίσματος-έγερσης μειώθηκε κατά 2,41 δευτερόλεπτα, μια διαφορά κοντά στην ΕΚΣΔ των 2,3 δευτερολέπτων. Η μέση απόσταση βάδισης (ISWT) αυξήθηκε κατά 87,39 μέτρα, ξεπερνώντας κατά πολύ την ΕΚΣΔ των 47,5 μέτρων. Το μέσο ολικό σκόρ του κλινικού ερωτηματολογίου για τη ΧΑΠ (CCQ) μειώθηκε κατά 0,53 μονάδες, μια διαφορά πάνω από την ΕΚΣΔ των 0,4 μονάδων. Το μέσο σκορ του ερωτηματολογίου αξιολόγησης της ΧΑΠ (CAT) μειώθηκε κατά σχεδόν 6 μονάδες, ξεπερνώντας την ΕΚΣΔ των 2 μονάδων. Το μέσο ολικό σκορ του ερωτηματολογίου SGRQ μειώθηκε κατά 23 μονάδες, μια διαφορά υψηλότερη της ΕΚΣΔ των 4 μονάδων. Το μέσο σκορ της κλίμακας Karnofsky βελτιώθηκε κατά 9,67 μονάδες. Τα σκορ των ερωτηματολογίων υγείας των ασθενών (PHQ-9) ήταν χαμηλά ήδη από την αρχική αξιολόγηση, παρ' όλα αυτά παρατηρήθηκε μια μείωση κατά 1,10 βαθμούς. Τα άμεσα οφέλη

της ΠΑ και η ανάγκη εφαρμογής παρόμοιων πρωτοβουλιών στις απομακρυσμένες περιοχές υπερτονίστηκαν από τους συμμετέχοντες.

Συμπεράσματα

Ξεκινώντας από την αξιολόγηση της κοινωνικό-οικονομικής επίδρασης των ΧΑΝ στην Ελλάδα (στόχος 1), τα ευρήματα της παρούσας διατριβής συνιστούν ότι η διαχείριση του έμμεσου φορτίου των ΧΑΝ, συμπεριλαμβανομένης της παρεμπόδισης των καθημερινών δραστηριοτήτων, φαίνεται να αποτελεί μια σημαντική περιοχή-στόχο για τις παρεμβάσεις υγείας.

Αναφορικά με τους παράγοντες που μπορούν να επηρεάσουν την εφαρμογή και υιοθέτηση παρεμβάσεων υγείας (στόχος 2), η γνώμη του κοινωνικού περιβάλλοντος και η αντιλαμβανόμενη σοβαρότητα της νόσου ήταν ειδικοί-για-το-υφιστάμενο-πλαίσιο προσδιοριστές της καπνιστικής συμπεριφοράς, και η γνώση αυτή μπορεί να φανεί χρήσιμη κατά το σχεδιασμό σχετικών παρεμβάσεων.

Τα παρατηρούμενα επίπεδα της ρύπανσης του ενδο-οικιακού αέρα ξεπερνούσαν τις διεθνείς οδηγίες για την ποιότητα του εισπνεόμενου αέρα (στόχος 3), επιβεβαιώνοντας την επιστροφή σε βλαβερές πρακτικές κατά την περίοδο της Ελληνικής οικονομικής κρίσης. Το συγκεκριμένο εύρημα συνιστά ότι οι στρατηγικές συνηγορίας για την ενεργειακή φτώχεια, αύξησης της επίγνωσης και ενδυνάμωσης των κοινοτήτων μπορεί να είναι ιδιαίτερης σημασίας σε περιόδους λιτότητας.

Ως προς τη διαχείριση της έκθεσης σε παράγοντες κινδύνου, φάνηκε ότι υπάρχει χώρος για αύξηση της επίγνωσης γύρω από τη ρύπανση του ενδο-οικιακού αέρα (στόχοι 2 και 3). Όμως, πιο δραστικές λύσεις φαίνεται να είναι απαραίτητες για το κάπνισμα καθώς, παρά την ύπαρξη ενημέρωσης/επίγνωσης, τα ποσοστά καπνίσματος ήταν υψηλά σε όλες τις μελέτες της διατριβής. Η εκπαίδευση στην «Πολύ Σύντομη Συμβουλή» φάνηκε να επηρεάζει την αυτό-αποτελεσματικότητα των ΓΙ στο να συμβουλεύουν τους ασθενείς τους σχετικά με τη διακοπή του καπνίσματος, υποδηλώνοντας ότι, στην περίοδο που έπεται της κρίσης, η εκπαίδευση ΓΙ στην παροχή αποτελεσματικής στήριξης για τη διακοπή του καπνίσματος κατά την καθημερινή κλινική πράξη μπορεί να εξεταστεί περαιτέρω ως μια στρατηγική αντιμετώπισης του καπνίσματος και πρόληψης των ΧΑΝ.

Σχετικά με τη βελτίωση της διάγνωσης των ΧΑΝ (στόχος 5), φάνηκε ότι, για αγροτικούς πληθυσμούς χωρίς άμεση πρόσβαση σε διαγνωστικές επιλογές, η εκπαίδευση ΓΙ στην πραγματοποίηση ελέγχων πνευμονικής λειτουργίας μπορεί να φανεί χρήσιμη για τη βελτίωση της υπο- ή της λανθασμένης διάγνωσης, διευκολύνοντας την κατάλληλη παρακολούθηση και την έγκαιρη παραπομπή σε εξειδικευμένη φροντίδα.

Η λειτουργία ενός προγράμματος ΠΑ (στόχος 6) για πρώτη φορά σε επίπεδο αγροτικής περιφέρειας και Ελληνικής ΠΦΥ έδειξε ότι τέτοιες χαμηλού κόστους, ανθρωποκεντρικές και ενδυναμωτικές

προσεγγίσεις μπορεί να αποτελέσουν μια εφικτή, ωφέλιμη και αποδεκτή επιλογή για τη θεραπεία των ΧΑΝ σε περιοχές χαμηλών πόρων.

Κλείνοντας, οι μελέτες που πραγματοποιήθηκαν φέρουν τους περιορισμούς που πηγάζουν από τους σχεδιασμούς και τα μικρά τους δείγματά καθιστώντας την περαιτέρω έρευνα απαραίτητη για την επιβεβαίωση των ευρημάτων.

Chapter 1. Introduction

1.1. Chronic respiratory diseases (CRDs)

1.1.1. Definitions and symptoms

The term ‘chronic respiratory diseases’ (CRDs) describes a group of non-communicable diseases that affect the airways and other structures of the lungs. Two of the most common CRDs are chronic obstructive pulmonary disease (COPD) and asthma. COPD refers to a range of inflammatory lung conditions that cause limitations in lung airflow and, subsequently, breathing-related problems. The most frequent symptoms of COPD are dyspnoea, excessive sputum production and chronic cough. Apart from the usual maintenance phase, people with COPD can suffer periods of symptoms’ exacerbation that may vary in terms of frequency, duration and severity. Asthma is a condition associated with airway hyper-responsiveness, causing the airways to narrow, swell and produce excessive mucus. This can result in recurrent attacks of breathlessness or breathing difficulties and trigger cough and wheezing when breathing out. Symptoms may occur several times in a day or week and can worsen during physical activity. Severity of CRD symptoms differs from person to person and can range from minor nuisance to major and/or life-threatening problems. In general, CRDs can affect patients’ quality of life, limiting ability to work and/or reducing capacity of performing regular activities (1).

1.1.2. Risk factors

CRDs often begin in childhood and persist through adulthood, with asthma being the most frequent chronic disease among children (2). However, CRDs present opportunities for prevention due to their slow evolution, chronic nature and modifiable risk factors. Namely, the most frequent risk factors for CRDs are tobacco smoking (including exposure to second-hand smoke), air pollution, allergens and occupational exposures. In particular, the causative relationship between smoking and COPD has been well established, with lifelong smokers having a 50% probability of developing COPD during their lifetime (3). In a prospective population-based cohort study of 14.619 participants, the incidence rate of COPD was found higher in current and former smokers than in never smokers [19.7 cases per 1000 people per year (95 % CI:18.1–21.4) in current smokers, 8.3 cases per 1000 people per year (95 % CI: 7.6–9.1) in former smokers and 4.1 cases per 1000 people per year (95 % CI:3.6–4.7) in never smokers (4).

Apart from smoking indoor air pollution, often caused by burning biomass fuels for heating and/or cooking purposes inside the households, is also an important risk factor for CRDs (5). Among the 3.8 million deaths caused by diseases related to household air pollution (HAP) every year, 20% is attributable to COPD (6). Because three billion people are exposed to HAP, compared with 1.1 billion

smokers, evidence suggests that exposure to biomass smoke is the biggest risk factor for COPD globally (7).

1.1.3. Treatment

Although they cannot be cured, symptoms of CRDs can be reduced. Various forms of treatment can help widen major air passages, improve breathlessness, prevent or control exacerbations and increase the quality of life for people with the disease. Asthma is more frequently managed though medications including inhaled corticosteroids which can control the progression of disease and prevent life-threatening attacks. COPD is diagnosed through spirometry, a test to determine how much and how quickly the patients can forcibly exhale air. When confirmed, COPD is treated with medications which including bronchodilators, inhaled corticosteroids, shot- or long-acting beta-agonists (SABA or LABA) and short- or long-acting muscarinic antagonists (SAMA or SABA). These medical treatments decrease disease progression and prevent COPD-related mortality (1). Non-pharmacological, physical treatments such as pulmonary rehabilitation have also been proven effective in amending the effects of CRDs (8).

Yet, despite the abundance of medical treatments, the most effective approach to prevent and/or tackle CRD is the reduction and avoidance of risk factors, namely tobacco smoking and household air pollution (9). Treatment and management of CRDs require a long-term and systematic approach which should constitute an integral part of healthcare services and public health activities, alongside acute and ambulatory care (1).

1.2. The epidemiological burden of CRDs

1.2.1. Global impact

CRDs impose a large burden in society, being placed among the leading causes of morbidity and mortality globally (9). The systematic analysis of the Global Burden of Disease study suggested that 44.9 million people worldwide were suffering from a CRD in 2017, representing an increase of 39.8% compared to 1990. According to the same analysis, the number of deaths due to CRD in 2017 was estimated at 3,914,196 (increased by 18·0% since 1990), making CRDs the third leading cause of death worldwide (7.0% of all deaths). Additionally, the total number of disability-adjusted life-years (DALYs) increased by 13·3%. More specifically:

COPD remains the most common CRD. The global prevalence of COPD was estimated at 3.9% in 2017, showing an increase of 5.9% since 1990 (10). According to the World Health Organization (WHO), 65 million people have moderate to severe COPD, from which about 3 million die each year, ranking COPD as third leading cause of death worldwide (1). The overall number of deaths due to COPD has been estimated at 41.85 per 100,000 people. Like all CRDs, COPD is also a major cause of morbidity due to symptoms, limited lung function and exacerbations that adversely affect functional

status and quality of life. In particular, DALYs attributed to COPD per 100,000 people reached 1,068.02 in 2017 (10).

The global burden of asthma is also significant. About 334 million people suffer from asthma (1), with the 2017-point prevalence estimate reaching 3.9%. This, however, represents a reduction by 3.9% since 1990. In 2019 asthma affected an estimated 262 million people and caused 461,000 deaths (11). The number of asthma-attributed deaths has been estimated at 6.48 per 100,000 people, while the respective DALY's were found at 297.92 per 100,000 of population.

1.2.2. Burden in Greece

As analysed in further detail in the extensive literature review of section 3 of the present thesis, CRDs constitute a substantial public health issue in Greece as well. In particular, the nationwide prevalence of COPD has been estimated at 8.4% in a 2004 study of people over 35 years old with a history of smoking (12). More recent evidence from a 2016 study conducted among people aged 40 years or older from the general population, suggest a COPD prevalence of 10.6% (13). In terms of asthma prevalence, the first nationwide epidemiological study of the Greek Thoracic Society suggests that 8.6% of the general population suffers from the disease (11). According to the same study, the frequency of asthma increases with age and is estimated at 3.8% in children 0-9 years old, 9.1% in adults of the 45-69 age group and at 11.8% in people over 70 years old. Mortality due to COPD is estimated at 10.9 deaths per 100.000 people while the number of DALYs has been found at 0.2 per 1000 capita per year. The figures for asthma suggest a similar number of DALYs, estimated at 0.4 per 1000 capita per year (14).

1.3. The economic burden of CRDs

1.3.1. Global impact

In addition to increased morbidity and mortality, the economic burden of CRDs is also considerable and it is predicted that it will continue to grow with the growing age of the population (1). The economic impact of CRDs consists of both direct and indirect costs. The direct costs are associated to healthcare expenditure related to CRD management and account for pharmaceutical and medical treatments, hospitalizations, admissions to intensive care units, laboratory tests and functional or imaging examinations. The indirect costs are often invisible, as they refer to non-medical costs (e.g. cost of patients' time) and productivity losses (e.g. cost of work loss days, impaired activity at work, impairment of daily activities, costs of non-paid caregivers' time) (15). Indirect costs including productivity loss may be of particular importance, especially for patients belonging to the active workforce and who contribute the most to local economies.

In the European Union, the direct cost of managing COPD is estimated at 38.6 billion euros annually, accounting for 6% of total healthcare spending and for 56% of the total cost of treating respiratory

diseases (16). Indirect costs of managing COPD have ranged between 451 million (in Spain) to 541 million euros per year (in Sweden), while COPD has been the leading cause of work days lost among respiratory diseases (1). In a study assessing the economic impact of COPD in 12 countries across the world, indirect annual costs of COPD per patient exceeded direct costs in many countries, accounting for 61%, 82% and 83% of the total cost in Italy, the Netherlands and the United Kingdom (UK) respectively (17). In the United States of America (USA), the direct costs of COPD were estimated at 32.1 billion dollars, while indirect costs reached 3.9 billion dollars (18).

Asthma is also associated with substantial economic burden. In a review of studies from global settings, direct costs of asthma management costs varied from less than 150 USA dollars per patient per year in Abu Dhabi, to more than 3,000 per patient per year in the USA. In the same study, the highest indirect costs of asthma were estimated at 1,274 USA dollars per patient per year (19). In an other USA study, the total cost of asthma to society was 56 billion dollars, with productivity losses due to morbidity accounting for $3.8 billion. In a study conducted in 11 European countries, the total cost o asthma management per patient per year was 1.583 euros and was largely driven by indirect costs which accounted for 62.5% of the total cost (20).

1.3.2. Burden in Greece

CLDs are responsible for substantial medical costs for patients and the health care system. The total costs of managing COPD are estimated at 4,730 per patient per year (21) and the respective costs for asthma at 2,281 euro per patient per year (22). The annual, per patient costs of maintenance pharmaceutical treatment for COPD and asthma are estimated at 639.9 and 916.9 euros respectively (21,22)

Apart from their economic impact, CLDs also constitute an important issue for the quality of life and work productivity of patients in Greece. Souliotis et all report that the mean number of work loss days per patient per year due to COPD is estimated at 16.9, with productivity losses of 968 euros (21). The respective mean number of work loss days due to asthma is estimated at 10.5 with the cost of work loss days reaching 602.6 euros (22). At the same time, disability adjusted life years (DALYs) for COPD and asthma reach 0.2 and 0.4 per 1000 capita per year respectively (23).

1.4. The burden of respiratory risk factors

1.4.1 The tobacco epidemic

About 1.3 billion people smoke tobacco worldwide. The tobacco epidemic is responsible for more than 8 million deaths per year, including more than 1.2 million deaths of people who do not smoke but who will die from exposure to second-hand tobacco smoke (24). Tobacco use is the leading global cause of preventable death (25). The urgent need to combat this epidemic led WHO to identify in 2008 six

evidence-based tobacco control measures, including among others monitoring tobacco use and prevention policies, offering help to quit tobacco use and promoting smoke-free policies. According to the latest WHO report on tobacco epidemic, three out of four countries and 5.3 billion people are now covered by at least one of these measures at the highest level of achievement. (26)

In addition, the same report found that, for the first time ever, the number of males using tobacco is declining globally. From 1.093 billion smokers in 2018, the report projects 2 million fewer smokers in 2020 and 6 million fewer by 2025. However, due to the slow decline among males, the WHO anticipates that the global target to reduce tobacco use by 30% by 2025 will not be met (26).

According to the latest Special Eurobarometer (2021), 23% of the respondents in the EU and the UK are smokers. This proportion has decreased by 3% since 2017. Among people who smoke, 89% report they consume at least one tobacco or related product daily, with an average of more than 14 cigarettes per day. In terms of social determinants, about 42% of the unemployed and 33% of manual workers are smokers compared with less than three in ten of those in all other occupational categories. Additionally, Respondents who perceive themselves as belonging to the working class (30%) and the lower middle class (25%) are more likely to be smokers than those in higher class brackets (14-20%) (27).

In Greece, the tobacco epidemic is a major public health problem. Rates of tobacco use in the country are the highest in Europe, estimated at 42% of the adult population (27). Tobacco use is responsible for an enormous burden of chronic disease and death (28) In particular 25.1% of deaths were caused by tobacco in 2016, while more than 22,7000 people are killed each year by a tobacco-caused disease (29). Moreover, tobacco use places an extraordinary burden on the national Greek health care system and is responsible for an estimated 200,000 hospital admissions (8.9% of the national total), with attributable hospital treatment costs calculated at over 554 million euros (10.7% of the national hospital budget) (30). The most recent Tobacco Atlas, highlights that the economic cost of smoking in Greece amounts to 4,663 million euro, including both direct costs related to healthcare expenditures and indirect costs related to lost productivity due to early mortality and morbidity.

Overall, the population of tobacco users in Greece report high rates of daily tobacco use (average 18.7 cigarettes per day) with daily consumption being the highest among countries in the EU. (27). A significant percentage (44%) of tobacco users in Greece are interested in quitting in the immediate future (31). The most recent Euroberometer report indicates that 34% of tobacco users have attempted to quit smoking and this is the second lowest proportion in the EU. Similar to most countries, less than one in ten report having received assistance with quitting from a health care professional (27).

1.4.2. Household air pollution

Breathing polluted air is a risk factor to most respiratory conditions (5). Improving air quality and reducing exposure to any kind of smoke are important steps towards promoting respiratory health (32).

In many low-resource settings, however, smoke produced by burning biomass inside households for heating and/or cooking is an important source of household air pollution (HAP) (33), the levels of which may often exceed the internationally established air quality standards (34,35). The WHO Global Health Observatory report estimates that HAP caused 3.8 million deaths worldwide in 2016, almost all in low-resource settings (36).

Particularly in low-resource settings, indoor biomass burning is mainly attributed to financial and awareness reasons, which impede the availability and purchase of clean fuels and the adoption of preventive measures (37). Yet, accumulating evidence suggests that exposure to HAP can substantially increase the burden and risk of chronic obstructive pulmonary disease (COPD) and can affect lung health in childhood (38-41). Specifically for Greece, about 1838 deaths and 31,611 disability-adjusted life years (DALYs) have been attributed to HAP (age-standardized rates of deaths and DALYs per 100,000 capita: 6 and 136.7, respectively) (42). Worldwide, biomass fuels are approximately used by 50% of households, exposing more than three billion people to the adverse effects of indoor air pollution (34).

In Greece, the issue of air quality deterioration received prominence during the peak of the financial crisis that started in 2008 and substantially affected the country. Outdoor air quality data from urban settings suggested a dramatic rise in the concentration of airborne particulate matters during the winter period, which, apart from morning traffic hours, also peaked at noon (43-45). Additionally, measurements of carbon monoxide during the night time suggested that emissions from biomass combustion contributed increasingly to the atmospheric pollution of urban areas (46). The phenomenon was attributed to an increased use of fireplaces which, due to the significant increases in the price of conventionally-used fuel oil, shifted from mostly decorative reasons to actual domestic heating (47,48). A survey of 598 Greek households showcased the impact of the economic crisis on energy consumption, highlighting that low-income households were even more vulnerable to being “fuel poor” (49).

Comparative figures demonstrate that biomass fuel use in Greece has increased between the pre- and post-financial recession periods. Namely, in 2005, slightly more than 2% of the total energy use in the household sector was attributed to biomass burning. In 2030, it is estimated that the respective share will reach almost 4%. These estimates exceed the European Unions’ overall use, where, in 2005, biomass combustion in the residential sector accounted for 1.9% of total energy use, while the respective estimate for 2030 is approximately 3% (50).

1.5. Low-resource settings and health inequalities in CRD

Low-resource settings and, in particular, low- and middle- income countries (LMICs), are disproportionally affected by CRDs, both in terms of morbidity/mortality and socioeconomic burden.

Namely, the greatest burden of disease is observed in low-resource settings, with over 90% of the global COPD mortality and 80% of asthma mortality being observed in LMICs (51). Such disparities can be attributed to several reasons including limited access to medication either due to general availability or individual cost holds a key role. The WHO suggests that asthma treatment is not available to people in low-resource settings, while asthma deaths are related to lack of proper treatment (1).

Additionally, it has been documented that exposure to respiratory risk factors, namely tobacco and HAP are more common in populations of lower socioeconomic status (52). Apart from the financial reasons that may impede, for example, the availability and purchase of clean solution is particularly related to limited awareness higher exposure to risk factors is related to limited awareness. Especially, in constrained-resources environment patients, stakeholders (healthcare professionals, government officials and local communities) and the public may be unaware of the damage to respiratory health caused by tobacco and biomass fuel smoke, a fact impeding the adoption of preventive measures (20).

Socioeconomic status affects not only the risk of developing COPD and other CRDs but also the severity of related health outcomes (53). In a study including 9,255 people from 12 settings, airflow obstruction was significantly increased even by 0.36% per unit of wealth score (p-value<0.001) (54). In combination with lack of access to proper diagnostic, medication and treatment options, patients with low socioeconomic status are faced with a more severe manifestations of their CRD and a particularly higher burden of disease (55). Due to higher exposures to risk factors and poverty in low-resource settings, CRDs often develop at an earlier age and affect younger, working people, who may be at the peak of their productivity (56-59). Apart from work, CRDs can significantly impact the performance of patients' daily activities. Lack of health coverage resulting from lack of health insurance in people of lower socioeconomic status or form the overall limitations of health and social-security systems in LMCIs results in further inequalities for substantial proportions of the population (61).

1.6. The Greek healthcare context

1.6.1. Care organisation

The Greek healthcare system combines elements from both the public and the private sector. Public services are provided universally and are financed by the state. They include emergency, primary and inpatient care, through hospitals, primary health care centers and rural practices. In addition, everyone has the right to social insurance, which covers services' use and reimburses prescription-only medications. A substantial proportion of the population is also covered by additional voluntary health insurance which, along with out-of-pocket payments, funds services such as private clinics and practices.

Primary health care in Greece is represented by vocationally-trained physicians in family medicine/ general practice (GPs). Unitil 2018, primary care was confined to rural areas with GPs typically serving in rural primary healthcare centers and satellite practices. GPs were mainly operating without any primary care team, due to the limited health professional support available in rural facilities. By 2018, community-based primary care units comprising of teams of primary care providers had been established in urban areas as well. Despite these reforms, integration and coordination within primary care, as well as between primary and secondary care requires extensive efforts.

Respiratory care in Greece is organized at three levels: i) GPs and private practice pulmonologists offering mainly primary care ii) hospitals providing secondary care iii) tertiary hospitals offering more specialized services. Until today, a comprehensive referral system is lacking in Greece and, in general, respiratory health services mainly focus on acute care with much lower emphasis on long-term, non-medical therapeutic and preventive services.

1.6.2. Preventive services

While smoke-free legislation has been passed in Greece in 2010, smoking bans in public places (e.g. restaurants, bars etc.) are frequently not adhered to (28). Moreover, a large proportion of adults report exposure to second hand smoke indoors in drinking establishments (83%), eating establishments (72%), and work places (41%) (27). All first line stop smoking medications are available in Greece, however there is currently no reimbursement within the publicly funded drug benefit plan to cover the cost of these. Likewise, there is no formal reimbursement for provider consultations for smoking cessation. At present, there are a limited number of specialized smoking cessation clinics operating mainly in hospitals of large urban settings.

1.6.3. The Greek economic crisis

In 2008 a severe economic crisis hit Greece. The gross domestic product and health expenditure declined by 25%, while unemployment increased from 9.6 to 26.5% (62). The austerity period lasted for about ten years, while its effects are evident until today. This financial crisis has meant reductions to healthcare budgets, resulting in cuts to several public services, staff and infrastructure. Furthermore, the use of private services has been limited for a substantial proportion of the population, due to reductions in personal income. The unmet needs for medical care increased between 2009 and 2014 (63), while the health effects of the crisis were likened to '*omens of a Greek tragedy'* (64).

Despite the substantial clinical and economic burden, care for respiratory conditions could not remain unaffected. Particularly in COPD, an extensive literature review suggested that restrictions imposed during the Greek austerity reduced capacity to prevent, diagnose and treat COPD in parallel with current higher detection rates. Patients were struggling to afford medications due to their decreased income (by up to 20%) and higher medication co-payments (up to 25%), resulting in 11.5% more exacerbations and 14.1% more hospitalisations annually (65). The situation was more aggravated in rural areas of the

country, where the burden of disease is substantial (12), while the population was already more deprived in terms of both income and healthcare provision (66,67). Reports from rural areas of the island of Crete, Greece suggested that COPD were trapped in the financial crisis, reporting behaviours like medication storage and sharing or non-adherence a result of their financial incapacity, along with deterioration of their psychological and emotional status (68).

1.7. Rationale

1.7.1. Focusing on and strengthening primary health care (PHC)

PHC engagement is essential in tackling the current and future burden of CRDs (69). Primary care takes a holistic approach to identify and manage people who may have multi-morbidity as opposed to treating single diseases. It also sees patients in the context of their families, homes and communities. This is particularly important in low-resource settings where access to specialized care may be hampered by costs and distance or transportation barriers, while appropriate treatments may either be unavailable or difficult to afford. Primary care in Greece is often the only option for people in rural and remote areas who were always more deprived than urban ones. Yet, PHC has been severely affected by the country's economic crisis, which significantly impacted both providers' and patients (68,70). Although recent actions have been undertaken to reform the Greek PHC, overall integration and coordination of PHC is still lacking (71). Since PHC has been acknowledged by the WHO as the most sustainable, accessible and cost-effective setting to tackle non-communicable diseases, additional efforts are necessary to strengthen primary care and empower communities.

1.7.2. Focusing on prevention

1.7.2.1. Research on contextual factors that affect awareness-raising and implementation of interventions

The most affordable and effective strategy for respiratory health is to prevent illness occurrence or progression by reducing exposure to risk factors and enabling diagnostic and treatment options (1,5). These would include actions such as enhancing the knowledge of healthcare professionals and raising public awareness about the damaging effects of smoke from tobacco and biomass burning, promoting smoking cessation, providing alternatives for cooking and/or heating on households with limited access to clean fuels and promoting pulmonary rehabilitation. However, it has been proven that implementation and successful adoption of respective interventions has been challenging, especially in low-resource settings (72-74).

For health interventions to be successful, understanding of and alignment with the local context is crucial (75,76). On the one hand, this includes the examination of the burden of the disease in terms of its epidemiological and economical impact (including impact of risk factors), since health behaviors depend largely on socio-economic determinants including poverty (77). On the other hand, however,

implementation of successful interventions encompasses the understanding and integration of local beliefs, perceptions and behaviours towards the respective health issue. The general knowledge, in combination with communities' health beliefs and perceptions about risk and need for change, are key determinants for linking symptoms with a particular disease, modify behaviour and take action to avoid exposure (37). In particular for CRDs, evidence suggests that public knowledge on the identity and implications of COPD and asthma is often limited in low resource-settings (5). Research on health and perceptions beliefs is generally scarce in Greece but, particularly for CRDs, it is even more limited.

In Greece, although relatively much research has been performed on the epidemiological burden of COPD and asthma, their financial impact has not been extensively explored (21). In particular, although a substantial aspect of CRD's social impact concerns patients productivity loss and activity impairment (78), little is known about their indirect economic burden. The evidence is even more limited for low-resource rural primary care settings which, have been disproportionally affected by the country's recent economic crisis (79-82).

In further terms of contextual knowledge, the evidence on the significant impact of Greece's economic recession on fuel use practices, little is known about the magnitude and health effects of HAP in Greek households. Data are even scarcer for the rural and mountainous areas of the country which are even more prone to fuel poverty than urban areas due to their increased heating needs, accessibility and economic restrictions (49). Despite, also the evidence regarding the particular impact on disease management for patients with chronic respiratory diseases (68) and on the general respiratory health of rural populations, the burden of residents' respiratory symptoms in parallel with their exposure to HAP has not been examined. (68,83)

1.7.2.2. Promoting smoking cessation support: Very Brief Advice on Smoking

Smoking is the single most preventable cause of death (83). Advice from health care professionals can trigger quit attempts from smokers (85). Apart from advice, offering patients support with quitting has been shown to be more effective (86,87). The odds of quitting smoking have been found 217% higher if support with quitting is offered by a healthcare professional compared to no advice (86). The odds of making a quit attempt have also been found higher if help is offered by the GP compared to no advice (87).

Very Brief Advice (VBA) on smoking is an intervention designed to be used opportunistically by healthcare professionals, in less than 30 seconds, in almost any situation with a smoker. The VBA model has been developed by the UK's National Center for Smoking Cessation and Training (NCSCT) and has been evaluated as effective in the UK (87). The three elements of the VBA model include:

- Establishing and recording smoking status (ASK)
- Advising on how to stop (ADVISE)
- Offering help (ACT)

VBA is designed to promote quit attempts and can be combined with referral to specialized smoking cessation services. VBA is a recommended clinical practice in the UK, with more than 55,000 healthcare professionals having received respective VBA training (88).

Despite the high burden of smoking in Greece, the majority of clinicians have not received formal training in tobacco treatment. However, training health care professionals in evidence-based approaches to address tobacco use with patients is critical to increasing the number of patients who make quit attempts. In a study conducted in Crete, Greece training GPs in providing effective smoking cessation support has demonstrated significant increases in the rates at which GPs helped their patients with smoking cessation (rates of asking about smoking status: 58.0% pre- vs. 82.8% post-training, $p=0.001$; advising on quitting: 52.5% vs. 81.5%, $p<0.001$; assisting with quitting: 16.1% vs. 64.8%, $p<0.001$). Under the limited resources imposed by the recent Greek financial crisis, primary care providers and, subsequently, patients and the population would benefit immensely from training on brief smoking cessation interventions (89).

1.7.3. Promoting early identification of CRD: Spirometry 360 training programme

Spirometry is essential for diagnosing COPD, according to international guidelines (90). The majority of individuals with asthma or COPD are receiving care that does not include pulmonary function testing as recommended (91,92). Lack of appropriate training in performance and interpretation have been identified as key barriers to the routine use of spirometry by PHC providers (91,93).

As part of FRESH AIR, the Spirometry 360 training was distributed to GPs in Crete, Greece. Spirometry 360 is an interactive, online training and feedback program designed by the University of Washington (http://www.spirometry360.org/). The Spirometry 360 training includes the Spirometry Fundamentals tutorial, interactive case-based Learning Labs, and monthly feedback on tests performed at the point of care. A randomized controlled trial of primary care practices demonstrated that the combination of training and feedback in the Spirometry 360 intervention significantly improved both the quality of performed spirometry and the provided treatment (92).

Like in many low-resource settings (94), spirometry is not generally available in Greek rural primary care settings. The financial crisis has further caused major shortages in equipment and barriers to diagnostic options (65). Barriers to healthcare access led to the proportions of patients with unmet healthcare needs doubling, with 12.2% of them citing cost as the main reason for not receiving treatment or diagnostic tests (95). Late diagnosis of CRDs leads to significantly worse health outcomes for patients In a UK study of more than 10,000 primary care patients, late COPD diagnosis was associated with shorter time to first exacerbation (14.5 vs 29.0 months for late vs early diagnosis), higher risk of first exacerbation and (OR=1.46, 95%CI :1.4-1.55) and increased exacerbation rate (108.9 vs. 57.2). In about two thirds of patients, the opportunity to diagnose COPD at an earlier stage was missed (96).

1.7.4. Promoting affordable treatment options: Pulmonary Rehabilitation (PR) programme

Given the financial restrictions for individuals and healthcare systems in low-resource settings, promoting affordable and equitable treatment solutions for patients with CRD is urgent and necessary. PR is an evidence-based, non-medical, low-cost treatment intervention, proven effective in amending the systemic effects of lung disease, including breathlessness, inactivity and deconditioning (90). PR is recommended by international guidelines for patients with COPD (90,97,98).

In 2015, a development study was conducted in Uganda aiming to assess the feasibility of a culturally adapted PR programme (99) developed based on UK standards (100). This was not a substitution of hospital-based PR, but rather a low-cost and locally tailored approach (e.g. PR training equipment was substituted by practical, everyday objects, while recruitment, referral and learning processes were based on local cultural demands). The pilot PR programme of Uganda resulted in substantial improvements in patient symptoms, exercise capacity (99, 101) and quality of life (102,103).

Despite the substantial burden, integrated services for patients with CRDs, including PR, are largely absent in Greece, especially at the primary care setting. While WHO places increasing emphasis on chronic diseases, integrating primary and secondary care in the management of long-term conditions remains a neglected area in the current health agenda (71). PR is still offered at a very limited scale, remaining restricted to few tertiary hospitals. PR programmes are not available in the rural periphery, where the burden of CRDs is substantial (12), while the population is more deprived in terms of both income and healthcare provision (66,67). Especially during Greece's economic recession, patients with CRD in rural areas were faced with further significant restrictions (68,104). Improving functional status with limited cost can be of particular importance for people with CRDs and their families in low-resource rural areas of Greece.

1.7.5. The need for implementation science

Implementation science is defined by the Journal of Implementation Science as *"The scientific study of methods to promote the systematic uptake of clinical research findings and other evidence-based practices into routine practice, and hence to improve the quality and effectiveness of health care. It includes the study of influences on healthcare professional and organisational behaviour"* (www.implementationscience.com/about). To study implementation and capture learning through implementation science the following interrelated questions are addressed (105):

1. What is the intervention (e.g. complexity, evidence-base)?
2. What is the outer setting (e.g. economic, social background)?
3. What is the inner setting (e.g. organisational structures)?
4. Which individuals are involved (e.g. patients, providers, stakeholders),

5. What are the process of implementation (e.g. methods and approaches used to facilitate, adopt, implement and sustain interventions)?

The essence of implementation science lies on understanding that contextual factors is key to translating evidence into practice. In the context of CRDs in low-resource settings, it has been acknowledged that implementation science research is urgently needed to explore how existing evidence-based solutions for prevention, diagnosis and treatment can be adopted and effectively applied in real life (106,107). Simple extrapolation from high-resource countries to low-resource settings can be particularly prone to errors since people experience different amount of risks or barriers, which is additionally determined by local socio-economic, cultural and other contextual factors (108). Since low-resource settings are seriously under-represented in CRD research (109), implementation science is necessary to create knew knowledge and facilitate the testing and sustainable adoption of existing practices with proven effectiveness.

1.8. FRESH AIR

The present PhD thesis was conducted in the framework of FRESH AIR (acronym for *Free Respiratory Evaluation and Smoke-exposure Reduction by primary Health cAre Integrated gRoups*), a 3-year implementation science programme funded by European Unions' Horizon 2020 framework under grant agreement no. 680997 (www.ipcrg.org/freshair). FRESH AIR addressed the need to prevent, diagnose and treat lung diseases in LMICs and other low-resource settings where the greatest burden of disease is experienced. The Consortium comprised of 13 organizations from nine different countries and brought together leading international respiratory researchers, clinicians and policy experts, along with healthcare providers, policy makers and implementers from four countries that represent very different low-resource settings.

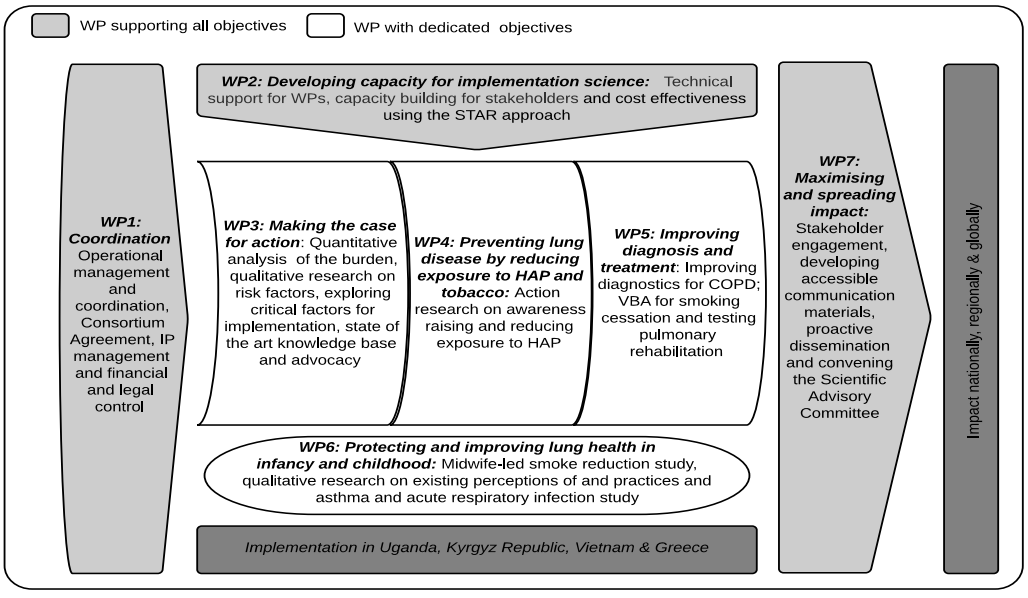
FRESH AIR was designed to adapt and test innovation and evidence-based practice in the prevention, diagnosis and treatment of lung disease in four low-resource settings in Uganda, Kyrgyz Republic, Vietnam and Greece with high levels of tobacco consumption and exposure to HAP. In so doing, the skills and technology were transferred from high-income countries to new contexts and a range of implementation science research questions were explored. The new knowledge was disseminated nationally, regionally and internationally to facilitate the scale-up of interventions tested by the project and global impact of research findings. The project provided new perspectives on policy issues, increased the international profile of EU funded research on key health challenges and opened up markets for healthcare innovations (110).

The overall aim of the FRESH AIR was to improve health outcomes for people at risk of CRDs in low-resource settings by developing capacity for implementation of evidence-based interventions for

prevention, diagnosis and treatment in these contexts. As shown in **Figure 1**, the project had seven specific objectives, formed in seven interrelated work packages (WPs), focusing on the following:

1. To identify the specific factors that influence the implementation of evidenced-based interventions in the prevention and treatment of CRDs in the participating low-resource settings (WP2 and WP3)
2. To explore which awareness-raising approaches are most effective in motivating behaviour change regarding smoking and HAP and to evaluate the feasibility, acceptability and effectiveness of HAP reduction interventions in selected communities in these countries. (WP4)
3. To provide access to smoking cessation support by adapting evidence-based VBA training interventions and delivering them to healthcare professionals in the participating countries. (WP5)
4. To test the feasibility and acceptability of methods for diagnosing COPD using innovative spirometry (WP5).
5. To test the feasibility and acceptability of PR as a low-cost treatment for CRDs in these countries. (WP5).
6. To test how to best protect children's' respiratory health (WP6)
7. To generate new knowledge, innovation and scalable models to ensure equitable access and to support their implementation through proactive dissemination regionally and internationally. (WP3 to WP7)

Figure 1. FRESH AIR interrelated work packages.



***Source**: Cragg L et al. 2016*

1.9. Thesis aim and objectives

As part of FRESH AIR, the overall aim of this thesis was to contribute to the improvement of prevention, diagnosis and treatment of CRDs in low-resource, primary care settings on the island of Crete, Greece. The thesis did so by identifying factors that influence the implementation of health interventions, raising professional capacity and promoting innovative, evidence-based and scalable approaches for healthcare professionals and the public.

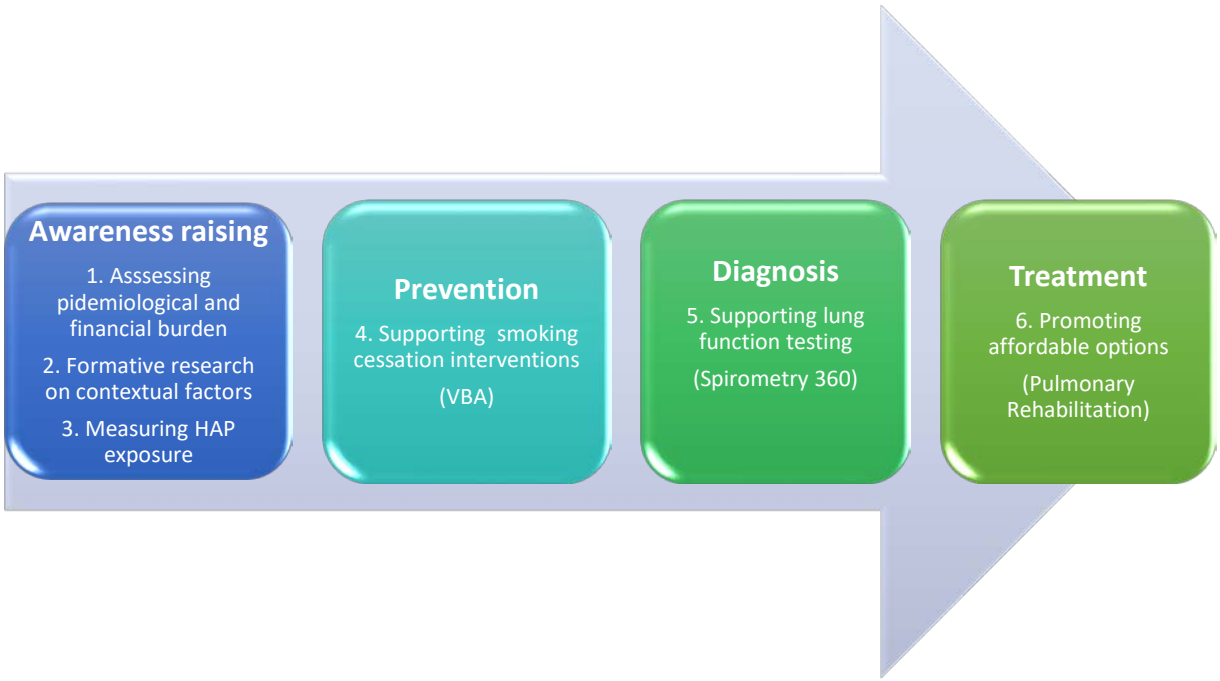
Acknowledging that effective actions to combat CRDs need to be performed holistically, throughout the continuum of respiratory care, the thesis explores following implementation research questions in the targeted setting:

1. What is the expected and observed burden of CRDs and relevant risk factors?
2. What are the contextual and cultural factors that may affect CRD interventions?
3. What is the magnitude of HAP exposure and its impact on respiratory symptoms?
4. How can PHC professionals be supported in providing brief smoking cessation interventions, contributing to CRD prevention?
5. How can PHC professionals be supported to use lung function testing for timely CRD identification?
6. How evidence based, low-cost treatment options be adopted and supported in the local context?

Based on the above research questions, this thesis employs a multi-step process to achieve the following objectives (**Figure 2**):

7. To assess the clinical and economic burden of asthma/COPD, illustrating the local health-economic impact of CRDs.
8. To explore community beliefs and perceptions towards CRD and examine how these are related to risk behaviours.
9. To measure levels of HAP, as a risk factor related to the recent economic crisis and examine exposure in parallel to respiratory health outcomes.
10. To assess the impact of a VBA on Smoking educational module on GPs knowledge, self-efficacy and self-reported practice
11. To assess the applicability of a remote spirometry training and feedback program (Spirometry 360) among local GPs
12. To adapt and examine the applicability and impact of a pulmonary rehabilitation programme on patients' health outcomes.

Figure 2. Continuum of respiratory care and thesis contribution.



Chapter 2. Methods

2.1. General overview

A general summary of methods employed by this thesis in is provided in **Table 1**. Detailed methods per objective are presented in section 2.2.

Table 1. Overview of thesis methods.

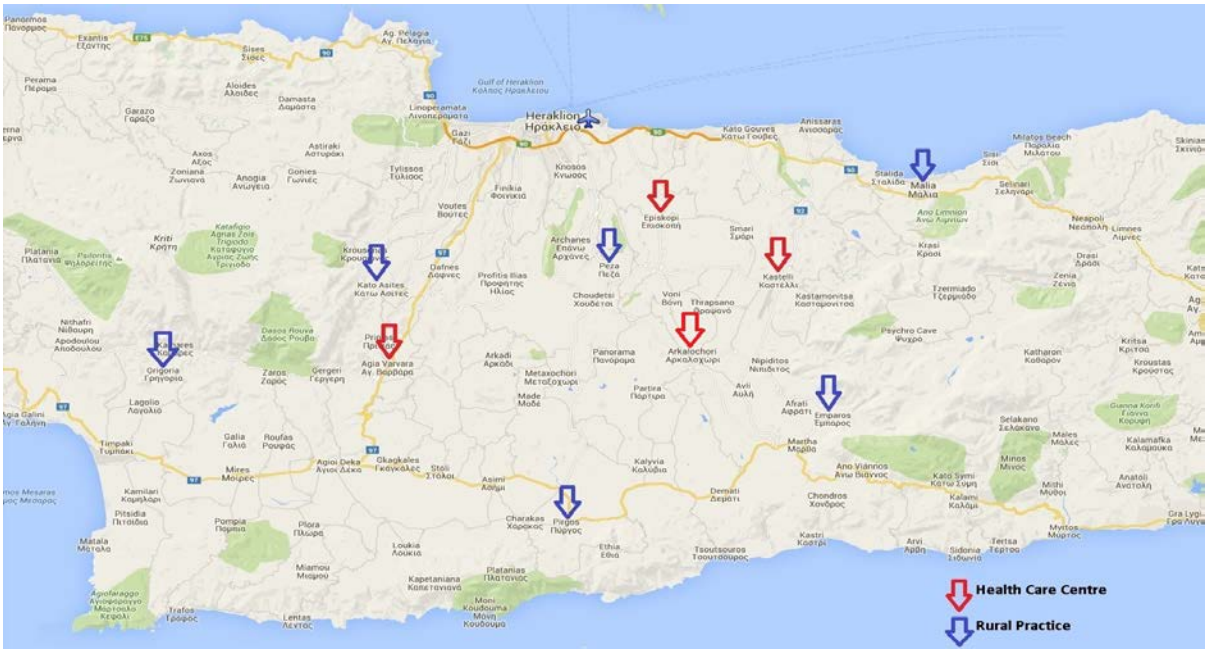
Objective	Design	Setting	Participants	Framework	Tools	Key outcomes	Analysis
1. Assessing the clinical and financial burden of CRDs in PHC	1. Scoping literature review 2.Observational study	1. PubMed and grey literature 2. 10 rural PHC units	1. 30 studies included 2. 100 consecutive PHC patients with asthma/and or COPD	N/A	1. Search terms: (COPD OR asthma) AND (Greece) 2. CRF incl. WPAI	▪ Clinical status ▪ Healthcare costs ▪ Productivity losses	1. Evidence synthesis 2. Descriptive statistics
2. Exploring community beliefs, perceptions and behaviours towards CRD.	Observational study	20 villages randomly selected	200 community members (door-to-door sampling)	▪ Health Belief Model ▪ Explanatory Model of Illness ▪ Theory of Planned Behaviour	▪ SETTING-tool	▪ Beliefs ▪ Perceptions ▪ Behaviours	▪ Descriptive statistics ▪ Binary logistic regression
3. Assessing HAP and respiratory health outcomes in rural households	Observational study with repeated design (pre, post)	8 rural villages	▪ 32 purposively selected households ▪ 42 residents	N/A	▪ RTI MicroPEM ▪ EasyLog USB ▪ CRF	▪ PM2.5 ▪ CO ▪ Symptoms	▪ Descriptive statistics ▪ McNemar ▪ Wilcoxont
4. Testing the VBA on Smoking training in PHC	Observational study with repeated design (pre, post, follow-up)	Heraklio and Rethymno	27 GPs	▪ PRIME theory of motivation ▪ COM-B	CRFs	▪ Knowledge ▪ Self-efficacy ▪ Self-reported practice	▪ Descriptive statistics ▪ Cohrane's Q ▪ Friedman ▪ McNemar ▪ Wilcoxon
5. Exploring applicability of remote spirometry training and feedback in PHC (Spirometry360)	Qualitative study	Heraklio	5 GPs in focus group	▪ Chronic Care Model ▪ COM-B	Interview guide	▪ Reception ▪ Attendance ▪ Comprehensiveness ▪ Usefulness ▪ Added value	Thematic Analysis
6. Evaluating a pulmonary rehabilitation programme in PHC	Implementation science study with repeated design (pre, post)	1 rural PHC centre	31 patients with chronic asthma or COPD	Health Belief Model	▪ MRC, CCQ, CAT, SGRQ, PHQ-9, ISWT ▪ Interview guide	▪ Respiratory health status ▪ Functional status ▪ Exercise ▪ Depression	▪ Descriptive statistics ▪ Fishers' exact

Abbreviations are defined in the list presented in the beginning of the thesis

2.1.1. Designs and settings

As part of FRESH AIR, this thesis is an implementation science project employing both quantitative (observational studies with or without repeated measurements) and qualitative research methods. Six studies were conducted to address each of the six thesis objectives across the catchment areas of ten purposively selected PHC units throughout the region of Heraklion, on the island of Crete, Greece (**Figure 3**). The island of Crete is located at the southern part of Greece and is characterised by reach culture and tradition. It has a population of approximately 600,000 people distributed to four regions (Chania, Rethymno, Heraklio, Lasithi). Each region has one urban capital and numerus small rural villages, many of which are fairly remote and mountainous. A specific focus was placed on rural settings since they have been more deprived both in terms of income and healthcare provision (66,67), while exhibiting more frequent exposure to respiratory risk factors including smoking and HAP than urban areas (12).

Figure 3. Setting of project conduction.



**Original: D. Sifaki-Pistolla, adaptation: M. Anastasaki*

2.1.2. Populations and tools

The project targeted diverse populations, including patients with CRD, community members, PHC professionals and other stakeholders. Several tools have been developed by the FRESH AIR teams based on literature, pre-defined theoretical frameworks and validated tools, such as case report forms (CRFs), questionnaires, interview/focus group guides and training materials. All tools were adapted to Greek standards by the local FRESH AIR team, including the PhD candidate. Within the tools that have

been used in the present thesis, the Greek versions of the following validated questionnaires, scales and tests are included:

- **The Clinical COPD Questionnaire (CCQ)**: The CCQ is a 10-item health-related quality of life questionnaire recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for measuring health status in patients with COPD (https://ccq.nl/). The questions of CCQ are answered on a 6-point Likert scale (0: never to 6: almost always) and are divided into three domains: symptoms, functional state and mental state. The total score is calculated by adding the scores of the ten items and dividing that number by ten (i.e. the number of items). Additionally, it is possible to calculate the scores on each of the three domains separately. The total CCQ score, as well as the score of each of the three domains range between 0 (which indicates very good health status) to 6 (which denotes extremely poor health status) (111). In a systematic review of 43 studies, internal consistency (reliability) of the CCQ total score ranged from 0.84 to 0.94, and test-retest reliability ranged between 0.70 and 0.99 (112). According to the same analysis, the overall CCQ correlates well with other validated respiratory instruments including the St. George's Respiratory Questionnaire (r correlation coefficient ranging from 0.71 to 0.88) and COPD Assessment Test (r ranging from 0.64 to 0.88) and is sensitive to exacerbations, pulmonary rehabilitation and smoking cessation. The Minimum Clinically Important Difference (MCID) for the CCQ is 0.4 (113). The CCQ has been widely-used in several COPD populations and clinical settings, exhibiting good reliability, validity and responsiveness to interventions (114).

- **The COPD Assessment Test (CAT)**: CAT is an 8-item questionnaire measuring the impact of COPD on a person's life and how it changes over time. Each of CAT's questions is answered on a 5-point Likert scale (0: I am very happy to 5: I am very sad). CAT score ranges between 0 and 40, with higher values indicating more severe impact of COPD on a patient's life (115). The intra-class correlation coefficient of CAT (reproducibility) is equal to 0.8, while the Cronbach's a (internal consistency) has been reported to 0.88 (116). In terms of validity, the CAT correlates well with the St. George's Respiratory Questionnaire with the r correlation coefficient ranging from 0.8 in the US to 0.84 across 7 European countries (117). The MCID for CAT is equal to two (118) A literature review of 36 studies suggests that CAT has good reliability and validity and that the tool is responsive to interventions, including pulmonary rehabilitation (115).

- **St. George's Respiratory Questionnaire (SGRQ)**: The SGRQ is a 50-item disease specific instrument measuring the impact of obstructive diseases of the airways on patients; overall health, well-being and daily life. Questions of SGRQ are divided in two parts with three

components each. The first part addresses symptoms (frequency and severity) with a 1, 3 or 12-month recall. The second part covers activities that cause or are limited by breathlessness and impact of disease on social functioning, psychological disturbances (119). Questions are answered in Likert or dichotomous (true/false) scales. Scores range from 0 to 100, with higher scores indicating more limitations. The intra-class correlation coefficient of SGRQ (reproducibility) ranges between 0.8 and 0.9, while the Cronbach's a (internal consistency) has been reported higher than 0.70 (120). In terms of validity, the CAT correlates well with other measures of disease severity including the Medical Research Council (MRC) dyspnoea scale (121). The MCID for SGRQ is equal to four (122). The psychometric properties of the SGRQ have been evaluated in patients with COPD and severe asthma, indicating that it is a reliable instrument for assessing patients' response to treatment but also highlighting areas for improvement (123,124).

- **Work Productivity and Impairment Questionnaire (WPAI):** The WPAI is a 6-item (Q1-Q6) tool designed to evaluate impairment in both paid and unpaid work due to a health problem. It measures absenteeism, presenteeism, overall work impairment (absenteeism and presenteeism combined) and impairment in regular activities attributed to the disease during the past week (125). Type of items vary from open-ended questions of scale nature to 10-point Likert scale questions, with 0 indicating no effect of disease and 10 indicating complete prevention of activity due to the disease. Namely, the WPAI questions are:
    - Q1: Are you currently employed
    - Q2: Hours missed from work due to the disease
    - Q3: Hours missed from work due to other reasons
    - Q4: Actual hours of work
    - Q5: Degree to which the disease affected productivity while working
    - Q6: Degree to which the disease affected regular activities

  All items are calculated into percentages by multiplying each item score by 100. Percentage of work time missed due to the disease (absenteeism) is then calculated as Q2/(Q2+Q4), while percentage of impairment while working due to problem (presenteeism) is equal to Q5/10. Percentage of overall work activity (absenteeism and presenteeism combined is calculated as Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)] and percentage of activity impairment due to the disease equals Q6/10. The resulting scales of scores range between 0 and 100%, with higher numbers indicating greater impairment and less productivity (http://www.reillyassociates.net/WPAI_General.html). The WPAI has been used and validated to quantify work impairments for numerous diseases, including asthma and COPD (126-128).

- **Patient Health Questionnaire - 9 (PHQ-9):** The PHQ-9 is a 9-item instrument measuring for assessing depression and other mental health disorders. It can be used as a symptom tracking tool to track a patient's overall depression severity as well as improvements due to intervention. The nine items of the PHQ-9 are based on the nine diagnostic criteria for major depressive disorder of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and each is scored in a 3-point Likert scale (0: not at all to 3: nearly every day). The resulting scale of scores ranges between 0 and 27. PHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively (129). The PHQ-9 has been validated through large-scale studies in primary care and other clinical settings which suggest that it has good diagnostic validity and constitutes a reliable measure of depression severity (129-131). The PHQ-9 has also been evaluated in COPD patients undergoing pulmonary rehabilitation, fulfilling important psychometric criteria, including validity and reliability (132).

- M**edical Research Council breathlessness scale** original (MRC) and modified (mMRC) version: The MRC and mMRC breathlessness scales are used to quantify the disability associated with breathlessness (rather than breathlessness itself). They comprise of five statements that describe the range of respiratory disability from none (Grade 1 for MRC or 0 for mMRC) to almost complete incapacity (Grade 5 for MRC or 4 for mMRC). The score is the number that best describes the patient's level of activity. The score correlates well with other breathlessness scales and lung function measurements (133,134). It has exhibited good responsiveness to interventions, including pulmonary rehabilitation (135). The MCID for the MRC and mMRC scales is equal to one (136).

- **Modified Borg Dyspnea Scale**: The Modified Borg Dyspnea Scale is used to measure patient-reported dyspnea during physical exercise testing. It consists of statements describing severity of dyspnea though a score ranging from 0 (no dyspnea) to 10 (unbearable dyspnea). It has been widely used during pulmonary rehabilitation in COPD in order to determine exercise workload (137,138) as well as the clinical significance of the rehabilitation outcome. The scale correlates well with pulmonary function tests (139).

- **Karnofsky Performance Status Scale**: The Karnofsky score is an index assessing functional impairement. The scale comprises of is an 11-point rating scale which ranges from normal functioning (100) to dead (0) in ten-point increments. According to their score. Patients are classified to 'unable to care for self' (scores 0, 10, 20, 30 and 40), 'unable to work' (scores 50, 60, 70) and 'able to carry on normal activity and work' (scores 80, 90, 100) (140,141). The reliability and validity of the Karnofsky scale have been re-examined and appraised since its

development (142) and it has been used to determine outcomes in several patient populations and clinical settings (143, 144).

- **Incremental Shuttle Walk Test (ISWT):** The ISWT is a standardized, externally paced test, incorporating an incremental and progressive structure, to assess functional capacity in patients with chronic airways obstruction (145). The test provides a measurement of disability and allows the comparison of patients' performance. It is conducted along a 10 meters course, with the walking speed increasing every minute, until the patient is too breathless to continue or can no longer maintain the required speed. The result is presented as the total distance achieved. The ISWT is responsive to maximal exercise capacity and exhibits good reliability, validity, interpretability (146,147). It has been widely used in pulmonary rehabilitation. The MCID for the ISWT is 47.5 meters (148).

- **The 5-Times Sit-to-Stand Test**: the sit-to-stand test is used for testing the strength and endurance of individuals and evaluate their functional capacity. While participants' performance is monitored to ensure proper performance, the time taken to complete the 5 repetitions is counted. The score is the total number of stands within 30 seconds. Various versions of the test have been used for pulmonary rehabilitation in COPD (e.g. the 30-seconds test, the 1-minute test). According to a literature review of 17 studies, the metrological properties of sit-to-stand tests and responsiveness to rehabilitation are excellent (149). The MCID for the sit-to-stand time is 2.3 seconds (150).

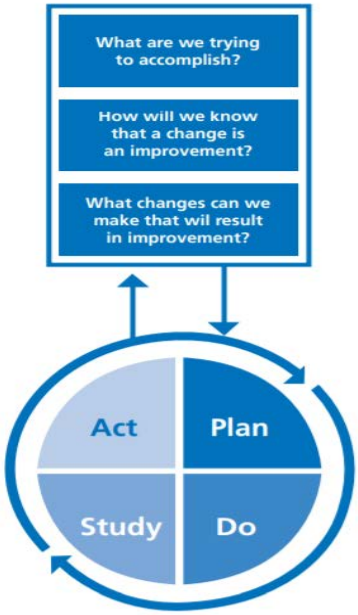
2.1.3. Theoretical frameworks and implementation strategies

Overall, as part of FRESH AIR, this thesis focuses on the processes of delivering interventions and other actions that, according to the evidence, lead to improved population health outcomes. As such, it is based on the concepts of the Model for Improvement which has been adopted by many healthcare providers, policy makers and other stakeholders as a framework for developing, testing and implementing changes leading to health improvements. The enables the pilot testing of evidence-based interventions and, if feasible and sustainable improvements are demonstrated, it progresses to wider scaling-up. The model combines elements of the Plan-Do-Study-Act (PDSA) cycle (**Figure 4**) to test changes in real-world settings and is easy-to-use, engaging, adaptive of proven interventions, robust and previously tested in low-resource settings (151). The four stages of the PDSA approach are:

- **Plan**: plan the change to be implemented
- **Do**: carry out the test or change

- **Study**: based on the measurable outcomes agreed before starting out, collect data before and after the change and reflect on the impact of the change and what was learned
- **Act**: plan the next change cycle or full implementation

Figure 4. The Plan-Do-Study cycle of the Model for Improvement.



***Source**: https://www.england.nhs.uk/wp-content/uploads/2021/03/qsir-plan-do-study-act.pdf*

The specific theoretical models have guided each of the thesis studies are described in detail in the following sub-sections.

2.1.4. Analyses

Depending on the study, analyses followed during this thesis ranged from descriptive and/or inferential statistics (including univariate tests of relationships and multivariate logistic regression analyses) to Thematic Content Analysis of qualitative data. For statistical analyses, normality of continuous variables was tested using Kolmogorov-Smirnov test. If the values of a variable follow the normal distribution, mean and standard deviation (SD) are reported and parametric tests are used. In case variables are not normally distributed median and interquartile range (IQR) are reported and non-parametric tests are used.

2.1.5. Reporting

The literature review performed as part of this thesis is reported using the PRISMA statement guidelines (152). Observational studies are reported using the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (153). Qualitative studies are reported using the Consolidated criteria for reporting qualitative research (COREQ) (154). Implementation science studies are reported using the Standards for Reporting Implementation Studies (StaRI) Statement (155).

2.2. Methods per objective

2.2.1. Objective 1: Assessing the clinical and financial burden of CRD in PHC

This study was part of a comparative FRESH AIR study whose detailed methods and results have been presented in a publication, co-authored by the PhD candidate, in Respiratory Research (156). The following methods were used for the Greek study, which was part of the present thesis.

Design

A mixed-methods study was conducted. At first, a scoping literature review was performed to identify existing data on epidemiological burden, healthcare utilization and costs of asthma and COPD in Greece. A scoping review design was followed since our aim was to provide a synthesis of the available evidence, rather than evaluating or weighting the findings of individual studies (157). Scoping reviews provide a snapshot of an overlooked or emergent field of research. The current scoping review was conducted following the five-stage methodological framework which entails (a) identifying the research question, (b) identifying relevant studies, (c) selecting relevant studies, (d) charting the collected data, and (e) synthesizing, summarizing, and reporting the findings (158).

Additionally, primary data were collected through a descriptive observational study among PHC patients to assess the direct and indirect impact of asthma and COPD, including work productivity loss. This primary, patient-reported data was subsequently compared to national-level cost data to determine the financial burden disease from the patient versus the system perspective.

Setting

For the literature review, the database of PubMed was used for the search of peer-reviewed articles and indexed publications. Grey literature was also included in order to avoid missing reports and local documents including Greek papers or European reports.

Primary data collection was performed in ten purposively selected PHC practices thought the region of Heraklion, Crete, Greece

Participants

The literature search strategy included all asthma/COPD-related evidence. We searched in English language for the terms “COPD” OR “asthma” AND “Greece”. The search was focused -but not limited to- studies conducted after 2005, written in English and with full text availability. Since it aimed to supplement the observational study, it did not employ specific criteria.

For the observational study, eligible participants were patients visiting the selected PHC practices, according to the following criteria.

Inclusion criteria

4. Presence of confirmed diagnosis of asthma or COPD in electronic or paper/based records
5. Willingness and ability to provide signed informed consent

Exclusion criteria

1. Age under 18 years old
2. Inability to provide consent

Sampling and sample size

For the observational study, no formal sample size estimations were performed, since our aim was to provide a broad picture of the context, rather than conducting a prevalence study. Therefore, ten individuals were consecutively recruited by each of the ten selected PHC practices, resulting in a convenience sample of 100 patients.

Data collection tools

The database of PubMed was used for the search of peer-reviewed articles and indexed publications. For grey literature, we hand-searched Google, Google Scholar and other publicly available sources such as reports of the Ministry of Health and other national or European organizations. Grey literature was included in order to avoid missing reports and local documents including Greek papers or European reports.

To collect data for the observational study, a survey form was developed by the FRESH AIR team of University Medical Center Groningen (156) based on literature and validated tools. The survey questionnaire can be found in **Appendix 4**.

Data and outcomes

For the literature review, epidemiological and cost data were collected, including respiratory care organisations, CRD incidence, prevalence, morbidity and mortality indicators, utilization of healthcare services, costs of services for the healthcare system, DALYs and quality of life indicators.

For the observational study, the survey collected information on the following outcomes:

- Demographic characteristics: age, gender
- Socio-economic status: health insurance, education, income, disability
- Clinical status: lung function, comorbidity

- Healthcare utilization: primary care visits, emergency department visits, hospitalizations, medication
- Healthcare costs: insurance covered and out-of-pocket expenses
- Productivity losses: assessed using the Work Productivity and Impairment (WPAI) questionnaire (125)
- Patients' quality of life: assessed using the Clinical COPD Questionnaire (COPD) (111) and the COPD Assessment Test (CAT) (115).
- Dyspnoea levels: assessed using the Modified Medical Research Council (mMRC) scale (159).

Procedures

The scoping review was performed in 2021, following a preliminary literature search that was conducted in 2018. The scoping review was conducted using medical databases (PubMed), publicly available international sources (e.g. WHO) and national databases, including the drug information system (Galinos) and the Ministry of Health's record on health expenditure (KEN). Studies were entered in a reference management system (Mendeley) and duplications were removed. Of the remaining documents information on the authors, publication date, design, setting and participants were extracted. Information on study outcomes was, subsequently, extracted.

For the observational study, asthma/COPD patients consecutively visiting the PHC practices were recruited during January-February 2017 by specifically trained GPs who had been engaged in FRESH AIR. GPs assessed inclusion/exclusion criteria and provided comprehensive information about the study to patients. GPs obtained signed informed consent from patients accepting participation and, subsequently, administered the survey. Upon completion, GPs performed an overall check of the surveys and returned them to the local FRESH AIR research team for data entry.

Analysis

For the literature review, healthcare utilization was calculated per category (e.g. hopsital, primary care, medication) and subsequently summed up in tabular format. Analysis of the primary data was performed using descriptive statistics in SPSS Version 25.0 (Armonk, NY: IBM Corp).

2.2.2. Objective 2: Exploring community beliefs, perceptions and behaviours towards CRD

This study was part of a comparative FRESH AIR study whose detailed methods and results have been presented in a Lancet Global Health publication, co-authored by the PhD candidate (160). Additional information on the context-mapping tool used in this study are also presented in a BMJ Global Health publication of the FRESH AIR group (161). The following methods were used for the Greek study, which was part of the present thesis.

Design

A descriptive observational study was conducted to determine CRD-related beliefs and perceptions and assess how they influence certain risk behaviours, including tobacco smoking, HAP-related practices and healthcare seeking.

Setting

The study was conducted in 20 randomly selected rural villages in the region of Heraklion, Crete, Greece.

Participants

Eligible participants were community members residing in the randomly selected villages, meeting the following criteria

Inclusion criteria

1. Age of 18 years or older
2. Willingness and ability to provide signed informed consent

Exclusion criteria

1. Permanent residency outside the selected village
2. Inability to provide signed informed consent

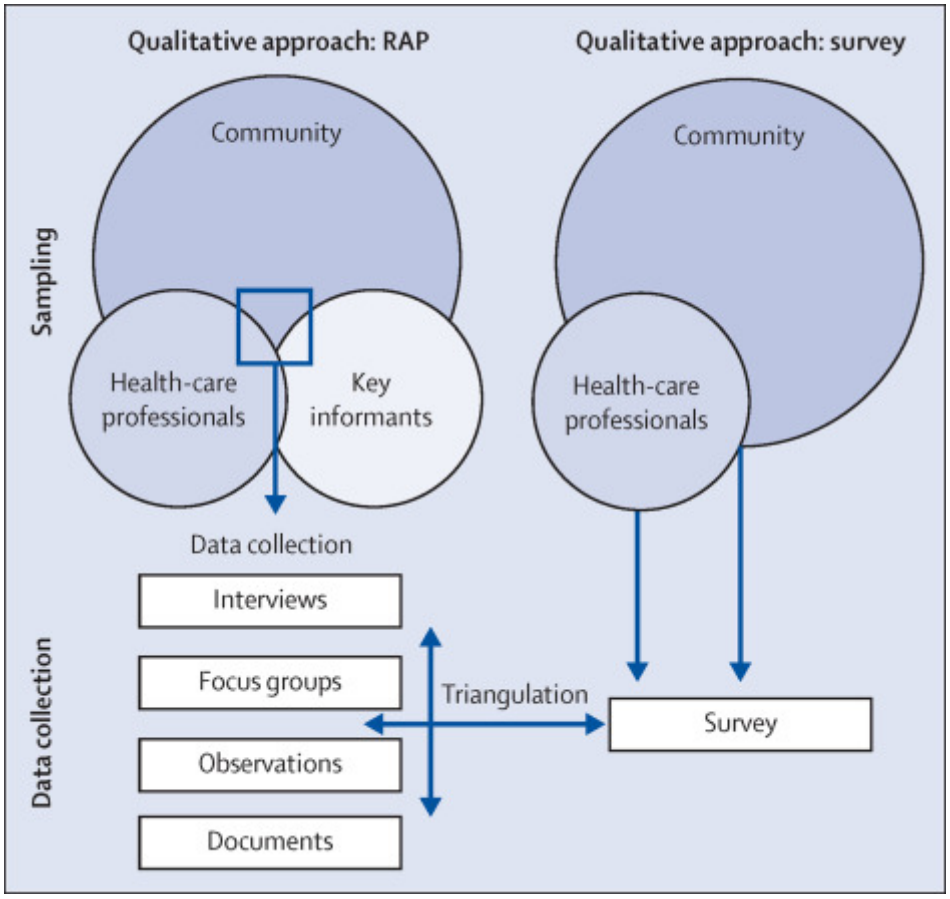
Sampling and sample size

Sampling was random at the village level. Twenty villages were selected from the regional listings of the region of Heraklion using a standard random process. From each village, ten community members were selected using the door-to-door sampling process proposed by the WHO, for research in limited-resource settings (162). As such, the total sample size was determined at 200 community members.

Theoretical framework

The theoretical framework used to guide this study was constructed by the FRESH AIR team of Leiden University Medical Center and was based on a combination of three health behaviour models: the Health Belief Model, the Explanatory Model of Illness, and the Theory of Planned Behaviour (160). The framework consisted of elements including perceptions of CRD identity, susceptibility, barriers towards behavioural change and risk reduction and help seeking behaviour (**Figure 5**). Detailed information on the framework has been published elsewhere (160).

Figure 5. Theoretical framework.



***Source**: Brakema EA et al. Lancet Glob Health. 2021*

Data collection tools

The Setting-Exploration-Treasure-Trail-to-Inform-implementatioN-strateGies (SETTING) tool developed by the FRESH AIR team of the Leiden University Medical Center (161), was used for mapping the context-related information. The context-sensitive questionnaire featured in the validation of the SETTING tool for lung diseases has been used for data collection in this study (161). The questionnaire started by presenting a vignette featuring a woman experiencing typical CRD symptoms (persistent cough, phlegm, breathlessness). Participants were asked to reflect on the vignette by

answering structured open and close-ended questions about their beliefs, perceptions and behaviours. The vignette and the questionnaire can be found in **Appendix 4**.

Data and outcomes

Information captured by the study questionnaire captured:

- Socio-demographic characteristics: gender, age, education, occupation
- Clinical characteristics: presence of vignette-like symptoms, presence of symptoms during HAP-related practices, presence of CRD diagnosis
- CRD-related beliefs: perceived identity (condition attributed to vignette-like symptoms), causes of disease/symptoms
- Perceptions: susceptibility, severity, impact, sense of control
- Behaviours: tobacco smoking, cooking and heating practices, healthcare seeking (including barriers and facilitators to care)

Procedures

Specifically trained researchers of the local FRESH AIR team visited the selected villages between December 2016 and March 2017 to conduct the door-to-door sampling and perform data collection. The main member of the household selected from the door-to-door sampling was invited for participation in the study, upon detailed information by the researchers. Community members who accepted participation provided signed informed consent prior to inclusion in the study. The questionnaire was administered by the researchers to the community members, either within the household or by the house door. Researchers started by reading the vignette and proceeded by filling out the answers of community members to the rest of the questionnaire.

Analysis

Analysis was performed using descriptive statistics in SPSS Version 25.0 (Armonk, NY: IBM Corp). Binary logistic regression models with forward selection were used to examine the effect of illness perceptions on risk behaviours (smoking and solid fuel use). Essential assumptions of logistic regression were tested as follows:

- **Linearity**: The Box-Tidwell test was performed by including all interactions between continuous variables and their log transformations in the binary logistic regression model. If the interaction term was significant, then the original predictor was not linearly related to the logit of the dependent variable (i.e. the linearity assumption was violated).
- **Absence of multicollinearity**: The tolerance and VIF test were obtained through running linear regression model (note: although the depended variables were dichotomous, the interested is

only on determining collinearity between covariates, as such linear regression was performed). A tolerance of 0.1 was considered as the threshold indicating more significant correlation between a specific covariate and the rest of covariates. A VIF exceeding 10 was considered as indicating a problematic amount of collinearity.

For the purposes of binary logistic regression, ordinal independent variables were treated as continous. Critical p-value was set at 0.05.

2.2.3. Objective 3: Assessing HAP and respiratory health outcomes in rural households

Detailed information about the methods followed in this study is presented in a paper published by the PhD candidate in the framework of this thesis in Atmosphere (163). The publication is provided at its full extent in **Appendix A3.6**. In particular, the following methods were implemented.

Design

An observational study with repeated design was conducted. Among rural households, levels of carbon monoxide (CO) and particulate matter smaller than 2.5 μg ($PM_{2.5}$) were measured at two time points to assess HAP attributed to biomass burning for heating purposes. Residents' heating activity respiratory symptoms and awareness was also assessed to reflect on the generalized impact of the country's economic recession on health-related practices and outcomes

Setting

The study was conducted in eight purposively selected villages in the region of Heraklion, Crete, Greece.

Participants

Eligible households were those owning and using traditional biomass burning devices, such as fireplaces and wood-burning stoves, for heating. In each house, a household survey was completed by the person most responsible for domestic issues and an individual questionnaire was administered to all adult residents. Eligible participants were those meeting the following criteria

Inclusion criteria

1. Age of 18 years or older
2. Willingness and ability to provide signed informed consent

Exclusion criteria

1. Resident of a household other than the selected
2. Inability to provide signed informed consent

Sampling and sample size

The study size was based on resource considerations (availability of CO and PM2.5 measuring devices, time and costs of performing measurements). Sampling was performed firstly at the village and, subsequently, at the household level. Four GPs engaged with FRESH AIR purposively selected two villages each from the catchment area of their practice and purposively recruited four eligible households per village. As such, a convenience sample of 32 households was obtained.

Data collection tools

CO and $PM_{2.5}$ levels were measured using the Lascar EasyLog USB (https://www.lascarelectronics.com/software/easylog-software/easylog-usb) and the RTI MicroPEM Sensor (https://www.rti.org/impact/micropem-sensor-measuring-exposure-air-pollution) devices respectively. A household survey questionnaire and a individual survey questionnaire were used to collect data. Both questionnaires included open- and close-ended questions and were developed based on literature and validated tools by the FRESH AIR team of University Medical Center Groningen (164). Questionnaires can be found in **Appendix 4**.

Data and outcomes

Apart from environmental outcomes (CO and $PM_{2.5}$ levels), the following were also documented:

Household survey

- Housing characteristics: dwelling condition and age
- Space heating activity: duration of heating, type of heaters owned and type of heaters used, reasons for differences between heaters owned vs. used and type of fuels used
- Presence of other respiratory exposures: tobacco smoking indoors and type of smoking products

Resident survey

- Demographic characteristics: age, gender
- Clinical outcomes:
    - General symptoms: cough phlegm, wheezing, breathlessness (MRC dyspnoea scale) and quality of life (CCQ)
    - Symptoms experienced specifically when the heater was on: cough, phlegm, wheezing, breathlessness, headache, irritated eyes, nasal congestion, running nose, irritated throat, chest tightness, nausea, fatigue, dizziness, irritability
    - Respiratory diagnosis: asthma, COPD, tuberculosis, pneumonia, lung cancer
    - Comorbidities: diabetes, heart disease, stroke, eye disease/cataract) were also recorded
    - Awareness: knowledge on the harmful effects of biomass burning for adults and children and sources of respective information

Procedures

GPs engaged with FRESH AIR identified the eligible households and conducted the first informative contact with residents. Trained researchers visited the identified households at two time points reflecting periods of lesser (baseline: November–December 2017) versus extensive heating (follow-up: January–March 2018). At the first visit, researchers provided explicit information about the study and obtained

signed informed consents from all participating individuals. All measurements (CO and $PM_{2.5}$) and assessments (household and residents surveys) were performed at both time points. CO and $PM_{2.5}$ levels were recorded for 48 hours each time. A stationary monitoring was performed. Namely, at both time points, researchers visited households and placed the CO and PM2.5 monitors above the central fireplace/stove. Researchers returned two days later to collect the monitors. Households of the same village were generally measured simultaneously. Measurements between different villages were performed on different days (due to a limited number of monitors available for this study). In case of fast monitor battery discharge, the measurement was repeated on another day.

Analysis

Analysis was performed using descriptive statistics in SPSS Version 25.0 (Armonk, NY: IBM Corp). Critical p-value was set at 0.05. Changes between baseline and follow-up measurements were explored using McNemar's tests for categorical variables and Wilcoxon signed rank test for continuous variables.

2.2.4. Objective 4: Testing the VBA on Smoking training in PHC

Details regarding the adaptation of the VBA training intervention in Greece and the other FRESH AIR countries have been presented in a paper co-authored by the PhD candidate published in the Journal of Smoking Cessation (165). The following methods were used in the part of the Greek study that is included in the present thesis.

Design

An observational study with repeated design (pre, post and follow-up evaluation) was conducted to assess the impact of a VBA training intervention on GPs' knowledge, confidence, self-efficacy and self-reported practice behaviour.

Setting

The study was conducted in the regions of Rethymno and Heraklion, Crete, Greece.

Participants

Eligible participants were GPs serving in the regions of Rethymno and Heraklion, Crete, Greece. The following criteria were applied.

Inclusion criteria

1. Being a GP working in either the private or the public sector
2. Having regular contact with tobacco users

Exclusion criteria

1. Participation in a previous tobacco treatment training programme of our research group

Sampling and sample size

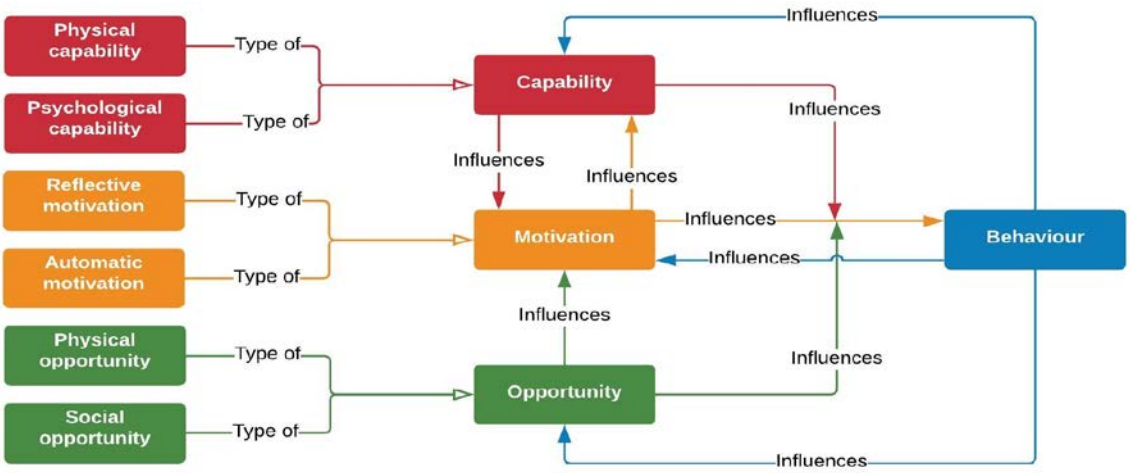
All 64 GPs from the public health centres in Rethymno and from a list of practising GPs in Heraklion were invited to participate in the study. According to previous audit of pilot studies in the UK, a sample size to be 30-36 was considered sufficient by the research team to assess the VBA training in Crete (166).

Theoretical framework

The VBA model is based upon the PRIME theory of motivation (167). The techniques of VBA training intervention are supported by a meta-analysis (168) and the Capability, Opportunity, Motivation and Behaviour (COM-B) theoretical model (169,170). The COM-B model is an integrative system, which

proposes that for someone to engage in a particular behaviour (B) at a given moment they must be physically and psychologically able (C) and have the social and physical opportunity (O) to perform the behaviour, along with the willingness to do the behaviour more than any other competing behaviour (**Figure 6**).

Figure 6. The COM-B system - a framework for understanding behaviour.



Source: Mitchie et al. Implementation Sci. 2011

Intervention

VBA is a novel approach comprising of behaviour change techniques for smoking cessation developed by the National Center for Smoking Cessation and Training (NCSCT), UK (165) (www.ncsct.co.uk/VBA). VBA is a simple piece of advice designed to be used opportunistically, in less than 30 seconds, in almost any situation with a smoker. VBA has been evaluated as effective in the UK (171). As shown in **Figure 7**, the VBA elements are:

- Establishing and recording current and past smoking status (ASK)
- Advising on the consequences of smoking and the ways to quit (ADVISE)
- Offering help through additional support, referral or quit smoking medication (ACT).

Figure 7. Very Brief Advice (VBA) on Smoking intervention

Source: McEwen et al. J Smok Cessat. 2019.

The VBA training module features a range of educational techniques, including didactic training, video, role-play, case-based learning, interactive discussions and group work. The content of the VBA training module was adapted to the Greek context by the local research team prior to implementation in Crete.

Data collection tools

Data were collected through a self-administered questionnaire, provided to GPs before, immediately after and one-month following the VBA training. The questionnaire was developed by the FRESH AIR team of NCSCT based on literature and can be found in **Appendix A4**.

Data and outcomes

Demographic characteristics of participating GPs (gender, age), sector of practice (private/public) and personal smoking status were collected before the training (baseline). The following intervention data and outcomes were also collected using the GP questionnaires:

- Knowledge: smoking and risk of lung cancer, cravings for cigarettes, smoking and COPD, actions to take with smoking patients, patient reactions to smoking cessation advice (assessed through multiple choice questions before, after and one month after the training)
- Confidence and self-efficacy in providing each of the VBA elements (ASK, ADVICE, ACT - assessed in a 5-point Likert scale before, after and one month after the training)

- Self-reported practice: number of times GPs provided VBA elements to their patients during the past week (assessed through open-ended questions before and one month following the training).

Procedures

GPs were invited to the training by the local FRESH AIR team and, those who accepted participation, provided singed informed consent prior to attending the training. The VBA training was delivered face-to-face to two groups of GPs (June 2017 and September 2017 respectively) by local trained trainers during an one-day educational session per group. A follow-up call was performed to all trained GPs one month after the training to complete the questionnaire for the reassessment of knowledge, confidence and practice.

Analysis

Analysis was performed using descriptive statistics in SPSS Version 25.0 (Armonk, NY: IBM Corp). Overall comparisons between the pre-training, post-training and one-month follow-up evaluation were performed using Cochranes' Q tests for categorical outcomes and Friedman's test for ordinal outcomes (treated as quantitative). Pairise comparisons of categorical outcomes were performed using McNemar's tests for categorical outcomes and Wilcoxon Signed Rank tests for ordinal outcomes, both with Bonferroni correction for multiple compartisons. Critical p-value was set at 0.05.

2.2.5. Objective 5: Exploring applicability of remote spirometry training and feedback in PHC (Spirometry360)

Design

A qualitative study employing a focus group discussion between GPs was performed to assess the applicability of a remote spirometry training and feedback programme in PHC.

Setting

The study was conducted in Heraklion, Crete, Greece.

Participants

Eligible participants were GPs who were offered the FRESH AIR-provided remote spirometry training and feedback programme 'Spirometry 360' (http://www.spirometry360.org/).

Inclusion criteria

1. Having completed the online Spirometry 360 courses
2. Having practiced spirometry in clinical practice for at least 2 months using a FRESH AIR-provided spirometer.

Exclusion criteria

1. Not meeting either of criteria 1 or 2.

Sampling and sample size

Spirometry 360 training programme was offered to 20 purposively selected GPs. Of these, 13 started the programme and 5 completed it. All five were invited to the focus group discussion of this study.

Theoretical framework

The Chronic Care Model and the COM-B model were used to guide this study. The COM-B model (169) has been described in previous sections of this thesis. The Chronic Care Model is designed to facilitate the improvement of care delivery for chronic conditions, with a special focus on the transformation of care from acute and reactive to preventive, proactive, patient-centered and evidence based (172). The Chronic Care Model addresses these goals through a combination of interrelated elements, namely: 1) delivery system redesign (effective team care, planned interactions and other changes in the organization of care delivery), 2) self-management support (efforts to increase patients'

involvement in their own care), 3) integrated decision support (guidelines, education, evidence and expertise to inform care decisions), 4) information systems and technology (registries and other supportive technology to facilitate use of information about patients, their care and their outcomes), 5) community linkages (activities increasing community involvement, making use of community involvement) and 6) health system support (leadership and financial support). These elements are designed to work together to strengthen the provider-patient relationship and improve health outcomes (172) and have been used effectively to inform many interventions for chronic diseases (173-175).

Intervention

Spirometry 360 remote training and feedback programme, developed by the University of Washington, is a series of interactive, evidence-based online courses which train providers to effectively perform spirometry and accurately interpret results. A variety of distance learning techniques are used in the training, which can be attended on demand, in order to account for providers' time constraints. Spirometry 360 is a quality-improvement course that helps providers integrate spirometry in their routine practice and take appropriate decisions regarding patient diagnosis, management and referral. Apart from access to the training materials, Spirometry 360 designed to provide trained professionals who subsequently practice spirometry in clinical routine with monthly feedback reports which summarize their spirometry test quality and offer guidance on where they succeed or need improvement (http://www.spirometry360.org/frequently-asked-questions). The Spirometry 360 training and feedback programme has three components, namely:

- **Spirometry Fundamentals**: Basic knowledge required to perform a high-quality spirometry test and interpret its results in clinical practice
- **Spirometry Learning Labs**: A series of case-based, interactive courses developed to provide comprehensive instruction for performing, interpreting, and implementing spirometry in primary care
- **Spirometry Feedback**: Personalized analysis of spirometry tests through customized experts' feedback reports (including grade and detailed commentary).

Data collection tools

A focus group interview guide was developed based on the study's theoretical framework and literature. The guide can be found in **Appendix 4**.

Data and outcomes

The focus group assessed the training experience in terms of reception, attendance (including barriers and facilitators to attendance and retention), comprehensiveness, usefulness and added value, i.e. raising

knowledge, confidence and practical skills. It also assessed GPs experience with practicing spirometry in terms of impact in clinical practice, patients' response and care delivery.

Procedures

Access to spirometry 360 training and feedback programme was provided by FRESH AIR team of the University of Washington to FRESH AIR implementation countries. In Greece, the training was disseminated to GPs affiliated to the Practice-Based Research Network of Crete (176) between July 2017 and March 2018. Trained GPs were subsequently equipped with a FRESH AIR-provided spirometer which they could use to practice spirometry in their clinical practice and upload their results for feedback by the Spirometry 360 team. GPs who had completed both the training and the feedback programme (practicing spirometry for at least two months after training) were invited to the focus group that was led by the PhD candidate. Before the initiation of the focus group, the terms of reference of the discussion were set (focusing on ensuring confidentiality), while detailed information was provided about the study was provided to participants. All participants provided signed informed consent prior to participation. The duration of the focus group was approximately one hour and the end of the discussion was determined by data saturation.

Analysis

The focus group was audio-recorded. Audio-recordings were transcribed verbatim and translated to English before coding. A draft report of the transcription was returned to the focus group participants, who approved it without any modification. An inductive-deductive coding approach was used for transcript analysis. Specifically, transcript coding was both open and deductive, following the study's theoretical framework, while allowing for new themes and concepts to emerge. Coding was conducted manually by the PhD candidate. Emerging themes were identified using thematic analysis (177).

2.2.6. Objective 6: Evaluating a pulmonary rehabilitation programme in PHC

Detailed information about the methods followed in this study is presented in a paper published by the PhD candidate in the framework of this thesis in Chronic Respiratory Disease (178). The publication is provided at its full extent in **Appendix A3.7**. In particular, the following methods were implemented.

Design

A pre–post implementation study of a community-based PR programme was conducted using quantitative and qualitative research. Namely, a quantitative study was conducted to assess recruitment, attendance and retain, along with patient outcome indicators. Qualitative research explored the feasibility and acceptability of the PR programme.

Setting

The study was conducted in a public PHC centre in ta rural area of the region of Heraklion, Crete, Greece.

Participants

Eligible participants were patients with confirmed diagnosis of a clinically stable CRD, including COPD and asthma. Patients were screened to determine respiratory status and physical capacity for inclusion in the study, according to the following criteria.

Inclusion criteria

1. Definite diagnosis of COPD and/or chronic asthma;
2. MRC dyspnoea score of two or higher.

Exclusion criteria

1. Within 4 weeks of an acute exacerbation;
2. Unwilling or unable to attend the programme;
3. Unstable cardiovascular disease or locomotor difficulties precluding exercise; and
4. Unable to provide informed consent.

Sampling and sample size

Based on previous studies suggesting that a sample of 30 patients is sufficient to measure before and after changes in the main outcome measures (Incremental Shuttle and Walking Test (ISWT) distance and CCQ total score), assessing at least 40 patients was set as the recruitment goal (101).

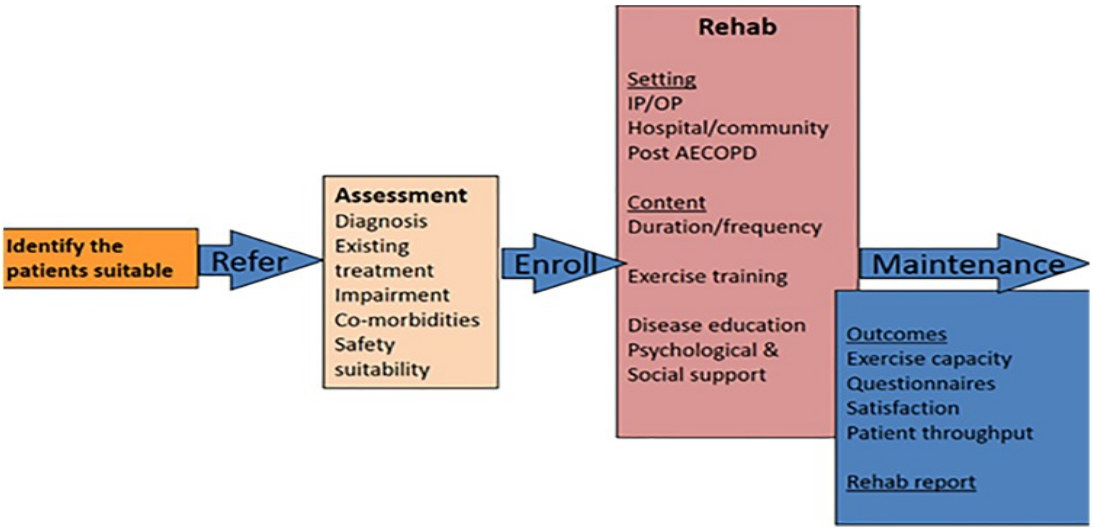
Theoretical framework

This study was developed within the theoretical framework of the Health Belief Model (179), according to which a person will engage in a health-related action if he/she: 1) perceives him/herself susceptible to a disease and believes that its consequences will be severe (threat perception), 2) feels that the benefits of the recommended action outweigh the barriers (behavioural evaluation) and 3) receives positive cues concerning the recommended action (cues to action).

Intervention

PR consists of a programme of exercises and health education based on international guidance (100, 180). Following the structure of the original programme, PR in Crete was delivered as a 6-week programme, with twice-a-week sessions of approximately 2 hours (**Figure 8**). In Crete, the PR programme was supervised by a multidisciplinary team if two physiotherapists, one nurse and one GP who were specifically trained in PR by the FRESH AIR team of the University of Plymouth. After baseline assessment, patients were assigned to one pilot (June–July 2016) and two main groups (September–October 2016) of 10–12 participants each. Programme completion was defined as attendance of 75% of classes.

Figure 8. Components of the PR programme of Crete.



***Source**: Anastasaki M et al. Chron Respir Dis. 2019*

Each PR session included half an hour of walking in the yard and 1 hour of resistance and strength exercising (bands and weights for upper and lower limbs, sit-to-stand, steps) and static bicycle. PR equipment was kept minimal, while practical solutions were provided to patients to maintain PR exercises at home (e.g., weights as bottles of water). Everyone followed the same exercise regime;

however, its level of difficulty was adjusted for each individual and monitored as programme progressed.

Seven educational sessions of one hour were also delivered per group by the trained PR team. Their contents were based on existing materials, adapted during groundwork (101,181). They covered causes of breathlessness, coping and relaxation techniques, secretion disposal, risk factor (tobacco and biomass smoke) avoidance, behaviour and lifestyle modifications (e.g. nutrition), medication intake (e.g. using inhalers), handling the CRD psychological impacts and understanding the importance of exercising and maintaining PR benefits. Written materials reminding the exercises and education were developed and provided to participants to encourage PR continuation and sharing with other community members.

Data collection tools

A CRF was developed by the FRESH AIR team of the University of Plymouth and adapted by the local FRESH AIR team (101,178). The CRF was completed by the PR team for patients before (baseline) and at the end of the PR programme (follow-up). Additionally, semi-structure interview guides for patients and PR stakeholders and a stakeholders' focus group guide were developed with input from the Health Belief Model. All study tools are presented in **Appendix A4**.

Data and outcomes

Patient socio-demographic characteristics, medical history and health habits were captured by the CRF along with the following outcomes:

- Respiratory health status: using the CCQ, CAT and Saint George Respiratory Questionnaire (SGRQ) (115,119,182)
- Dyspnoea levels: using the MRC and Borg Dyspnoea Scales (134)
- Functional impairment: using the Karnofsky Score (140)
- Depression: using the Patient Health Questionnaire-9 (PHQ-9) (183)
- Biometric indicators: height, weight, limb circumference
- Functional measures: using the sit-to-stand time (184)
- Exercise capacity using the ISWT with before and after pulse oximetry (145).

Additionally, qualitative research assessed the feasibility and acceptability of the PR programme. Respective outcomes included:

- Programme's practicality: e.g. how easy was it to attend and follow the programme
- Implementation: e.g. what went wrong or well, recruitment, retain, achievement of expectations
- Barriers/facilitators: e.g. to attendance, implementation
- Programme's sustainability: e.g. maintenance of benefits, scaling up

Procedures

Eligible patients were recruited and referred to the PR programme by GPs serving the study site who also performed an initial medical review to confirm diagnosis. Explicit written and verbal information would be given to referred patients by the PR team about the programme. Patients accepting participation provided signed informed consent prior to the initiation of any programme activity. The PR supervising team subsequently screen referred patients for eligibility and complete the baseline CRF. Patients followed the programme as described in the 'Intervention' subsection of this section. The PR supervising team monitored patients throughout and ensured safety and optimal conduction of the programme. At the end of PR, patients underwent the same as baseline assessment by the PR supervising team using the study CRF.

In addition, semi-structured interviews were performed by local researchers before and after the PR programme with a sample of purposively selected patients. A focus group with stakeholders (site healthcare and administrative staff, community leaders, PR team members, specialized doctors) led by a local qualitative expert was also conducted at the end of the programme. All patients and stakeholders accepting participation to qualitative activities provided signed informed consent prior to their inclusion.

Analysis

Patient outcomes were summarized using descriptive statistics. 95% confidence intervals (95% CIs) were estimated for quantitative variables. Fishers' exact test was used to compare independent proportions. Critical p-value set at 0.05. Analysis was performed using SPSS Version 25.0 (Armonk, NY: IBM Corp). Published Minimal Clinically Important Differences (MCIDs) are reported in relation to observed changes in clinical outcomes.

All qualitative activities were audio-taped, transcribed and analysed using thematic content analysis by a local qualitative expert. The majority of qualitative data was translated into English and a qualitative scientist from the University of Plymouth FRESH AIR team cross-checked results. Conclusions were based on consensus between the two teams.

Chapter 3. Results

Objective 1: Assessing the clinical and financial burden of CRDs in PHC

For this study, a literature review and an observational study were conducted. Results are summarized below.

Literature search

Over 700 results were returned when searching PubMed on 'COPD' AND 'Greece'. The search focused on articles providing data on COPD and asthma incidence, prevalence, quality of life, healthcare utilization and costs. As such, 21 studies were selected for inclusion in the present repot. **Supplementary Tables 1 and 2** of **Appendix A2**, present in detail the search results per outcome of interest.

COPD prevalence ranged between 5.6%, in a study involving patients from the general adult population, to 17.8% in a study of primary patients with a smoking history (185,186). The nationwide prevalence of COPD is estimated from 8.4% in people over 35 years old with a history of smoking (12) to a self-reported 10.6% in people aged 40 years or older from the general population (13). Asthma prevalence ranged between 4.3% and 9.1%, with a nationwide epidemiological study of a representative sample of the Greek population providing an estimate of 9% (8.5 for rural areas without statistically significant difference from urban areas) (11).

Mortality due to COPD is estimated at 10.9 deaths per 100.000 people (14), while the number of DALYs is relatively low (0.2 per 1000 capita per year). The figures for asthma suggest and equally low number of DALYs (0.4 per 1000 capita per year) (187).

The impact of COPD on patients' quality of life also seems substantial. Up to 91% of patients reported a CAT score of 10 or higher in a population-based, nationwide telephone survey (188). The proportions of people with a mean mMRC dyspnoea score equal or higher than 2 ranges from 22% to 61% (186,188). Furthermore, mean CCQ score has been reported to 1.87 (189). The mean score of the Hospital Anxiety Depression Scale was 8 in a study involving adult patients with asthma (190).

Direct annual costs of managing COPD ranged between 1034.5 and 2955.8 euros, with 1512.4 being spent for managing exacerbations. Indirect annual costs of managing COPD ranged between 998 and 17741 euros, with 986 euros being attributed to work loss days (21). Direct costs for asthma management were estimated at 1622.1 euros with 42% of this cost being attributed to pharmaceutical treatment. Indirect costs of asthma were estimated at 659.7 euros (22).

Demographic characteristics and socio-economic status

Table 2 presents data on the demographic and socioeconomic characteristics of the 100 patients participating in the observational study. The majority were men (60.0%), with a median (IQR) age of 72.5 years, residing in rural areas (88.0%). Most participants were retired (61.0%), with a median (IQR) income of 500 (315) euros per month. Only three patients (3%) did not have a health insurance.

Table 2. Demographic and socioeconomic characteristics of 100 primary care patients with asthma/COPD in Crete.

Variable (N=100)	**n (%)**
Gender	
Male	60 (60.0)
Female	40 (40.0)
Age (years), median (IQR)	72.5 (15)
Place of residence	
Urban	12 (12.0)
Rural	88 (88.0)
Education (years)	
None	19 (19.2)
Primary	57 (57.6)
Secondary	17 (17.2)
University	6 (6.0)
Occupational sector	
Unemployed	2 (2.0)
Retired	61 (61.0)
Housewife/man	13 (13.0)
Civil servant	3 (3.0)
Private sector	5 (5.0)
Worker	5 (5.0)
Farming/agriculture	9 (9.0)
Other	2 (2.0)
Monthly income (euros), median (IQR)	500 (315)
Health insurance	
Yes	97 (97.0)
No	3 (3.0)

***Abbreviations**: IQR: interquartile range*

Clinical status and exposure to risk factors

Clinical status and respiratory exposures of participants are presented in **Table 3**. Overall, 81.0% of patients had COPD, 27.0% had asthma and 8.0% had asthma-COPD overlap syndrome (ACOS). Median (IQR) score of the mMRC breathlessness scale was 2 (2), with 46.0% of the participants reporting a score larger than 2. The median (IQR) score was 1.9 (1.2), exceeding the threshold of 1.0-1.5 suggested by guidelines for identifying more symptomatic patients (191). Breathlessness and cough

were the most frequently reported symptoms (66.0 and 65.0% respectively). In total, 68% of participants had ever smoked, while 49.5% were using biomass fuels for cooking and/or heating reasons.

Table 3. Clinical status and exposure to respiratory risk factors for 100 primary care patients with asthma/COPD in Crete.

Variable (N=100)	**n (%)***
Diagnosis (yes)	
Asthma	27 (27.0)
COPD	81 (81.0)
ACOS	8 (8.0)
mMRC, median (IQR)	2 (2)
mMRC>2	46 (46.0%)
CCQ total score, mean (SD)	1.9 (1.2)
Symptoms during past 7 days (yes)	
Chronic cough	65 (65.0)
Sputum	56 (56.0)
Fatigue	54 (54.0)
Breathlessness	66 (66.0)
Chest tightness	28 (28.0)
Wheezing	46 (46.0)
Family history of COPD	
Yes	21 (21.4)
No	77 (78.6)
Comorbidities	
Hypertension	19 (24.4)
Diabetes	7 (9.0)
Heart diseases	7 (9.0)
Other	45 (57.7)
Disability	
Yes	9 (9.2)
No	89 (90.8)
Vaccinations	
Influenza	77 (77.0)
Pneumococcal	44 (44.0)
Smoking (ever)	
Yes	68 (68.0)
No	32 (32.0)
Biomass fuel use (heating and/or cooking)	
Yes	49 (49.5)
No	50 (50.5)

**Refers to valid percentage*

***Abbreviations**: **COPD**: chronic obstructive pulmonary disease, **mMRC**: modified Medical Research Council breathlessness scale*

Healthcare utilization and direct costs

Table 4 shows data on healthcare utilization and respective costs for the participating patients with asthma and/or COPD, including comparisons with the unit costs of each service for the public sector of the Greek healthcare system.

Participants visited a GP for their CRD a median (IQR) of 1 (2) time during the past three months, ranging for 0 to 7 times. GP visits were reimbursed from participants' health insurance 93.0% of the time. In case of no reimbursement, patients had to pay a median of 35 (14) euros. This was translated to a cost of 140 (460) euros per year, accounting for 2.3% of their annual income (as derived from the reported median monthly income of 500 euros). The respective unit cost for the public sector was 10 euros.

The median (IQR) times participants visited a pulmonologist for their CRD during the past three months was 0 (1) ranging from 0 to 5. Visits to the pulmonologist were reimbursed 61.0% of the time, with the median (IQR) out-of-pocket payment in case of no reimbursement being 32.5 (20) euros. This was translated to a cost of 150 (80) euros per year, accounting for 2.5% of their annual income. This was the highest annual co-payment.

Hospitalizations were always reimbursed but a median (IQR) co-payment of 45 (28) euros was reported for performing diagnostic tests during the past year, including spirometry, computed tomography (CT), chest CX-ray and ultrasound. This accounted for 0.8% of patients' annual income, with the respective unit cost for the public sector ranging between 4.05 (spirometry) to 71.11 (CT-scan) euros.

The vast majority of participants (91.8%) had used medicines for their CRD during the past year. Medications were reimbursed 76.5% of the time, with a median (IQR) co-payment of 20 (10) euros in case of no reimbursement. This cost accounted for 0.3% of patients' annual income, with the respective unit cost varying depending on medication type.

Table 4. Healthcare utilization and costs among primary care patients in Crete.

Variable (N=100)	n (%)[a]	Number median (IQR) (min- max)	Reimbursed n (%)*	Co-payment (euros) median (IQR) (min- max)	Annual co-payment (euros) median (IQR) (min- max)	% of annual income[b]	Unit cost (euros)[c]
Visits to GP (last 3 months)	N/A	1 (2) (0-7)	66 (93.0)	35 (14) (30-45)	140 (460) (120-720)	2.3	10
Visits to pulmonologist (last 3 months)	N/A	0 (1) (0-5)	25 (61.0)	32.5 (20) (20-60)	150 (80) (80-480)	2.5	10
Days in hospital (last 3 months)	N/A	0 (0) (0-12)	16 (100.0)	0	0	0	COPD: 863 Asthma: 361 for 5 days hospitalization
Diagnostics (last year) *Spirometry* *CT-scan (n=11)* *X-ray (n=39)* *ECG (n=37)* *Ultrasound (n=11)*	**Total**: 88 (88.0) 52 (52.0) 21 (21.0) 59 (59.0) 56 (56.0) 20 (20.0)	 1 (0) (0-4) 1 (0) (1-1) 1 (1) (0-3) 1 (1) (1-5) 1 (0) (1-2)	71 (78.9)	45 (28) (25-100)	45 (28) (25-100)	0.8	 4.14 71,11 4.05 4.05 40.00
Respiratory medication (last year) *Yes* *No*	 90 (91.8) 8 (8.2)	N/A	65 (76.5)	20 (10) (8-80)	20 (10) (8-80)	0.3	▪ Indacaterol: 30.27 ▪ Indacaterol + glycopyrronium: 58.96 ▪ Umeclidinium bromide: 33.57 ▪ Salbutamol + Ipratropium: 7.62 ▪ Budesonide: 4.30

[a]Refers to valid percentage, [b]considering the reported median monthly income of 500 euros, [c]for the public sector
***Abbreviations**: **GP**: general practitioner, **CT**: computed tomography, **ECG**: electrocardiography, **IQR**: interquartile range, **COPD**: chronic obstructive pulmonary disease*

Work productivity and impairment

Results regarding the analysis of the WPAI questionnaire and the associations between work productivity and activity impairment with modifiable respiratory risk factors have been presented in a publication co-authored by the PhD candidate in Respiratory Research (ref). In this section, we present the raw results derived from the WPAI questionnaires, as an indicator of work and activity time losses due to CRD.

As shown in **Table 5**, only 15.2% of participants were currently employed in a played job. The working population reported missing a median (IQR) of 2 (6) hours of work within the past week due to their CRD. They also reported a mean (SD) of 33.6 (23.8) hours of actual work during the past week, out of 40 hours which is the typical weekly working schedule for Greece. The mean (SD) degree to which their working productivity was affected by their CRD (scored in a 0-10 Likert scale) was 1.5 (1.4). For the overall sample, the median (IQR) degree to which regular activities were affected by CRDs was 4 (5).

Table 5. Raw data on work productivity and activity impairement among primary care patients in Crete.

Variable	**Median (IQR)**
Currently employed, n (%)*	
Yes	15 (15.2)
No	84 (84.8)
Work hours missed due to CRD during past week (n=15)	2 (6) (0-48)
Work hours missed due to any other reason during past week (n=15)	0 (0) (0-2)
Actual hours worked during past week (n=15), *mean (SD)*	33.6 (23.8) (0-72)
Degree of productivity impairment while working due to CRD during past week (n=15),** *mean (SD)*	1.5 (1.4) (0-4)
Degree of regular activity impairment due to CRD during past week (n=100)**	4 (5) (0-10)

**Refers to valid percentage, **Measured in a 10-point Likert scale (0: not at all – 10: completely)*
***Abbreviations**: **IQR**: interquartile range, **CRD**: chronic respiratory disease, **SD**: standard deviation*

Objective 2: Exploring community beliefs, perceptions and behaviours towards CRD

The results of this observational study are presented in a structured format below, while part of the Greek data has been published by our group in Lancet Global Health (160).

Socio-demographic characteristics.

Table 6 presents the basic sociodemographic characteristics of the 200 community members that participated in the present study. Slightly more than half were women (53.5%), with a median (IQR) age of 60 (31) years. Overall, 72 (36.0%) of participants were currently retired, while 28 (14.0) were working in the agricultural sector. The median (IQR) education of the sample was 9 (6) years. The majority (64%) reported that they were not experiencing any of the symptoms presented by the story of the vignette and that they did not have any previous CRD diagnosis (73.0%).

Table 6. Basic sociodemographic characteristics of 200 community members in rural Crete.

Variable	**N=200**
Gender, n (%)	
Male	93 (46.5)
Female	107 (53.5)
Age (years), median (IQR)	60 (31.0)
Education (years), median (IQR)	9 (6.0)
Occupational sector, n (%)	
Housewife/man	33 (16.5)
Unemployed	9 (4.5)
Retired	72 (36.0)
Farming/agriculture	28 (14.0)
Education	3 (1.5)
Healthcare	7 (3.5)
Manufacture	12 (6.0)
Transportation	4 (2.0)
Construction	1 (0.5)
Other	31 (15.5)
Presence of vignette-like symptoms, n (%)	
Yes	72 (36.0)
No	128 (64.0)
CRD diagnosis, n (%)	
Yes	54 (27.0)
No	146 (73.0)

CRD-related beliefs

Beliefs towards CRD were examined in terms of perceived identity, i.e. diseases that were attributed to the condition presented in the vignette, and reported causes for this condition. As shown in **Figure 9**,

about half of participants (51.5%) connected the vignette symptoms to a respiratory condition, followed by flu-like infections (10%). Asthma was mentioned by 8% of participants as the potential disease described in the vignette, while the respective proportion for COPD was 8.5%.

Figure 9. Attributed disease for the symptoms described by the vignette (N=200).

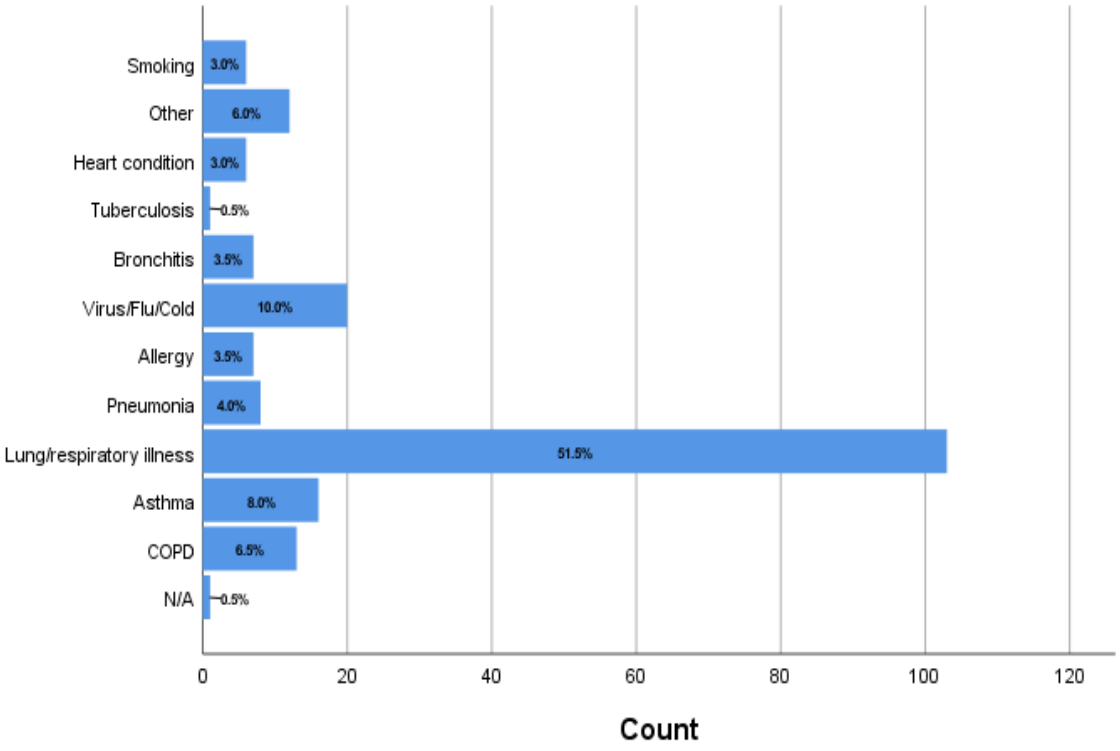
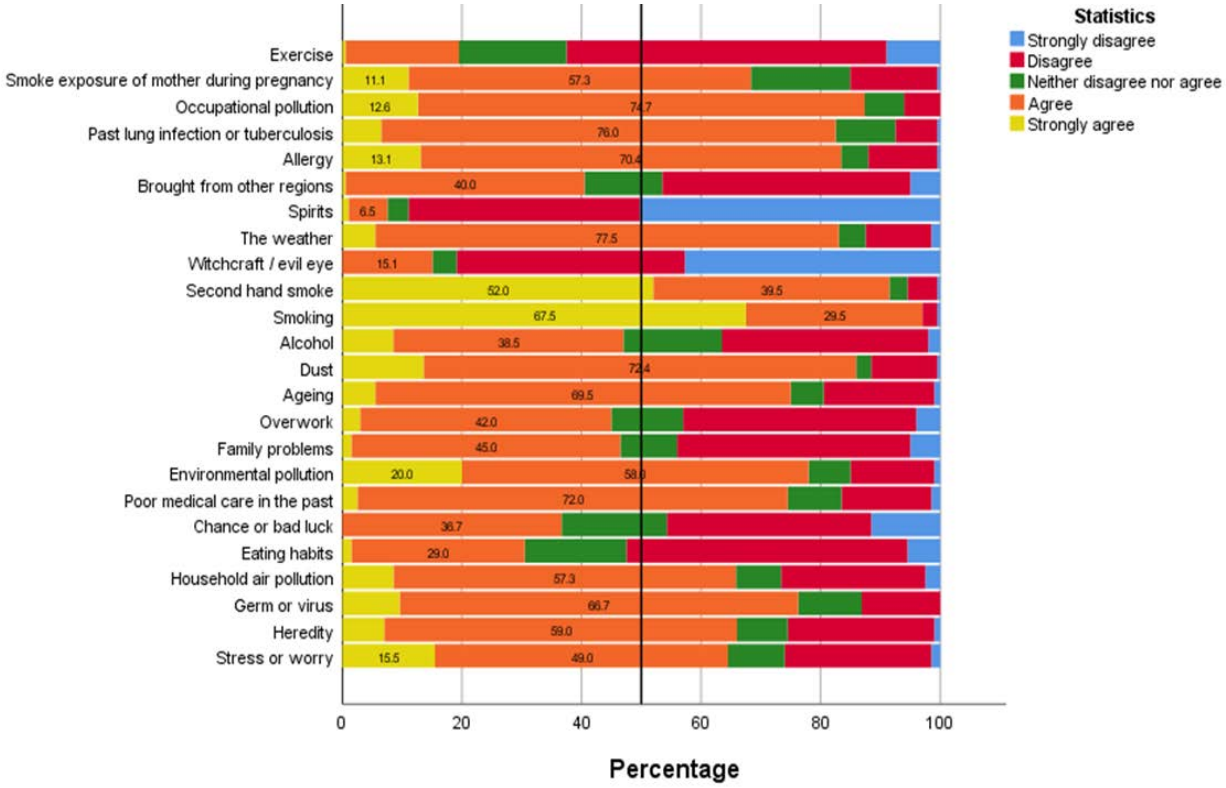


Figure 10 presents the level of agreement of participants regarding the possible causes of the symptoms presented in the vignette. The highest levels of strong agreement concerned smoking as 67.5% of participants strongly agreed that smoking can cause vignette-like symptoms. The respective proportion for second had smoking was 52.0%, while for HAP it was 8.5%. High levels of agreement (% agreed) were reported for weather conditions (77.5%), past lung infection/tuberculosis (76.0%), occupational pollution (74.7%), dust (72.4%), allergies (70.4%), viral infection (66.7%), environmental pollution (58%) and HAP (57.3%).

Figure 10. Level of agreement regarding the causes of the symptoms presented in the vignette.



CRD-related perceptions

Perceptions towards the chronic respiratory symptoms described in the vignette were assessed in terms of susceptibility, disease severity, control over the disease (internal and external) and impact of the disease in life. Perceived barriers to care were also assessed. **Figure 11** illustrates participants' responses in questions assessing CRD-related perceptions.

In terms of susceptibility, similar proportions of participant (36%) reported that they were slightly or fairly likely to develop vignette-like symptoms. Additionally, 60% of the participants answered that they would fairly much experience symptoms by a similar condition.

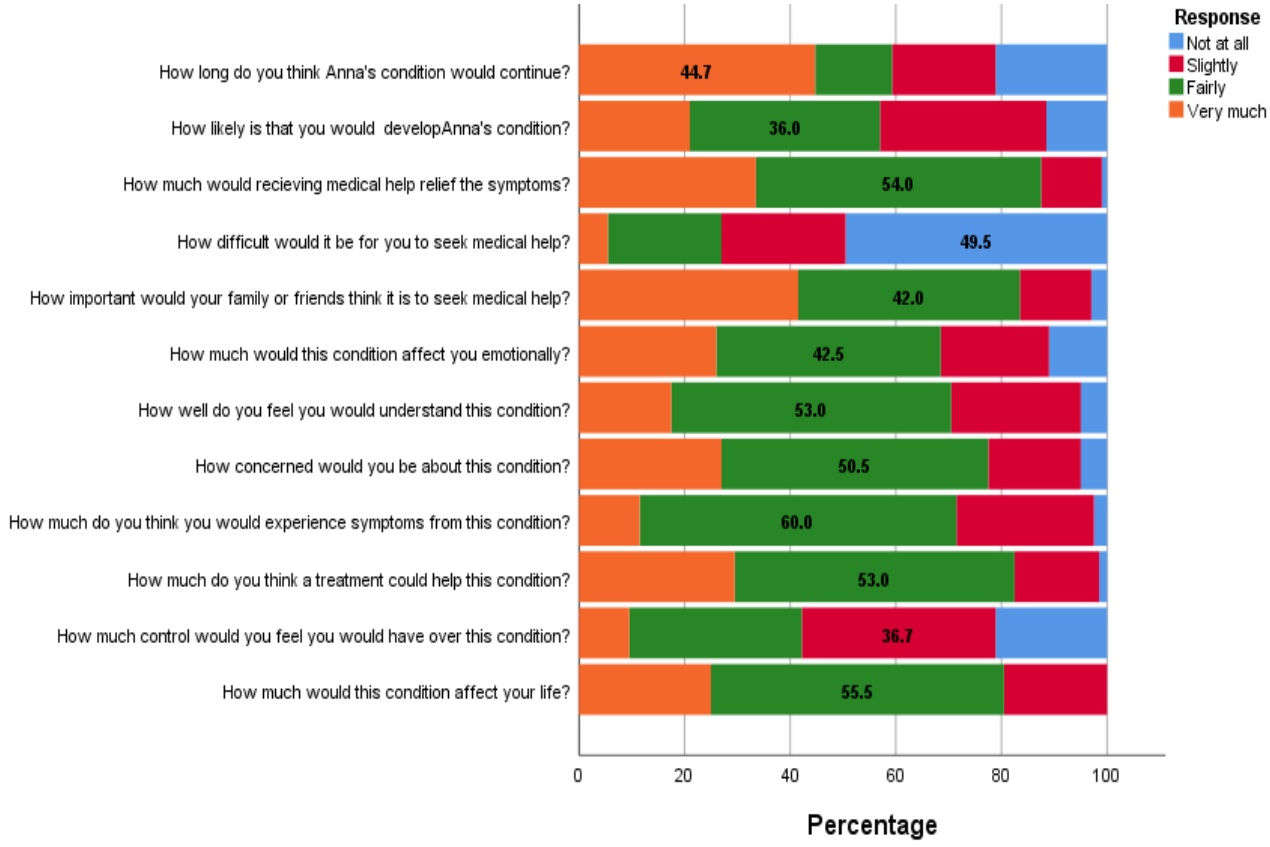
Regarding severity, about half of the participants (50.5%) reported that they would be fairly concerned about the symptoms of the vignette, while 44.7% reported that such a condition would continue for a very long time.

In terms of internal control, 53% of the participants mentioned that they understand the condition fairly much. Most participants felt that they could have some control over the condition (36.7%), with similar proportions reporting fairly much control.

As far as external control is concerned, 54.0% of the participants answered that medical help would fairly much relieve such symptoms, while 53.0% reported that treatment could help this condition fairly much. Overall, 49.5% of the participants, would not face any difficulty at all in seeking help for a similar condition.

Considering the impact of the disease, 55.5% of the participants mentioned that such a condition would affect their lives fairly much, with 42.5% reporting that it would have a fairly high emotional impact.

Figure 11. Perceptions regarding vignette-like respiratory symptoms among 200 community members in rural Crete.



Risk behaviours

As shown in **Table 7**, the majority of the participants were current smokers (73.5%), with 30.2% having attempted to quit during the past year. Most participants reported smoking both indoors and outdoors 79.2%, while 30.2% mentioned that other people are exposed to their smoke.

In terms of behaviours related to household air pollution, a minority reported use of clean fuels for heating (33.0%), while 61.0% were using solid fuels for heating purposes. In total, 71% of participants

used fireplaces and/or wood-burning stoves as main heating devices, with wood being used as fuel by slightly more than half (55.0%).

Considering healthcare seeking behaviour, 70% of participants reported that they would seek help from a pulmonologist for a vignette-like condition. Additionally, 53.5% of the participants would visit a GP and 48.5% would seek help from their family or friends.

Table 7. Risk behaviours related to vignette like respiratory symptoms for 200 community members in rural Crete.

Behaviours (N=200)	**N (%) or median (IQR)**	
Related to tobacco smoking		
Current smoking, n (%)		
Yes	53 (73.5)	
No	147 (26.5)	
Pack-years index, median (IQR)	23.0 (26.9)	
Quitting intention, n (%)		
Yes	39 (73.6)	
No	14 (26.4)	
Quitting attempts (past year), n (%)		
Yes	16 (30.2)	
No	37 (69.8)	
Smoking area, n (%)		
Indoors	1 (1.9)	
Outdoors	10 (18.9)	
Both	42 (79.2)	
Exposing others to passive smoke, n (%)		
Yes	37 (69.8)	
No	16 (30.2)	
Past smoking, n (%)		
Yes	61 (35.9)	
No	109 (64.1)	
Related to HAP	**Cooking practices**	**Heating practices**
Use of clean fuels, n (%)		
Yes	196 (98.0)	66 (33.0)
No	4 (2.0)	134 (67.0)
Use of solid fuels, n (%)		
Yes	29 (14.5)	122 (61.0)
No	171 (85.5)	78 (39.0)
Type of cooker/heater used (yes), n (%)		
Fireplace/woodburning stove	9 (4.5)	142 (71.0)
Improved stove	189 (94.5)	N/A
Central heating	N/A	100 (50.0)
Other	22 (11.0)	25 (12.5)
Fuel type used (yes), n (%)		
Wood	29 (14.5)	111 (55.5)
Other biomass (grass, dung, charcoal, crop residues)	0 (0)	16 (8.0)
Gas	61 (30.5)	6 (3.0)

Electricity	159 (79.5)	62 (31.0)
Other	0 (0)	76 (38.0)
Ventilation type used (yes), n (%)		
Open window	159 (79.5)	119 (60.1)
Hood	159 (79.5)	31 (15.7)
Chimney	20 (10.0)	35 (17.7)
No ventilation	0 (0)	13 (6.6)
Related to healthcare seeking		
Point of contact for vignette-like symptoms (yes), n (%)		
Family	97 (48.5)	
Friend	11 (5.5)	
General practitioner	107 (53.5)	
Pulmonologist	141 (70.5)	
Other healthcare professional (nurse, pharmacist, health worker)	65 (32.5)	
Healer (homeopath, herbalist, traditional healer)	6 (3.0)	
Other (incl. teacher, religious leader, internet, books)	28 (14.0)	
No help seeking	2 (1.0)	

***Abbreviations**: **HAP**: household air pollution, **N/A**: not assessed*

Effect of illness perceptions on risk behaviours: smoking

Binary logistic was performed to explore the effect of illness perceptions (ordinal independent variables that were treated as continuous) on smoking behaviour (dichotomous dependent variable). Firstly, the essential assumptions of logistic regression, linearity and absence of multi-collinearity were explored through the Box-Tidwell and Tolerance/VIF tests respectively. Both assumptions were met, since all interactions of the Box-Tidwell test were non-significant and all VIFs were lower than 10.

A forward model selection process was performed to explore which illness perception variables had a statistically significant influence on smoking behaviour, also controlling for gender, age and presence of previous CRD diagnosis. The final model - produced after six steps of selection - was statistically significant (Chi-square test p-value<0.001) and explained 29.2% of the variation in smoking (Nagelkerke's R^2=0.292). The model exhibited good fit to the data (Hosmer and Lemeshow test p-value=0.723>0.05) and correctly classified 77.7% of cases.

As shown in **Table 8** and **Figure 12**, six predictors remained statistically significant and were included in the final model: perceived duration of illness, family's perception on the importance of seeking medical help, perceived susceptibility to the disease, presence of previous CRD diagnosis, gender and age. Namely, controlling for all other variables:

- Increase in the class of family's perception on the importance of seeking medical help by one (i.e. for increasing levels of family's perception that seeking help is important), suggests a decrease in the odds of smoking by 32.7% (OR=0.628, 95%CI: 0.401-0.985).

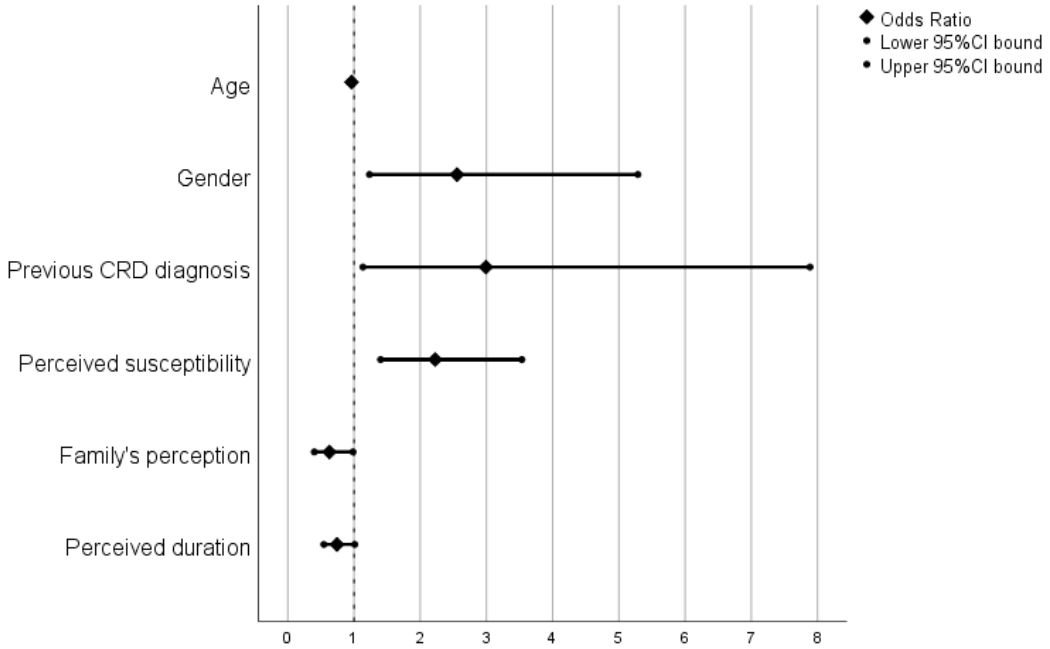
- Increase in the class of perceived susceptibility by one (i.e. for increasing levels of perceived likelihood of developing a CRD condition), suggests an increase in the odds of smoking by 2.225 times (OR=2.225, 95%CI: 1.401-3.534)
- Compared to people without a previous CRD diagnosis, people who had one were 2.992 (almost 3) times more likely to be smokers (OR=2.992, 95%CI: 1.135-7.887)
- Increase in the class of perceived duration of disease by one (i.e. for increasing perceived duration), suggests a decrease of borderline statistical significance in the odds of smoking by 25.8% (OR=0.742, 95%CI: 0.545, 1.010)
- Compared to women, med had 2.555 times higher odds of smoking (OR=2.555, 95%CI: 1.234-5.288).
- For one year increase in age, there is decrease in the odds of smoking by 3.7% (OR=0.963, 95%CI: 0.943-0.983)

Table 8. Binary logistic regression table of illness perceptions (independent variables) on smoking behaviour (dependent variable).

	B	**SE**	**p-value**	**OR**	**95% CI for OR**	
How important would your family or friends think it is to seek medical help?	-.465	.230	.043	.628	.401	.985
How likely do you think it is that you would indeed develop the same condition as Anna?	.800	.236	.001	2.225	1.401	3.534
Have you ever been diagnosed with a chronic respiratory disease? (ref. yes)	1.096	.494	.027	2.992	1.135	7.887
How long would you think this condition would continue?	-.299	.157	.058	.742	.545	1.010
Gender (ref. women)	.938	.371	.011	2.555	1.234	5.288
Age	-.038	.010	.000	.963	.943	.983
Constant	-.228	1.204	.850	.796		

***Abbreviations**: **SE**: standard error, **OR**: odds ratio, **CI**: confidence interval, **ref**: reference category*

Figure 12. Binary logistic regression of illness perceptions (independent variables) on smoking behaviour (dependent variable).



***Abbreviations**: **CRD**: chronic respiratory disease, **CI**: confidence interval*

Effect of illness perceptions on risk behaviours: biomass fuel use

Binary logistic was performed to explore the effect of illness perceptions (ordinal independent variables that were treated as continuous) on biomass fuel use for heating, as a HAP-related behaviour (dichotomous dependent variable). Testing the assumption of linearity through the Box-Tidwell test, only the interaction of perceived usefulness of medical treatment with its log transformation was found with borderline statistical significance (p-value=0.048). The assumption of no multi-collinearity was met, since all VIFs were lower than 10.

A forward model selection process was performed to explore which illness perception variables had a statistically significant influence on solid fuel use, also controlling for gender, age and presence of previous CRD diagnosis. The final model - produced after one step of selection - was statistically significant (Chi-square test p-value<0.009) but explained only 4.6% of the variation in solid fuel use (Nagelkerke's R^2=0.046). The model exhibited good fit to the data (Hosmer and Lemeshow test p-value=0.385>0.05) and correctly classified 59.6% of cases.

As shown in **Table 9**, illness perceptions did not seem to have a statistically significant impact on solid fuel use behaviour. The only variable that remained statistically significant and was included in the final model was perceived control over the disease. Namely:

- Increase in the class of perceived control over symptoms by one (i.e. for increasing levels of perceived control), suggests an increase in the odds of using solid fuels for heating by 1.537 times (OR=1.537, 95%CI: 1.106-2,137)

Table 9. Binary logistic regression table of illness perceptions (independent variables) on solid fuel use (dependent variable).

	B	**SE**	**p-value**	**OR**	**95% CI for OR**	
How much control would you feel you would have over this condition?	.430	.168	.011	1.537	1.106	2.137
Constant	-.526	.404	.193	.591		

***Abbreviations**: **SE**: standard error, **OR**: odds ratio, **CI**: confidence interval*

Objective 3: Assessing HAP and respiratory health outcomes in rural households

Detailed information about the results of this study is provided in the paper published by the PhD candidate in the framework of this thesis in Atmosphere (163). The publication is provided at its full extent in **Appendix A3.7**. Key results are presented below.

Household and sociodemographic characteristics of residents

Baseline measurements and household surveys were completed by all 32 identified households. Two households were lost-to-follow-up due to family issues. Household questionnaires were collected from all 32 houses at baseline and from 30 houses at follow-up **(Table 10)**. Dwelling condition was considered good by most households (n=15 or 48.4%), although most were traditional residencies constructed before 1940 (n=21 or 34.4%). There were 43 adult questionnaires completed at baseline and 42 at follow-up. In total, 33 individuals had paired data for both assessments and are included in the present analysis. Their mean age was 66.8 years (SD=14.9), while 24 participants (72.7%) were women **(Table 11)**.

Space heating activity and fuel use

Table 10 presents data on space heating activity and air pollution sources between the baseline and follow-up assessments. The vast majority of house-holds owned local heating devices (n=29 or 90.6%), most of which were stand-alone wood-burning stoves (n=17 or 53.1%) and fireplaces (n=13 or 40.6%).

Non-biomass heaters including petroleum radiators, portable electric devices and air-conditioners were owned by 9 (28.1%), 5 (15.6%) and 2 (6.3%) houses respectively. When asked what devices are actually used for heating at baseline, most households still reported stand-alone stoves (n=16 or 50%) and fireplaces (n=13 or 40.6%). Petroleum radiators and electric heaters were only used in 4 (12.5%) households, while none was using the air-conditioner. Among nine households reporting reasons for differences between devices owned versus those used (n=9), all were all attributed to financial restrictions. At follow-up, trends regarding the use of stand-alone stoves and fireplaces were similar to baseline.

At baseline, all households were using wood as biomass fuel and, to lesser extent, olive cores (n=3 or 9.4%). Petroleum was used by 8 (25%) households and electricity by 9 (28.1%). Wood remained the main fuel used at follow-up (n=29 or 96.7%), while non-biomass fuels were reported less frequently (petroleum: n=1 or 3.3%, electricity: n=0).

Table 10. Housing characteristics, space heating activity and fuel use at baseline and follow-up in rural Crete.

Variables, n (%)		**Baseline (N=32)**	**Follow-up (N=30)**
Condition of dwelling			
	excellent	5 (16.1)	N/A
	good	15 (48.4)	N/A
	average	9 (29)	N/A
	poor	1 (3.2)	N/A
	very poor	1 (3.2)	N/A
Year of construction			
	after 1991	3 (9.4)	N/A
	1969-1990	8 (25.0)	N/A
	1940-1968	6 (18.8)	N/A
	before 1939	5 (15.6)	N/A
	I don't know	10 (31.3)	N/A
What <u>do you have</u> to heat the rooms?			
purpose-built heater		32 (100)	N/A
	central heating	14 (43.8)	N/A
	petroleum radiators	9 (28.1)	N/A
	olive cores radiators	2 (6.3)	N/A
	unspecified	3 (9.4)	N/A
	local heating	29 (90.6)	N/A
	stand-alone stoves	17 (53.1)	N/A
	fireplace	13 (40.6)	N/A
	portable electric heater	5 (15.6)	N/A
	air conditioner	2 (6.3)	N/A
What <u>do you use</u> to heat the rooms?			
purpose-built heater		31 (96.9)	28 (93.3)
	central heating	9 (28.1)	1 (3.3)
	petroleum radiators	4 (12.5)	0 (0)
	olive cores radiators	2 (6.3)	0 (0)
	unspecified	3 (9.4)	1 (3.3)
	local heating	28 (87.5)	27 (90.0)
	stand-alone stoves	16 (50.0)	15 (50.0)
	fireplace	13 (40.6)	12 (40.0)
	portable electric heater	4 (12.5)	0 (0)
	air conditioner	0 (0)	0 (0)
Reason of difference between <u>what you have</u> and <u>what you use</u>? (n=9)			
	financial reasons	9 (100)	
Type of fuel for heating			
	wood	32 (100)	29 (96.7)
	petroleum	8 (25.0)	1 (3.3)
	olive cores	3 (9.4)	1 (3.3)
	Electricity	9 (28.1)	0 (0)

***<u>Abbreviation</u>**: **N/A**: not assessed*

HAP levels, respiratory health and awareness

Table 11 presents data on environmental outcomes of HAP in parallel with respiratory health outcomes of participating residents. Weather conditions happened to be similar between the two with the average temperature being 14.4oC (min: 12^{o}C, max: 16^{o}C) at baseline and 14.8oC (min: 10^{o}C, max: 18^{o}C) at follow-up.

Median (IQR) values of household $PM_{2.5}$ levels between measurements were 27.4 (30) μg/m^3 at baseline and 27.5 (40) μg/m^3 at follow-up. This difference was not statistically significant (p-value=0.607). However, these values are above the safe air quality cut-off points (25 μg/m^3 for 24 hours mean) indicated by WHO (42). At baseline, the overall median (IQR) value of CO levels was 0.02 (1) parts per million (ppm), while the median of maximal values was 12.3 (32) ppm. At follow-up, the overall median of CO values was 0.01 (0.4) ppm and the median of maximal CO values was 4.3 (12) ppm. The difference between the overall levels was not statistically significant (p-value=0.414), in contrast to the difference between the maximal CO values (p-value=0.007). Still, these CO levels are below the WHO air quality guidelines (26.6 ppm for one hour and 6.1 ppm for 24 hours mean) (42).

The most frequently reported general respiratory symptom at both time points was phlegm (n=9 or 27.3% vs. n=5 or 15.2%), followed by cough (n=8 or 24.2% vs. n=4 or 12.1%). Differences in all general respiratory symptoms including cough, phlegm, wheezing and breathlessness were not significant between assessments. At baseline, fatigue was the most common symptom experienced specifically when the heater was on (n=12 or 42.4%), followed by headache (n=12 or 36.4%). At follow-up the respective symptoms were headache and irritated eyes (n=6 or 18.2% for both). Among symptoms experienced specifically when the heater was on, nausea, fatigue, dizziness and irritability were reported at significantly higher rates during base-line compared to follow-up (n=6 or 18.2% vs n=0, p-value=0.03; n=14 or 42.4% vs n=5 or 15.2%, p-value=0.004; n= 9 or 27.3% vs n=1 or 3%, p-value=0.02 and n=8 or 24.2% vs n=0; p-value=0.008 respectively). The occurrence and frequencies of symptoms reported specifically when the heater was on are in line with the CO exposure data and contrary to $PM_{2.5}$ concentrations. However, differences between baseline and follow-up levels were not statistically significant.

No participant reported having a previous asthma diagnosis. COPD diagnosis was reported by 2 (6.1%) of participants, while 5 (15.2%) reported having experienced pneumonia. Heart disease was the most common comorbidity (n=12 or 36.4%). The most frequently reported comorbidity was diabetes (n=12 or 36.4%), followed by eye disease/cataract (n=11 or 33.3%)

In terms of awareness, less than half of participants (n=16 or 48.5%) knew that indoor biomass burning for heating could harm their health, of which the majority (n=12 or 75%) had heard so from media, followed by a healthcare professional/physician (n=4 or 25%).

Table 11. HAP levels and respiratory health and awareness of residents (N=33) in 32 rural households of Crete.

Variables	Baseline	Follow-up	p-value*
Environmental exposures, median (IQR)			
$PM_{2.5}$ ($\mu g/m^3$)	27.4 (30)	27.5 (40)	0.607
CO (ppm)	0.02 (1)	0.01 (0.4)	0.414
CO max (ppm)	12.3 (32)	4.3 (12)	0.007
Demographic characteristics			
Age (years), mean (SD)	66.8 (14.9)	N/A	
Gender (female), n (%)	24 (72.7)	N/A	
General symptoms, n (%)			
Cough (yes)	8 (24.2)	4 (12.1)	0.34
Phlegm (yes)	9 (27.3)	5 (15.2)	0.22
Wheezing (yes)	1 (3)	1 (3)	1
Breathlessness (yes)	4 (12.1)	4 (12.1)	1
MRC dyspnea scale, median (IQR)	2.0 (3)	2.0 (1)	0.07
CCQ total score, median (IQR)	0.2 (5)	0.2 (10)	0.82
Symptoms during heating (yes), n (%)			
Cough	5 (15.2)	3 (9.1)	0.69
Phlegm	0 (0)	0 (0)	
Wheezing	1 (3)	0 (0)	1
Breathlessness	3 (9.1)	2 (6.1)	1
Headache	12 (36.4)	6 (18.2)	0.70
Irritated eyes	6 (18.2)	6(18.2)	1
Nasal congestion	3 (9.1)	1 (3)	0.63
Running nose	2 (6.1)	1 (3)	1
Irritated throat	3 (9.1)	1 (3)	0.5
Chest tightness	2 (6.1)	1 (3)	1
Nausea	6 (18.2)	0 (0.0)	**0.03**
Fatigue	14 (42.4)	5 (15.2)	**0.004**
Dizziness	9 (27.3)	1 (3)	**0.02**
Irritability	8 (24.2)	0 (0)	**0.008**
Previous respiratory diagnosis (yes), n (%)			
Asthma	0 (0)	N/A	
COPD	2 (6.1)	N/A	
Tuberculosis	1 (3.0)	N/A	
Pneumonia	5 (15.2)	N/A	
Lung cancer	0 (0)	N/A	
Comorbidities (yes), n (%)			
Diabetes	9 (27.3)	N/A	
Heart disease	12 (36.4)	N/A	
Stroke	4 (12.1)	N/A	
Eye disease/cataract	11 (33.3)	N/A	
Lung cancer	9 (27.3)	N/A	
Awareness (yes), n (%)			
Did you know that biomass burning may harm your health?	16 (48.5)	N/A	
Source of information		N/A	
Healthcare professional	2 (12.5)	N/A	
Physician	2 (12.5)	N/A	
Media (radio, newspaper, TV)	12 (75.0)	N/A	
Family	2 (12.5)	N/A	
Villagers	0 (0)	N/A	
Own experience	1 (6.3)	N/A	
Did you know that biomass burning may harm your children's health?	17 (51.5)	N/A	

McNemar's test for categorical variables and Wilcoxon Singed Ranks test for continuous variables.* ***Abbreviations**: **HAP**: Household Air Pollution **N/A**: not assessed, **SD**: Standard Deviation, **IQR**: Interquartile range, **$PM_{2.5}$**: Particulate matter smaller than 2.5 μg, **CO**: Carbon monoxide, **ppm**: Parts per million, **COPD**: chronic obstructive pulmonary disease.*

Objective 4: Testing the VBA on Smoking training in PHC

In this descriptive study, a VBA on Smoking training intervention was provided to GPs. Outcomes related to knowledge, confidence and self-reported practice were evaluated before, immediately after and one month following the training.

Recruitment and demographic characteristics

The study recruitment flow-chart is illustrated in **Figure 13**. In total, 64 GPs were invited to the training, of which 35 agreed to participate (acceptance rate: 54.7%). The most frequently reported reason of declining participation was busy schedule and/or lack of time (n=23). Twenty-nine GPs attended the training (attendance rate: 82.9%), with family responsibilities being the most frequent reason for missing the training (n=3). Pre- and post-training assessments were completed by all 29 attendants, while 28 GPs returned the one-month follow-up questionnaire and completed their participation in the study (completion rate: 96.6%).

Figure 13. GPs' recruitment flow-chart for the VBA training of Crete.

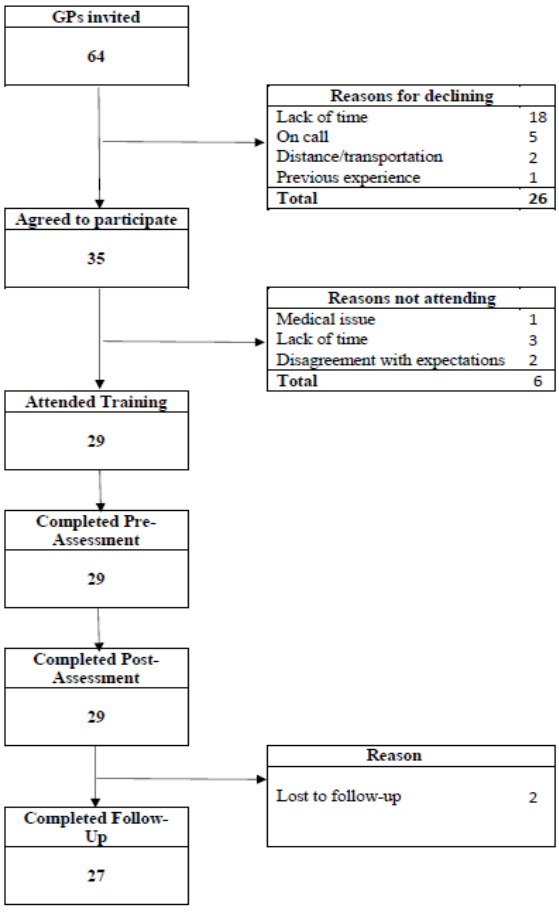


Table 12 shows the basic demographic characteristics of the 29 GPs that attended the VBA training. Overall, 18 (62.1%) were men, with a median (IQR) age of 44.5 (5.8) years. The vast majority (n=25 or 96.2%) were working in the public sector, while more than half were never smokers (n=15 or 57.7%).

Table 12. Characteristics of GPs participating in the VBA training in Crete (N=29).

Variables	**n (%)***
Age, median (IQR)	44.5 (5.8)
Gender,	
Male	18 (62.1)
Female	11 (37.9)
Sector of practice	
Private	1 (3.8)
Public	25 (96.2)
Smoking status, n (%)	
Current smoker	4 (15.4)
Ex-smoker	7 (26.9)
Never	15 (57.7)

**Refers to valid percentage*

Knowledge

Table 13 presents the proportions of GPs who answered correctly the five knowledge questions during the three assessments. Improvements documented in all knowledge questions among assessments were not statistically significant, either overall (all Cochrane Q tests' p-values >0.005) or pairwise (all McNemars test' p-values >0.005).

At baseline, the lowest proportions of GPs who answered knowledge questions correctly were documented for the questions regarding patients' reaction to quit smoking advice (n=9 or 31.0%), followed by the question regarding smoking and risk of lung cancer (n=18 or 66.7%). Although increased, these proportions remained low both after (n=10 or 35.7%) and one month following the training (n=14 or 51.9%).

The highest proportions of GPs who answered knowledge questions correctly at baseline were documented for the questions regarding smoking and risk of COPD (n=28 or 96.6%), followed by the question regarding action to take with patients who smoke (n=25 or 86.2%). These proportions increased further, reaching 100% (n=27) and 96.3% respectively during the one-month follow-up assessment.

Table 13. Proportion of GPs who responded correctly to tobacco treatment knowledge questions before, after and one month following the VBA training.

Question, n (%)[a]	Pre -training N=29	Post-training N=29	1-month f/u N=28	p-value[b]	Pre vs postp-value[C]	Pre vs f/u p-value[C]	Post vs f/u p-value[C]
Smoking and risk of lung cancer	18 (66.7)	20 (71.4)	20 (74.1)	0.913	1	1	1
Cravings for cigarettes	22 (75.9)	18 (64.3)	21 (77.8)	0.338	1	1	0.867
Smoking and COPD	28 (96.6)	26 (96.3)	27 (100.0)	0.607	1	1	1
Action to take with patients who smoke	25 (86.2)	24 (88.9)	26 (96.3)	0.247	1	0.750	1
How patients might react to smoking cessation advice	9 (31.0)	10 (35.7)	14 (51.9)	0.338	1	0.681	1

[a]Refers to valid percentage, [b]Cochrane's Q test, [c]Post hoc McNemar's test with Bonferroni correction for pairwise comparisons

***Abbreviations**: **f/u**: follow-up, **COPD**: chronic obstructive pulmonary disease*

Confidence

Table 14 and **Figure 14** illustrate the median (IQR) levels of GPs' confidence in providing each of the VBA elements (ASK, ADVICE, ACT). At all three assessments, GPs appeared fairly confident in regards to asking patients about their smoking status and informing them about the health risks of smoking and the benefits of quitting, with all respective medians reaching 5 (Likert scale with 1 indicating no confidence and 5 indicating very much confidence). Overall, statistically significant improvements were documented in GPs' confidence in advising their patients about the best methods to quit smoking (Friedman test's p-value=0.002) and acting on the patient's decision (Friedman test's p-value=0.030). Of these, confidence in advising patients on best cessation methods remained statistically significantly improved between pairwise comparisons of pre- versus post assessments (Wilcoxon Signed Rank test p-value=0.008) and pre- versus one-month follow-up assessments (Wilcoxon Signed Rank test p-value=0.015).

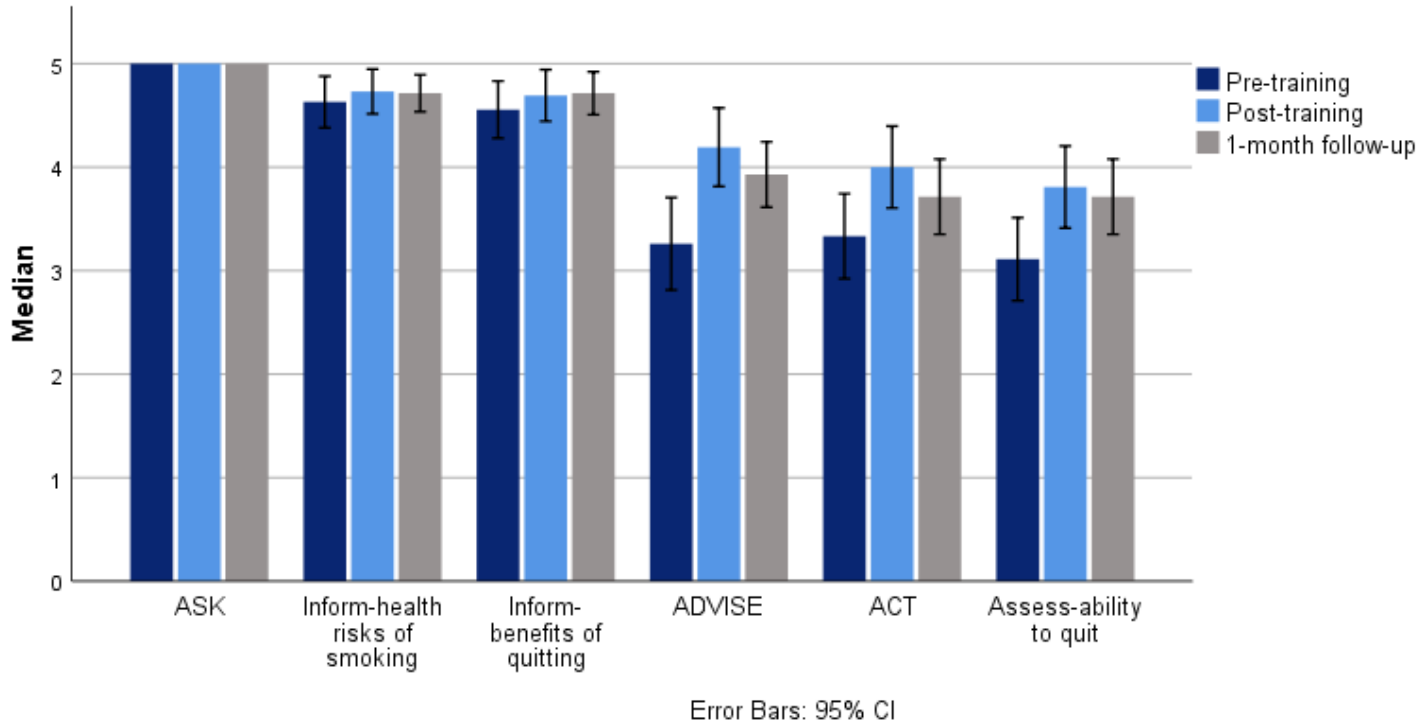
Table 14. GPs' self-reported efficacy in delivering VBA elements before, after and 1-month following the training.

How confident are you in doing each of the following, median (IQR)*	**Pre -training N=29**	**Post-training N=29**	**1-month f/u N=28**	**p-value[a]**	**Pre vs post p-value[b]**	**Pre vs f/u p-value[b]**	**Post vs f/u p-value[b]**
ASK	5 (0)	5 (0)	5 (0)	0.779	1	1	1
Inform patients on health risk of smoking	5 (1)	5 (0)	5 (1)	0.401	0.471	0.618	1
Inform patients on benefits of cessation	5 (1)	5 (0)	5 (1)	0.507	0.396	0.813	1
ADVISE	3 (1)	5 (2)	4 (2)	**0.002**	**0.008**	**0.015**	0.264
ACT	3 (1)	4 (2)	4 (1)	**0.030**	0.113	0.290	0.845
Assess commitment/ readiness/ability to quit	3 (0)	4 (2)	4 (2)	0.235	0.126	0.09	1

**Assessed in a 5-point Likert scale (1:not at all – 5: very much), [a]Friedman's test, [b]Post hoc Wilcoxon Signed Rank test with Bonferroni correction for pairwise comparisons*

***Abbreviations**: **IQR**: interquartile range , **f/u**: follow-up*

Figure 14. GPs' self-reported efficacy in delivering VBA elements before, after and 1-month following the training.



Self-reported practice

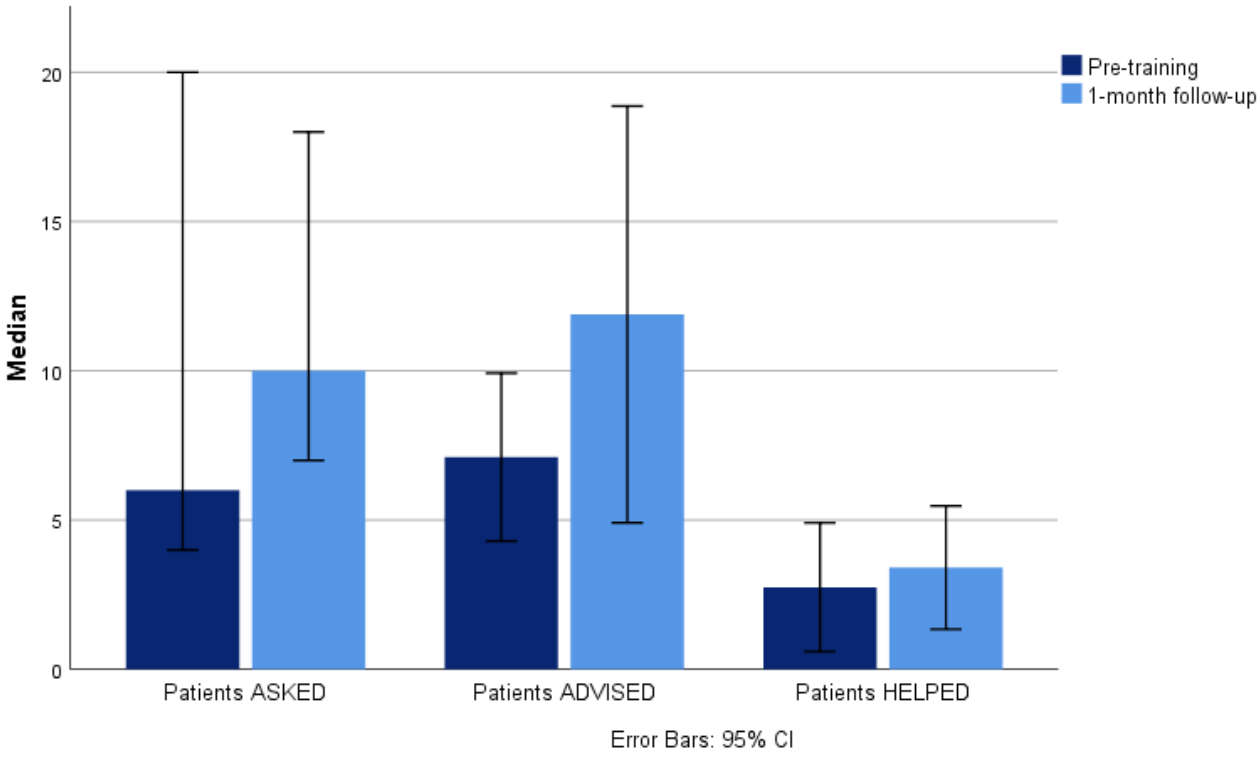
Table 15 and **Figure 15** presents data on self-reported rates of VBA delivery assessed before and one-month following the training. Improvements documented in the delivery of all VBA elements did not reach statistical significance (Wilcoxon Singed Rank tests' p-values = 0.110, 0.139 and 0.188 respectively).

Table 15. GPs' self-reported practice in terms of VBA delivery, assessed before and one-month following the training.

Number of times each of the following was delivered during the past week, **median (IQR)**	**Pre-training** **N=29**	**1-month f/u** **N=28**	**p-value[a]**
ASK	6 (18)	10 (15)	0.110
ADVICE	5 (10)	7 (8)	0.139
ACT	0 (2)	2 (5)	0.188

[a]Wilcoxon Signed Rank test
***Abbreviations**: **IQR**: interquartile range, **f/u**: follow-up*

Figure 15. GPs' self-reported practice in terms of VBA delivery, during the past seven days.



Objective 5: Exploring applicability of remote spirometry training and feedback in PHC (Spirometry360)

Of the five GPs invited in the study focus group assessing the applicability of a remote spirometry training and feedback programme (Spirometry 360), one did not accept participation citing working responsibilities. Among participating GPs, two were women and two were men. All belonged to the age group of 45-50 years old and worked in the public sector. GPs served diverse populations, with one serving a rural population, two serving in semi-urban areas and one working in an urban PHC unit. There was also diversity in terms of previous experience with spirometry training and practice but all GPs mentioned that their experience was based on individual efforts rather than formal education. The seven themes emerging from the in-depth analysis are summarized in **Table 16** and are further elaborated on below.

Table 16. Main themes regarding applicability of remote spirometry training and feedback in primary care in Crete.

Theme	Key points
1. Usefulness of spirometry training and impact on GPs' confidence	▪ Increased their confidence in performing spirometry and interpreting results
2. Diagnostic capability and the need for timely intervention	▪ Identification of alarming results, recognition of undiagnosed patients and provision of timely referral to specialized care
3. Motivation for GPs and patients	▪ Motivation to seek further information about respiratory care ▪ Motivational for patients for being tested.
4. Patients' response, benefit and importance of enabling proper chronic care delivery	▪ Opportunity for patients who would lack access to care to be monitored or referred properly
5. The need for team work and training integration to ensure sustainability	▪ Upgrade of medical curricula and central support ▪ Team work to facilitate spirometry performance and expansion to other professionals too
6. Barriers and facilitators to training attendance and use of obtained knowledge	▪ Facilitators: on-demand and time-effective nature of training were mentioned, the trust of patients to their family doctor ▪ Barriers: busy working schedules, lack of equipment
7. Overall satisfaction with the training programme	▪ Training format and delivery ▪ Wish to repeat and/or continue it

1. The usefulness of spirometry training and impact on GPs' confidence

All participants highlighted their good experience with the training, pointing out its usefulness and agreeing that it enhanced their confidence in both performing spirometry and interpreting results. The

feedback reports that they received from Spiromety 360's expert team were also positively evaluated in terms of raising confidence.

- *…Because spirometry is 60% technique. It is a test that requires the cooperation of the patient so that you can have a good result. So, such trainings are very good and useful and I would very much like to repeat it (GP1)*

- *After the training, I was feeling surer when I was looking at a spirometry. That was the most important part (…) The feedback was important, I think because you may not understand what you do wrong or you may be imagining that there is a mistake somewhere and it is good if someone, more specialized, points it out (GP2)*

- *…And I also improved my technique. This is definite. I improved certain things that I either neglected or ignored in the past and, for sure (GP4)*

2. Diagnostic capability and the need for timely intervention

Participants stressed that the spirometry training and practice helped them with interpreting results and providing patient assessments, but highlighted that this cannot replace the role of pulmonologists in setting official diagnoses and initiating treatments. They highlighted their role as the first and most accessible point of contact for the patient and pointed out the usefullness of the training in enabling them to better understand alarming indications, recognize undiagnosed patients and provide timely referral to specialized care.

- *In order to prescribe medicines for COPD, it is necessary to have a diagnosis from a pulmonologist. So, there is a limitation regarding what we can do... The important thing is that we can understand what happens so that we can timely refer. So, having a good training on that, means that we would better prevent some things (…) Because many times patients turn a blind eye. They say 'I am well' but they may not understand that they have been deteriorated. They might not want to admit it. So, our role is to interpret their symptoms (…) because they won't speak about it. You need to ask 'Do you get breathless, when waling on straight light? Can you walk on slope? How many times do you cough? How many times do you wake up in the night with cough or phlegm or dyspnea?' So, you ask 'How are you' and they say 'I am well' but when you ask further you see that they are not (…) So, there is our important role. To understand that they are not well and refer accordingly (GP2)*

- *And the even most important part, to my view, are the undiagnosed patients with CRD who come, because primary care is accessible. There is a large proportion in the first or second*

stage of COPD, who are undiagnosed, who do not evaluate the more frequent cough and phlegm. There, to my view, the role of GP is even more important... The diagnosis part comes afterwards (GP3)

3. Motivation for GPs and patients

GPs reported that the training motivated them to revisit their previous diagnosis and provide better care for their patients. They also stated that the training triggered them to seek for further information about spirometry and CRDs in general. In addition, GPs mentioned the fact that they were trained and able to conduct spirometry in their practice was advertised between patients, motivating them be tested.

- *Firstly, it was the motive to re-examine a group of patients, who according to our knowledge so far, did not meet past criteria. And since we, then, had the ability through the spirometer to confirm the clinical results, sure it was very efficient and we were able to identify some cases that, in other cases, might have been lost. Also, during the period that we had the spirometer, we scheduled many appointments with patients whom we already suspected that met certain criteria and performed spirometry to those who could not be transported, either due to distance or financial reasons (GP4)*

- *Sure, it gave us motives. I attended another programme (…) to go one step further, after spirometry, to understand patients better and the pathophysiology of CRD (GP1)*

- *Also, it was a good advertisement. Family or friends of those patients who possibly had the same symptoms (were triggered) to enter a screening procedure (GP4)*

4. Patients' response, benefit and importance of enabling proper chronic care delivery

According to GPs, their training and practice had a direct impact on patients, as it led to providing the opportunity to patients who would, otherwise lack access to diagnostic testing, to receive indications about their condition, to be advised on risk reduction (i.e. smoking cessation) and to be monitored or referred accordingly. Additionally, participants noted the benefit on the overall monitoring of patients' chronic disease in a holistic way.

- *…There was a part of patients that would not go (for spirometry), they wouldn't have access. They came, they were happy. It was a positive experience (…) There was a reinforcement of reminding them to quit smoking (…) and some patients begun a more frequent monitoring and got what they needed in terms of referral and so on (GP3)*

- *Firstly, it was the direct service. This (training and practice programme) gave them the ability to be served in their area, without any other transportation or appointment (GP4)*

- *…(In my former practice) when a patient had a COPD stage deterioration, nobody could deal with updating his treatment and he only knew that 'If I get a gold, I will go to the healthcare center to get an oxygen mask'. This is not (proper) treatment of a chronic disease (GP1)*

5. The need for team work and training integration to ensure sustainability

All participants stressed the need for well-trained physicians in PHC. However, in order the spirometry training to be integrated in PHC, GPs highlighted that an overall upgrade of medical curricula is required, along with a central support of such educational activities, including funding and provision of Continuous Medical Education certifications. GPs finally stressed the importance of team work in order to facilitate performance of spirometry in primary care and agreed that, in order to be sustained, the training should be expanded to other professionals too.

- *We need to move forward to an overall upgrade of the medical training. I recently finished a training provided by a European Association and I was like 'Why don't we have such things in Greece as well? Why do I need to attend the European ones which is also very expensive?' (GP1)*

- *This is true for every country. You need to prove that you have continuous medical education. Only in Greece we don't have it officially. Everyone else seeks for such things. Here, if you want to attend something ok, if you don't it is (also) ok (GP2)*

- *If we had start over, we would need to train the nursing stuff to do it. If we had to set up a programme again, we would need to put nurses in performing (spirometry) and doctors to just interpret the results (GP2)*

6. Barriers and facilitators to training attendance and use of obtained knowledge

The on-demand and time-effective nature of the training were mentioned as facilitators of training attendance. The trust of patients to their family doctors was reported, on the other hand, as a facilitator of continuing spirometry performance in clinical practice.

- *Since it was possible to be watched on demand, this was very beneficial. We did not have any pressure or deadline. It was easy and comprehensive (…) such trainings that do not require much time or effort to be completed, leave you the necessary time (…) Additionally, (patients) always trust their family doctor, so they found all this package directly and were benefited in multiple ways (GP4)*

However, GPs noted that lack of time attributed to busy working schedules and lack of equipment were the most significant barriers that preventing them from practicing spirometry routinely after the training.

- *We have the skills but we don't have the time. You don't have the time to have quality primary care. Even if you want or have the qualifications. I come from the second night shift of this week, I have not slept at all, I have the emergencies, will I (be able) to assess the COPD patient or the undiagnosed patient properly? So, the big problem is time and this huge diffusion (GP3)*

- *I don't have any spirometer anymore. Mine got broken and they (administrative authorities) are not going to provide me (his practice) with one (GP1)*

7. Overall satisfaction with the training programme

Participants expressed vividly their satisfaction with the spirometry training format and delivery and all agreed in their wish to repeat and/or continue it.

- *Spirometry 360 was an excellent training. Both the fundamentals and the techniques were very good (GP1)*

- *I was enthusiastic because the programme was amazing, it was very good. It solved all your questions; it was to the point. I think it was among the best that I have taken (GP2)*

- *I am also satisfied. It would be good if knowledge could be repeated (GP3)*

- *It was excellent, without any gaps and even an unexperienced doctor could understand a lot so that they can practice them daily. The course was incredibly good (GP4)*

Objective 6: Evaluating a pulmonary rehabilitation programme in PHC

Detailed information about the results of this study is provided in the first publication of this thesis in Chronic Respiratory Disease (178), which is provided in its full extent in **Appendix A3.6**. Key results are presented below.

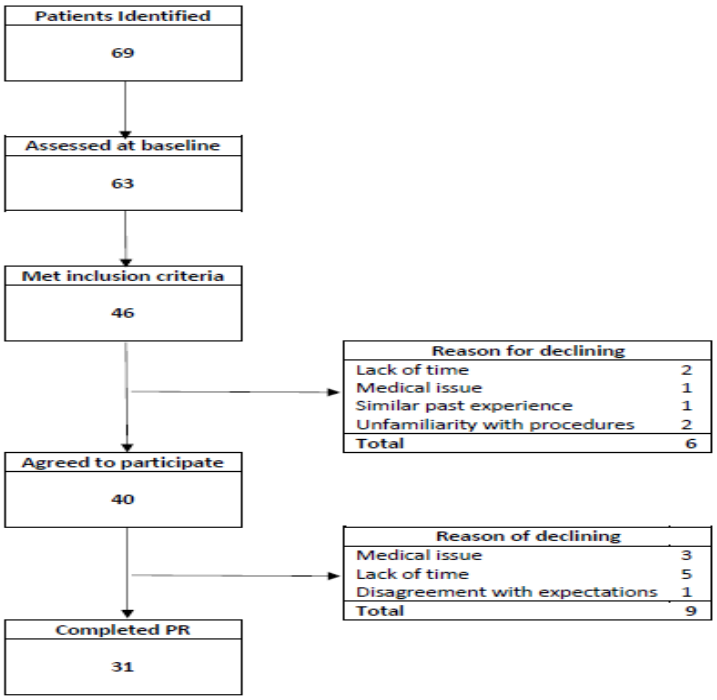
Developing the implementation strategy and intervention

Relatively minimal adaptation to the original PR programme was performed. Adaptations were mainly cultural and included translation of documents, exclusion of post-tuberculosis patients due to the very low prevalence in Greece (192) and addition of the disease-specific SGRQ and CAT questionnaires which have been validated and widely used in Greece (193,194), delivery of walking exercises outdoors due to suitable weather and purchase of training equipment instead of practical, daily-used objects.

Recruitment and intervention delivery

A total of four healthcare professionals were trained and delivered the PR programme in one primary healthcare center. Patient flow in the study is illustrated in **Figure 16.** Overall, 63 patients underwent baseline assessment and 46 were found eligible. In total, 40 patients started PR (participation rate: 87%), with 31 completing the programme (completion rate: 77.5%). Lack of time and reluctance due to unfamiliarity with PR procedures were mentioned as main reasons for not engaging with the programme. Medical issues and lack of time were reported as main reasons for dropping out the programme.

Figure 16. Recruitment flow-chart of the PR programme of Crete.



Demographic and baseline health characteristics

Table 17 presents the main baseline characteristics of the original sample of patients, along with differences among individuals who dropped out and those who completed the programme. Overall, slightly more than half of patients were females (55.0%), with a mean age of 67.2 years (95%CI: 63.9, 70.5). COPD was the main diagnosis for 60.0%, while 65.0% had ever smoked. With the exception of education (p-value=0.019), no differences were observed between people completing and dropping out of PR with respect to socio-demographic characteristics.

In addition, mean BMI of the total sample was 31.24 kg/m2 (95%CI: 29.63, 32.84), namely 33.79 (95%CI: 31.17, 36.41) for patients dropping out and 30.58 (28.69, 32.47) for those completing the programme. Patients who dropped out also had lower ISWT than their counterparts (mean difference: -53.84, 95%CI: -134.26, 26.59), with the mean value for the overall sample being 244.36 meters (95%CI: 211.21, 277.51). Total CCQ score was 1.86 (95% CI: 1.51, 2.21) with a difference of 1.04 (95%CI: -0.41, 2.49) between individuals dropping out and completing PR.

Table 17. Baseline characteristics of the original sample of COPD and asthma patients (N=40) and differences between patients dropping out and completing the PR programme in Crete.

Outcomes	**Total sample (N=40)**	**Dropped-out (N=9)**	**Completed (N=31)**	**Difference**
Socio-demographics, n (%)				
Gender				
Male	18 (45.0)	2 (22.2)	16 (51.6)	p=0.15*
Female	22 (55.0)	7 (77.8)	15 (48.4)	
Age (*years*), mean (95% CI)	67.2 (63.9, 70.5)	67.6 (59.5, 75.6)	67.1 (63.3, 70.9)	0.43 (-7.51, 8.37)
Diagnosis, n (%)				
COPD	24 (60.0)	5 (55.6)	19 (61.3)	p=1.0*
Chronic asthma	16 (40.0)	4 (44.4)	12 (38.7)	
Education, n (%)				
None	1 (2.5)	1 (11.1)	0 (0.0)	
Incomplete primary	1 (9.1)	3 (33.3)	2 (6.5)	
Complete primary	8 (72.7)	3 (33.3)	25 (80.6)	p=0.019*
Incomplete secondary)	1 (9.1)	1 (11.1)	2 (6.5)	
Complete secondary	1 (9.1)	1 (11.1)	2 (6.5)	
Income (*euros*), *mean (95% CI)*	460.8	420.0	472.6	-52.75

	(385.3, 536.4)	(139.1, 700.9)	(398.9, 546.6)	(-235.69, 130.19)
Smoking, n (%)				
Yes, currently	6 (15.0)	1 (11.1)	5 (16.1)	
Yes, in the past	20 (50.0)	5 (55.6)	15 (48.4)	p=1.0*
No	14 (35.0)	3 (33.3)	11 (35.5)	
Biometrics, *mean (95% CI)*				
BMI (kg/m^2)	31.24 (29.63, 32.84)	33.79 (31.17, 36.41)	30.58 (28.69, 32.47)	3.21 (-0.68, 7.10)
Symptoms, *mean (95% CI)*				
MRC dyspnea scale	3.23 (2.91, 3.55)	3.50 (0.34, 4.68)	3.16 (2.85, 3.48)	0.28 (-0.77, 1.33)
Exercise capacity, *mean (95% CI)*				
ISWT (meters)	244.36 (211.21, 277.51)	117.50 (97.47, 257.53)	261.61 (225.66, 297.56)	-53.84 (-134.26, 26.59)
Health status, *mean (95% CI)*				
CCQ total score	1.86 (1.51, 2.21)	2.85 (1.26, 4.44)	1.61 (1.39, 1.82)	1.04 (-0.41, 2.49)
CAT total score	16.97 (14.32, 19.62)	19.38 (11.18, 27.57)	16.35 (13.51, 19.20)	3.02 (-3.56, 9.60)

**Fischer's Exact test*

***Abbreviations**: **CI**: Confidence Interval, **BMI**: Body Mass Index, **ISWT**: Incremental Shuttle Walking Test, **CCQ**: Clinical COPD Questionnaire, **CAT**: COPD Assessment Test*

Effect of the PR programme on patient health outcomes

Data on pre- and post-PR outcomes are presented in **Table 18**, for patients who completed the programme. Mean dyspnoea levels as measured by the MRC scale was reduced by 1.03 points, reaching the MCID of 1. Functional and exercise capacity measurements were improved by the end of PR. The mean sit-to-stand time was reduced by 2.41 seconds, a change close to the MCID of 2.3 seconds. The mean ISWT increased by 87.39 meters greatly exceeding the MCID of 47.5 m. The mean dyspnoea levels after performing ISWT, as measured by the Borg scale, decreased by 0.94 units.

Substantial improvements were also documented in all health status indicators. The mean CCQ total score was reduced by 0.53 units, a difference above the MCID of 0.4. Mean CAT score dropped by almost 6 units, exceeding the MCID of 2. The mean SGRQ total score decreased by 23 units, a

difference higher than the MCID of 4. The mean Karnofsky score was improved by 9.67 units. PHQ-9 scores were low already from baseline, yet a reduction of 1.10 points was observed.

Table 18. Patient outcomes at baseline and at the end of the PR programme in Crete.

Outcomes	Baseline Mean (95% CI)	End of PR Mean (95% CI)	Difference Mean (95% CI)
Biometrics (N=30)			
BMI (kg/m^2)	30.56 (28.69, 32.47)	30.44 (28.50, 32.38)	-0.12 (-0.31, 0.08)
Mid-upper arm circumference (cms)	29.63 (28.41, 30.86)	29.80 (28.63, 30.97)	0.17 (-0.16, 0.49)
Thigh (cms)	45.45 (43.33, 47.57)	46.75 (44.67, 48.83)	1.30 (0.34, 2.26)
Symptoms (N=30)			
MRC dyspnea scale	3.17 (2.84, 3.49)	2.13 (1.88, 2.39)	-1.03 (-1.45, -0.61)
Functionality (N=31)			
Sit to stand time (seconds)	14.49 (12.97, 16.01)	12.08 (10.98, 13.18)	-2.41 (-3.58, -1.23)
Exercise capacity (N=31)			
ISWT (meters)	261.61 (228.66, 297.57)	349.00 (301.19, 396.81)	87.39 (59.37, 115.40)
Borg score (before ISWT)	1.15 (0.54, 1.75)	0.97 (0.41, 1.52)	-0.18 (-0.78, 0.43)
Pulse oximetry (before ISWT)	95.39 (94.52, 96.25)	95.35 (94.40, 96.31)	-0.03 (-0.90, 0.84)
Borg score (after ISWT)	4.90 (4.16, 5.65)	3.97 (3.23, 4.70)	-0.94 (-1.55, -0.32)
Pulse oximetry (immediately after ISWT)	95.13 (93.62, 96.64)	94.13 (92.48, 95.77)	-1.00 (-2.34, 0.34)
Pulse oximetry (2 minutes after ISWT)	96.61 (95.87, 97.36)	96.61 (95.98, 97.24)	0,00 (-0.66, 0.66)
Health status (N=30)			
CCQ total score	1.59 (1.37, 1.81)	1.06 (0.79, 1.33)	-0.53 (-0.81, -0.24)
CCQ symptom score	1.50 (1.10, 1.89)	1.08 (0.71, 1.44)	-0.43 (-0.94, 0.09)
CCQ mental state score	2.10 (1.61, 1.59)	1.10 (0.63, 1.57)	-1.00 (-1.50, -0.49)
CCQ functional state score	1.43 (1.11, 1.74)	1.03 (0.68, 1.39)	-0.39 (-0.77, -0.02)
CAT total score	16.13 (13.22, 19.05)	10.20 (8.17, 12.23)	-5.93 (-8.27, -3.60)
SGRQ total score	43.20 (36.86, 49.54)	20.20 (15.15, 25.25)	-23.00 (-29.42, -16.58)
SGRQ symptoms score	46.96 (37.68, 56.24)	19.76 (14.39, 25.14)	-27.20 (-37.16, -17.23)
SGRQ activity score	55.02 (47.33, 62.72)	23.69 (15.83, 31.54)	-31.34 (-40.55, -22.12)
SGRQ impacts score	35.19 (28.61, 41.77)	18.31 (13.10, 23.65)	-16.82 (-23.31, -10.32)
Karnofsky score	77.67 (74.78, 80.56)	87.33 (84.09, 90.58)	9.67 (7.37, 11.96)
PHQ-9 total score	4.70 (2.92, 6.48)	3.60 (2.31, 4.89)	-1.10 (-2.32, 0.12)

***Abbreviations**: **CI**: Confidence Interval, **BMI**: Body Mass Index, **cms**: centimeters, **MRC**: Medical Research Council, **ISWT**: Incremental Shuttle Walking Test, **CCQ**: Clinical COPD Questionnaire, **CAT**: COPD Assessment Test, **SGRQ**: Saint George Respiratory Questionnaire, **PHQ-9**: Patient Health Questionnaire-9*

Feasibility and acceptability of the PR programme

Interviews were conducted with a total of 8 patients (4 males, mean age: 64.5 years) pre- and post-PR. Seven stakeholders attended the focus group, including the PR physiotherapists and nurse, one GP facilitating patient recruitment, the site director (also a GP), the community vice-mayor and a pulmonologist from a public hospital of the city.

The main themes of qualitative interviews and focus groups are presented in **Table 19**. Patients' expectations included an overall health improvement and less medication dependence, partly to alleviate the financial burden of drugs. At the end of PR, both patients and stakeholders positively assessed the programme, noting the significant symptoms' reduction, the improvement and increase of physical activity and the benefits of received education on disease self-management. Patients and stakeholders recommended that the PR programme should be sustained and similar actions should be implemented in remote areas.

Table 19. Main themes emerging from patient interviews and stakeholders' focus group about the PR programme in Crete.

Themes	Patient interview	Stakeholder focus groups
Expectations of the programme	▪ Overall health improvement ▪ Less medication dependence	-
Assessment of the programme	▪ Respiratory symptoms' reduction ▪ Improvement and increase of physical activity	▪ Significant reduction in respiratory symptoms
Benefits of education	▪ Dyspnoea control ▪ Appropriate exercise performance ▪ Overall health education	▪ Disease self-management ▪ Panic avoidance during exacerbation
Sustainability	▪ Importance of implementing similar programmes in remote areas	▪ Implementation in primary care for remote populations ▪ Expansion in all healthcare facilities including hospitals ▪ Central funding for continuation

Barriers and facilitators of implementation

Key barriers and facilitators identified by patients and stakeholders are summarised in Table 20. According to patients, barriers mainly concerned caring responsibilities, while few were related to accessing the programme. A key facilitator enhancing participation, as perceived by both patients and stakeholders, included the opportunity offered to patients by the programme to socialize while

improving their health. Additionally, stakeholders identified timely information and comprehensive GPs' referral as core elements facilitating optimal recruitment. In contrast to patients, barriers to attending PR according to stakeholders concerned transportation and an initial hesitation of patients attributed to lack of experience with such initiatives.

Table 20. Key barriers and facilitators to implement the PR programme in Crete, according to patients and stakeholders.

Key barriers	Key facilitators
Caring responsibilities	Opportunity for socializing while improving health
Convincing patients to initiate this novel programme	Timely information of stakeholders
Transportation	Comprehensive GPs' referral

Chapter 4. General discussion

A summary of key thesis findings and their implications for research, implementation, policy and practice is provided in **Table 21** below and further analysed in the following subsections.

Table 21. Key thesis findings and for research, implementation, policy and practice

Obj	Key findings	Implications
1	▪ Healthcare expenditure is mostly reimbursed ▪ Diagnostic tests represented the highest individual copayment, while at an annual basis, this accounted for visits to pulmonologists ▪ Indications on substantial impairment of regular activities due to CRD were documented	▪ Relieving the indirect burden of CRDs, including activity impairment is a contextual factor to be targeted of respiratory interventions
2	▪ About half of participants attributed long-term respiratory conditions to a respiratory illness ▪ Reported beliefs, perceptions and the associations of these with risk behaviours were indicative of presence of awareness about smoking but not for HAP ▪ Large proportions were using biomass fuels (61%) and even larger proportions were smokers, despite awareness on smoking ▪ Smoking was inversely associated with the opinion of participants' social environment regarding the importance of seeking help about long-term symptoms ▪ Smoking was inversely associated with perceived duration of the disease	▪ Interventions should target raising awareness about CRD identity and HAP, but more drastic actions seem to be needed for smoking ▪ The social environment (family and friends) and perceived duration of disease are contextual factors that seem to affect smoking behaviours and their further examination needs to be taken into consideration by respiratory interventions
3	▪ PM2.5 levels in rural households exceeded international guidelines on air quality ▪ About 72% had clean heating devices but about 41% actually used them. In contrast 90% were using wood burning stoves and/or fireplaces. These differences were attributed by participants to financial reasons ▪ Clean fuels were used by one in four households ▪ Less than half of participants knew that biomass burning harms health (48.5%) and, for most, this knowledge came from media (75%)	▪ Results agree with indications about returning to harmful practices during the financial crisis ▪ Interventions need to consider advocating for combating austerity-related fuel poverty and raising awareness of harmful effects of HAP ▪ Community and media engagement seem important areas for consideration by interventions
4	▪ GPs seemed knowledgeable already before the VBA training, except regarding the question on patients' reaction to smoking cessation advice.	▪ Increasing GPs confidence on how to address patients' reaction to smoking cessation advice seems an area for intervention

	▪ Statistically significant improvements were documented immediately after and one month following the VBA training on GPs self-reported efficacy in advising patients about the risks ▪ Differences in self-reported practice were not statistically significant	▪ VBA training seems impactful in increasing GPs confidence on advising patients and could be further examined as a strategy for addressing tobacco use in low-resource settings ▪ Self-reported practice did not present significant improvements, suggesting the need for further training
5	▪ GPs reported increased confidence in performing and interpreting lung function testing after the Spirometry360 training ▪ This was highlighted as important for their rural settings since it facilitates the timely identification and referral of patients who may lack direct access to specialized care ▪ Busy working schedules and lack of equipment were reported barriers to attendance and practice	▪ Raising GPs' capacity to enable timely identification of patients in a time-effective manner seems an important action towards improving under- or mis-diagnosis of CRD diagnosis in low-resource rural settings
6	▪ A low-cost and culturally adapted PR programme functioned for the first time in Greek PHC and in a low-resource rural setting in particular ▪ Improvements exceeding minimum clinically important differences were seen in all patients' health outcomes ▪ Participation in therapeutic process, opportunity to socialize while improving health and trust developed between patients and PR professionals were important facilitators of successful implementation	▪ The PR program could be feasible, beneficial and acceptable option for the treatment of CRD in low-resource PHC settings ▪ Increasing patient-centeredness, participatory involvement and engagement of patients in treatment process seems to be an important message for therapeutic interventions

4.1. Summary of findings

The first objective of this thesis assessed the socio-economic burden of asthma and COPD was assessed among 100 PHC patients with asthma and/or COPD. Healthcare utilization was mostly reimbursed (from 61.0% of the time for visits to pulmonologists to 93% of the time for visits to GPs). In case of no reimbursement, the highest co-payments were observed for performing diagnostic tests, with a median (IQR) of 45 (28) euros spent during the last year. If all reported healthcare expenditure is annualized, visits to the pulmonologist represent the highest out-of-pocket payments [median (IQR) of 150 (80-480) euros]. Our results indicate generally lower direct costs of CRDs compared to other Greek studies (21,22). This might be partially explained by the fact that the vast majority of the sample (97%) were insured, with indications of mild disease severity [median (IQR) MRC: 1.9 (46%)] and low frequency of healthcare utilization [median (IQR) visits to GPs and pulmonologist the past 3 months: 1 (2) and 0 (1) respectively]. Indirect impacts of CRD were also documented, including indications on substantial impairment of regular activities due to CRD [median (IQR) of 0-10-point Likert scale score: 4 (5)]. Indeed, in the comparative study published by the FRESH AIR group, Greece had the second highest percentage of activity impairment due to CRD among the four low-resource countries, although this could be partially attributed to the higher age of participants (155).

Examining the local beliefs and perceptions towards CRDs and their relationship with risk behaviors among 200 community members, about half of participants (51.5%) linked respiratory symptoms to a respiratory condition. While 67.5% strongly agreed that smoking causes respiratory symptoms, the respective percentage for HAP was 8.5%. Compared to the other low-resource settings of FRESH AIR, Greek participants more strongly attributed long-term respiratory symptoms to a respiratory illness, rather than an infection (160). Despite the presence of relative awareness regarding smoking, 73.5% of the sample were current smokers, a result that agrees with the general figures for Greece (27). Also, 61.0% were using biomass fuels. Smoking behaviour was associated among others with the opinion of patients' social environment regarding the importance of seeking medical help for respiratory symptoms (OR=0.628, 95%CI: 0.401-0.985). The impact of family has been acknowledged among the important socio-cultural influences of smoking behaviour in Greece, while its general impact on health promotion has been further highlighted in a scoping review of international studies (195-197).

To the best of our knowledge, our HAP study is among the first to provide insights about the levels of HAP and relevant health-related practices and outcomes during a period of economic recession in Greece. Our results revealed levels of household PM2.5 exceeding the WHO air quality guidelines. These values are lower than those reported in a similar FRESH AIR study conducted in global low-resource settings (163), and further investigation is warranted to determine whether this can suggest a public health issue in rural Crete. Still, although direct comparisons cannot be performed, a recent study including outdoor data from the second largest Greek city showed that biomass burning during winter comprised the second largest PM2.5 source, indicating an important health-related issue deserving prompt attention (198). Additionally, another study assessing personal PM exposure through an indoor–outdoor experiment in Athens showed that, in general, 24 hours averaged PM2.5 concentrations frequently exceeded the limits set by the European Union (199). Interestingly, although clean fuel devices were owned by a considerable proportion of households in our study, they were used at substantially lower rates, with disparities being attributed to financial limitations. This is in accordance with previous evidence highlighting the negative impact of the economic crisis on heating practices in Greece (47). In another study exploring indoor environmental conditions in low-income, urban households during the Greek recession, temperatures in participating houses were found to be much lower than the appropriate thresholds for comfort and health, suggesting that the significant barriers to buying energy had placed the population under serious environmental and health-related risks (200). Lastly, an awareness gap was observed, since less than half of participants knew that burning biomass inside the household may be harmful health (48.5%). Similarly low levels of HAP awareness have been documented in other low-resource settings too (201).

Statistically significant overall and pairwise increases were documented in the reported confidence of GPs in advising patients on smoking cessation after the VBA training (p-value=0.002). Also, significant overall increase in GPs' self-efficacy with assisting their patients with quitting was observed (p-

value=0.003). These results are in line with those of a similar study conducted in Crete where a significant increase in GPs self-efficacy was documented between the pre and post assessment of a tobacco treatment intervention which was based on the Ottawa model (12.5% vs. 64.3%; p=0.016) (89). Still, a gap in the knowledge of GPs was observed regarding patients' reaction to their quit smoking advice (% answered correctly: 31.0% at baseline, 35.7% after and 51.9% at one-month follow-up), indicating the previously documented need of raising GPs' skills and confidence in approaching and effectively engaging their patients (202).

In terms of improving CRD diagnosis, our results suggested that, for rural populations who may lack direct access to diagnostic options, training GPs in lung function testing may be helpful for improving under- or mis-diagnosis and facilitating proper monitoring and timely referral to specialized care. These findings are in line with the quantitative results of an international study exploring the achievenments and dicision-making practice of GPs trained in spirometric diagnosis, where trained GPs were able to differentiate between normal and obstructive disease patterns, while spirometry reduced their number of alternative diagnoses (OR=0.266 95%CI: 0.200, 0.353) and increased referral rates (OR=7.26, 95%CI: 4.71, 11.2) (203).

The findings of the evaluation of the PR programme in Crete (objective 6) are in accordance with international literature documenting the beneficial effects of PR for patients with CRDs (97,180). The documented pre- and post-PR differences in main clinical outcomes (CCQ and ISWT) were generally close to those observed in the development study of Uganda (99). By reading other studies, differences in ISWT and CCQ recorded in our study were generally higher. In a comparative review, the change in ISWT was found 39.77 m higher in COPD patients receiving PR versus usual care, a result much lower than the pre-/post-ISWT difference documented in this study (87.39 m) (204). Similarly, in a prospective study of 419 COPD patients, CCQ improved by 0.6 points after PR, a change close the one observed in this study (−0.53) (205). Changes in SGRQ total score (−23.00) were also higher than in other studies (−21.07 and −12.3, respectively) (206,207). Improvements observed in SGRQ scores were impressive. This may explained by the fact that, as disease-specific questionnaire, the SGRQ is more likely to be responsive to changes after PR and more sensitive to specific respiratory issues (208). Additionally, the fact that the programme served patients in a holistic manner, including medical, psychological and social support, may have increased their overall positive response and assessment.

4.2. Strengths and limitations

To the best of our knowledge, this is the first project to address the continuum of actions for protecting and improving the respiratory health of low-resource rural populations in Greece. Evidence, tools and

infrastructure was obtained and novel interventions were piloted for the first time in the Greek PHC context.

However, all studies performed in this thesis are prone to common limitations that may hamper generalizability of results. These sources of bias include the observational designs of studies, the small and purposively/consecutively selected samples, the lack of statistical power, the self-reported nature of data, the contextual particularities and the absence of control groups for robust comparisons. As part of FRESH AIR, this thesis was, however, an implementation science project that followed a pragmatic approach, reflecting the fact that in this type of research the methods can be impacted by complex contextual factors and limited resources (209). Further study-specific limitations were:

Objective 1: Data collection took place in PHC facilities and, in order to be eligible, patients needed to have a confirmed diagnosis of asthma and or COPD in their electronic or paper-based record. This may lead to selection bias, as undiagnosed or patients may have been missed. Also, since recruitment was consecutive, less severely ill patients might have been missed since people tend to use healthcare services when experiencing more severe symptoms (210). As such the magnitude of activity impairment may have been over-estimated. However, since spirometry is not available in rural settings of Crete, this was the only way to select our participants.

Objective 2: Many researchers were involved in data collection, a fact that may have impacted the results. Also, we did not collect information on participants' income and thus we were not able to assess the effect of this important factor on risk behaviour, particularly biomass fuel use. However, we collected data on participants occupation which may be a relevant proxy of income. This study was, however, among the first to use a systematic approach and a robust tool (160) to map contextual factors of the Greek low-resource rural setting to prepare for subsequent respiratory interventions.

Objective 3: Different investigators performed the baseline and follow-up evaluations, facts that may have had an impact on the results. Also, we did not collect data on residents' educational level, a factor that may influence knowledge regarding smoke and HAP. Other challenges faced during implementation were related to the function of measuring devices, including recording duration due to fast battery discharge and device calibration. Although these were tackled immediately during field work, there is a chance that they may have affected the measurements' quality. It should also be noted that the ingress of outdoor pollutants indoors may have influenced our observed measurements, while the limited of data we collected on ventilation may also impact the interpretation of findings. The limited availability of data before the economic crisis does not further allow for the comprehensive interpretation of the observed health outcomes with respect to the noted levels of HAP. Finally, although we intended to reflect on outcomes between periods of lesser versus extensive heating, weather conditions encountered during the two data collection periods were unusually similar, a fact that may have hampered the identification of meaningful differences. Despite the resource restrictions and the

complex nature of data collection, this study is among the first to attempt the measurement of HAP attributed to indoor biomass-burning, offering valuable lessons regarding measuring practices and implementation design within the local context.

Objective 4: As part of this study, we did not also assess VBA delivery from GPs through their patients. However, this was the aim of a subsequent study with published results (211). Additionally, we did not capture an overview of the longer-term effects of the training, however this does not affect our before, after and 1-mont follow-up indicators Interpretation of results also requires caution due to two sources of potential bias which may have influenced the provided self-reported information: the free-for-service nature of the present training and the close relationships established between participating GPs and trainers. Yet, to the best of our knowledge, this the first study to introduce VBA and assess the training in Greece and among the first to evaluate this intervention in general.

Objective 5: Since only one focus group was conducted in this qualitative study, data and results are of limited scale and representativeness. Triangulation of data through other data collection methods or resources was also not performed. Interview, coding and analysis was performed by only one investigator. However, results were cross-checked with participants, while opinion of senior members of the research team was asked. However, this was the first attempt to discuss the applicability of a remote spirometry training in the Greek PHC context.

Objective 6: This was a PR programme but, unfortunately, we were unable to report on patient lung function characteristics. Spirometry is not available in Greek primary care and our efforts in overcoming this by using a portable spirometer did not provide quality results (most frequent errors: reduced expiration time, obstruction of the spirometer mouthpiece, poor patient collaboration and reduced peak expiratory flow). Additionally, we did not capture an overview of the long-term effects of the PR programme; however, this does not affect our before and after indicators. Interpretation of results also requires caution due to two sources of potential bias which may have influenced the provided self-reported information: the free-for-service nature of the present PR programme and the close relationships established over time between patients and healthcare professionals. To the best of our knowledge, however, this is the first attempt to establish and assess a community-based PR programme in Greek PHC and in the low-resource rural periphery in particular.

4.3. Implications for research, implementation, policy and practice

Starting with assessing the socioeconomic burden of CRDs in Greece (objective 1), the findings of this thesis suggested that relieving the indirect burden of CRDs, including activity impairment, seems to be an important area to be targeted by health interventions. Considering other factors that may influence implementation and adoption of health interventions (objective 2), the opinion of the social environment

and perceived disease severity were context-specific predictors of smoking behaviour and this may be useful to consider when respective actions are designed. Understanding local cultural and socio-economic backgrounds and enabling the active involvement of local communities in decision making is crucial for the successful implementation of any intervention aiming to reduce HAP and improve health (73).

This thesis adds to literature by demonstrating HAP levels in rural Greek households that exceed the internationally established air quality standards were documented (objective 3), confirming the return to harmful practices during Greece's austerity. During the last decade, the economic recession of Greece has meant changes in health-related practices, including the switch to biomass burning for domestic heating. The impact of the subsequent indoor air pollution on respiratory health has been studied in several settings (including Greece) and the particular susceptibility of both young children and older adults has been recognised (212, 213). Although further research is necessary to confirm our results, several implications are raised for both healthcare and policy actions.

As in the case of Greece, HAP is generally linked to poverty. The inability of households to cover their heating needs - described as "fuel poverty" - is a growing problem in Europe. Energy and fuel poverty for low-income households is a complex issue, which has a strong societal and economic aspect. It, thus, demands a multidisciplinary approach for which the strong collaboration and engagement of diverse stakeholders at both the governmental and the international partnerships' level is necessary (39, 214). Interventions to reduce HAP exposure have been implemented in several countries and their positive effects have been well-documented (215-217). In the comparative FRESH AIR study, a community-oriented intervention of implementing clean cooking/heating stoves was associated with lower exposures and improved short-term health benefits. Local adaptation of the intervention and vigorous inclusion of the community in the selection and installation of clean alternatives was, indeed, central to the success of implementation (163). In the long-term, experience can also be drawn from other European countries that have developed concrete policies for tackling low-income household problems, including the provision of incentives to improve housing stock, replace heating systems and raise households' energy awareness (218). The European Fuel Poverty and Energy Efficiency Project (216) has also identified several key interventions for fighting energy poverty. Specifically for Greece, discussed strategies include the distribution of natural gas, the development of catalytic domestic wood stoves and the upgrade of buildings' energy efficiency (47,199,219). Although national action plans integrating the above measures are necessary (220), a European response setting common criteria for energy poverty should be examined for the development of sustainable actions (221).

In terms of addressing exposure to risk factors, there seemed to be space for raising public awareness regarding HAP (objectives 2 and 3). Increasing public and professional awareness on HAP is an area deserving special attention when considering interventions for preventing respiratory disease, which, in

fact, constitutes the most affordable and effective way to reduce the burden (5). In a FRESH AIR study conducted in global low-resource settings, the researcher and local stakeholders co-created a train-the-trainer awareness programme empowering communities to take action against biomass and tobacco smoke. They showed significant increases in lung health awareness and the damaging effects of HAP, while the high compatibility of the programme with local contexts was key to its acceptability and eventual success (222). However, more drastic actions seem to be needed for smoking, as despite presence of awareness, rates were high in all thesis studies. The VBA training (objective 4) appeared to influence GPs self-efficacy in advising patients on smoking cessation, suggesting that, in a period following austerity, GPs' training in providing effective smoking cessation support during their daily practice may be further examined as a strategy for addressing tobacco use and contributing to CRDs' prevention.

The training of local GPs in lung function testing and the function of a PR programme (objective 6) for the first time in the rural periphery and Greek PHC suggested that such low-cost, patient-centered and empowering approaches may constitute feasible, beneficial and acceptable options for the identification and treatment of CRD in low-resource settings. The experience and novel evidence gained through the PR programme of Crete may provide ground for future research to elicit precise estimates about the effectiveness and cost-effectiveness of PR and to ensure the optimal implementation of similar efforts addressing respiratory, as well as other non-communicable diseases. The PR programme achieved to bring together a group of diverse healthcare professionals and engage patients in an interactive procedure of education and health improvement. This is particularly relevant for informing clinical practice and service delivery in a country which is missing high performance in several aspects of quality-based care, including proactive involvement of patients in their therapeutic process, use of multidisciplinary teams and focus on disease prevention and health promotion (223,224). Creating the health and social environments to support patients' participatory engagement and motivation to act for their health, along with exploring how medical curricula could be adjusted to include education on PR and other team-based approaches, seem to be important messages of this thesis.

All thesis activities were implemented in times of an economic recession which has significantly impacted the size, structure and quality of healthcare services in Greece, with particular evidence capturing these unfavourable effects on patients' health (64,68,225). PHC is the most sustainable, accessible, equitable and cost-effective setting to tackle respiratory and other non-communicable diseases according to the WHO (201,226). The findings of this thesis speak to the need to work with policymakers to advocate for integration of PHC, the provision of universal coverage and the investigation potential synergies with existing services to offer high-quality and affordable respiratory care for all. GPs and PHC were central to the engagement of people and the implementation of studies throughout this project. For the community to commit to positive action, long-term support from PHC is critical, with trained primary care providers holding a key role in awareness raising, community

motivation and behaviour change (201). PHC provides the ground for multidisciplinary collaboration, patient empowerment and community reactivation, which are all core components of the interventions piloted in this thesis. Instigating such interventions in PHC may assist, not only with improving patient outcomes and quality of life (227,228), but also with increasing the overall level of care integration with positive effects on systems and communities (229). Taking into consideration the Primary Healthcare Reform and the changes in the curriculum of General Practice unfolding in Greece during the last few years (230), evidence from FRESH AIR and this thesis may serve as a starting-point for exploring organizational issues to strengthen the health system and support local communities in agreement with the agenda of the Sustainable Development Goals (231).

4.4. Conclusion

As part of FRESH AIR, this thesis approached the continuum of respiratory care in Greece and explored contextual factors that affect implementation, while piloting novel preventive, diagnostic and treatment interventions for the first time in low-resource, rural, PHC settings of the country. Further research is required to overcome project limitations and confirm results. However, thesis results may offer several insights regarding implementation challenges and impact of holistic respiratory interventions for local populations. FRESH AIR has contributed to improving direct patient outcomes, raising professional skills and capacity, upgrading healthcare infrastructure, addressing health inequalities and preventing new CRD cases through awareness-raising and behavioural change. Lessons learnt can be used to assess the scaling-up of proposed approaches and ensure the sustainability of the projects' benefits.

References

1. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases. A comprehensive approach. 2007. Available from: https://www.who.int/gard/publications/GARD%20Book%202007.pdf
2. Brakema EA, van Gemert FA, van der Kleij RMJJ, et al. COPD's early origins in low-and-middle income countries: what are the implications of a false start? NPJ primary care respiratory medicine. 2019;29(1). doi: 10.1038/s41533-019-0117-y
3. Laniado-Laborín R. Smoking and chronic obstructive pulmonary disease (COPD). Parallel epidemics of the 21 century. Int J Environ Res Public Health. 2009;6(1):209-224. doi:10.3390/ijerph6010209
4. Terzikhan N, Verhamme KM, Hofman A, et al. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. Eur J Epidemiol. 2016;31(8):785-92. doi: 10.1007/s10654-016-0132-z.
5. Forum of International Respiratory Societies. The Global Impact of Respiratory Disease, 2nd ed.; Forum of International Respiratory Societies: Sheffield, UK, 2017.
6. World Health Organization. Household air pollution and health. Available from: https://www.who.int/news-room/fact-sheets/detail/household-air-pollution-and-health
7. Salvi S, Barnes PJ. Is exposure to biomass smoke the biggest risk factor for COPD globally? Chest. 2010;138(1):3-6. doi: 10.1378/chest.10-0645.
8. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532-55. doi: 10.1164/rccm.200703-456SO.
9. GBD 2017: a fragile world. Lancet. 2018;392(10159):1683. doi: 10.1016/S0140-6736(18)32858-7.
10. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585-596. doi: 10.1016/S2213-2600(20)30105-3.
11. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-1222. doi: 10.1016/S0140-6736(20)30925-9.
12. Tzanakis N, Anagnostopoulou U, Filaditaki V, et al. Prevalence of COPD in Greece. Chest. 2004;125(3):892-900. doi: 10.1378/chest.125.3.892.
13. Kourlaba G, Hillas G, Vassilakopoulos T, et al. The disease burden of chronic obstructive pulmonary disease in Greece. Int J Chron Obstruct Pulmon Dis. 2016;11:2179-2189. doi: 10.2147/COPD.S110373.
14. Atsou K, Chouaid C, Hejblum G. Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic review. BMC Med. 2011;9:7. doi: 10.1186/1741-7015-9-7.

15. Guarascio AJ, Ray SM, Finch CK, et al. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. Clinicoecon Outcomes Res. 2013;5:235-45. doi: 10.2147/CEOR.S34321.
16. European Respiratory Society. European Lung White Book. Sheffield, 2013. Available from: http://www. erswhitebook.org/
17. Foo J, Landis SH, Maskell J, et al. Continuing to Confront COPD International Patient Survey: Economic Impact of COPD in 12 Countries. PLoS One. 2016;11(4):e0152618. doi: 10.1371/journal.pone.0152618.
18. Ford ES, Murphy LB, Khavjou O, et al. Total and state-specific medical and absenteeism costs of COPD among adults aged ≥ 18 years in the United States for 2010 and projections through 2020. Chest. 2015;147(1):31-45. doi: 10.1378/chest.14-0972.
19. Ehteshami-Afshar S, FitzGerald JM, Doyle-Waters MM, et al. The global economic burden of asthma and chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2016;20(1):11-23. doi: 10.5588/ijtld.15.0472.
20. Accordini S, Corsico AG, Braggion M, et al. The cost of persistent asthma in Europe: an international population-based study in adults. Int Arch Allergy Immunol. 2013;160(1):93-101. doi: 10.1159/000338998.
21. Souliotis K, Kousoulakou H, Hillas G, et al. The direct and indirect costs of managing chronic obstructive pulmonary disease in Greece. Int J Chron Obstruct Pulmon Dis. 2017;12:1395-1400. doi: 10.2147/COPD.S132825. PMID: 28546747
22. Souliotis K, Kousoulakou H, Hillas G, Bakakos P, Toumbis M, Loukides S, Vassilakopoulos T. Direct and Indirect Costs of Asthma Management in Greece: An Expert Panel Approach. Front Public Health. 2017;5:67. doi: 10.3389/fpubh.2017.00067.
23. WHO-EBD. Country Profile: Greece. Available from: https://www.who.int/teams/environment-climate-change-and-health/monitoring/environmental-burden-of-disease/country-profiles/who-ebd-country-profile-greece
24. World Health Organization. Tobacco. Available form: https://www.who.int/news-room/fact-sheets/detail/tobacco
25. World Health Organization. WHO report on the global tobacco epidemic, 2013. Available at http://www.who.int/tobacco/global_report/2013/en/
26. World Health Organization. WHO report on the global tobacco epidemic, 2021 Addressing new and emerging products. Available from: https://www.who.int/publications/i/item/9789240032095
27. Special Eurobarometer 506. Attitudes of Europeans towards tobacco and electronic cigarettes. 2020. Available from: https://www.drugsandalcohol.ie/33761/1/Eurobarometer_2020_cigarettes_ebs_506.pdf
28. Filippidis FT, Tzoulaki I. Greece giving up on tobacco control. Addiction. 2016 Jul;111(7):1306-7. doi: 10.1111/add.13357.

29. The Tobacco Atlas. Greece. Available from: https://tobaccoatlas.org/country/greece/
30. Tsalapati K, Vardavas CI, Athanasakis K, et al. Going up in ashes? Smoking-attributable morbidity, hospital admissions and expenditure in Greece. Eur J Public Health. 2014;24(3):477-9. doi: 10.1093/eurpub/cku040.
31. Schoretsaniti S, Filippidis FT, Vardavas CI, et al. 5-Year trends in the intention to quit smoking amidst the economic crisis and after recently implemented tobacco control measures in Greece. Addict Behav. 2014;39(1):140-5. doi: 10.1016/j.addbeh.2013.09.015.
32. van Gemert F, van der Molen T; Jones R, et al. The impact of asthma and COPD in sub-Saharan Africa. Prim. Care Respir. J. 2011, 20, 240–248.
33. World Health Organization. Indoor Air Pollution—The Killer in the Kitchen; WHO: Geneva, Switzerland, 2010.
34. World Health Organization. Household Air Pollution and Health; WHO: Geneva, Switzerland, 2018.
35. World Health Organization. WHO Guidelines for Indoor Air Quality: Household Fuel Combustion; WHO: Geneva, Switzerland, 2018.
36. World Health Organization Burden of disease from household air pollution for 2016. WHO: Geneva, Switzerland, 2018.
37. Fullerton DG, Bruce N, Gordon SB. Indoor air pollution from biomass fuel smoke is a major health concern in the developing world. Trans. R. Soc. Trop. Med. Hyg. 2008;102:843–851.
38. Gordon SB, Bruce NG, Grigg J, et al. Respiratory risks from household air pollution in low and middle income countries. Lancet Respir. Med. 2014;2: 823–860.
39. Thurston GD, Kipen H, Annesi-Maesano I, et al. A joint ERS/ATS policy statement: What constitutes an adverse health effect of air pollution? An analytical framework. Eur. Respir. J. 2017;(49)1600419.
40. Kurmi OP, Lam KB, Ayres JG. Indoor air pollution and the lung in low- and medium-income countries. Eur. Respir. J. 2012; 40:239–254.
41. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: Definition, assessment, and prevention. Lancet 2015; 385:1778–1788.
42. World Health Organization. Household Air Pollution: Burden of Disease. 2016. Available from: https://www.who.int/data/gho/data/themes/air-pollution/household-air-pollution#
43. Manoli E, Kouras A, Karagkiozidou O et al. Polycyclic aromatic hydrocarbons (PAHs) at traffic and urban background sites of northern Greece: Source apportionment of ambient PAH levels and PAH-induced lung cancer risk. Environ. Sci. Pollut. Res. Int. 2016;23: 3556–3568.
44. Argyropoulos G, Besis A, Voutsa D, et al. Source apportionment of the redox activity of urban quasi-ultrafine particles (PM0.49) in Thessaloniki following the increased biomass burning due to the economic crisis in Greece. Sci. Total. Environ. 2016;68: 124–136.
45. Vouitsis I.; Amanatidis S, Ntziachristos L, et al. Daily and seasonal variation of traffic related aerosol pollution in Thessaloniki, Greece, during the financial crisis. Atmos. Environ. 2015;122:577–587.

46. Gratsea M, Liakakou E, Mihalopoulos N, et al. The combined effect of reduced fossil fuel consumption and increasing biomass combustion on Athens' air quality, as inferred from long term CO measurements. Sci. Total. Environ. 2017;592: 115–123.
47. Saffari A, Daher N, Samara C, et al. Increased biomass burning due to the economic crisis in Greece and its adverse impact on wintertime air quality in Thessaloniki. Environ. Sci. Technol. 2013;47: 13313–13320.
48. Sindosi O, Hatzianastassiou N, Markozannes G, et al. PM10 Concentrations in a Provincial City of Inland Greece in the Times of Austerity and Their Relationship with Meteorological and Socioeconomic Conditions. Water Air Soil Pollut. 2021;232: 1–19.
49. Santamouris M, Paravantis JA, Founda D, et al. Financial crisis and energy consumption: A household survey in Greece. Energy Build. 2013;65: 477–487.
50. Amann M, Cofala J, Klimont Z, et al. Measures to address air pollution from small combustion sources. IIASA 2018;8–10.
51. World Health Organization. Chronic respiratory diseases. 2018. Available from: http://www.who.int/respiratory/en/.
52. Pleasants RA, Riley IL, Mannino DM. Defining and targeting health disparities in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2016;11: 2475-2496.
53. Gershon AS, Dolmage TE, Stephenson A, et al. Chronic obstructive pulmonary disease and socioeconomic status: a systematic review. COPD. 2012;9: 216–226.
54. Townend J, Minelli C, Mortimer K, et al. The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study. Eur Respir J. 2017 Jun 1;49(6):1601880. doi: 10.1183/13993003.01880-2016
55. Magitta Ng'weina F, Walker Richard W, Apte Komalkirti K, et al. Prevalence, risk factors and clinical correlates of COPD in a rural setting in Tanzania. Eur Res J. 2018;51(2):1700182.
56. Lee AG, Kaali S, Quinn A, et al. Prenatal Household Air Pollution Is Associated with Impaired Infant Lung Function with Sex-Specific Effects. Evidence from GRAPHS, a Cluster Randomized Cookstove Intervention Trial. Am J Respir Crit Care Med. 2019;199(6):738-746. doi:10.1164/rccm.201804-0694OC
57. Soriano JB, Polverino F, Cosio BG. What is early COPD and why is it important? Eur Respir J. 2018 Dec 6;52(6):1801448. doi: 10.1183/13993003.01448-2018.
58. Martinez FD. Early-life origins of chronic obstructive pulmonary disease. N Engl J Med. 2016;375:871–878. doi: 10.1056/NEJMra1603287
59. Brakema EA, van Gemert FA, van der Kleij R, et al. COPD's early origins in low-and-middle income countries: what are the implications of a false start? NPJ Prim Care Respir Med. 2019;29:6. doi: 10.1038/s41533-019-0117-y.
60. McKee M, Balabanova D, Basu S, et al. Universal health coverage: a quest for all countries but under threat in some. Value Health. 2013;16:S39–S45. doi: 10.1016/j.jval.2012.10.001.

61. Lionis C, Symvoulakis EK, Markaki A, et al. Integrated primary health care in Greece, a missing issue in the current health policy agenda: a systematic review. Int J Integr Care. 2009;9:e88. doi: 10.5334/ijic.322.
62. Hellenic Statistical Authority. Statistics 2016. Available from: www.statistics.gr
63. Simou E, Koutsogeorgou Effects of the economic crisis on health and healthcare in Greece in the literature from 2009 to 2013: a systematic review. Health Policy 2014; 115: 111–119.
64. Kentikelenis A, Karanikolos M, Papanicolas I, et al. Health effects of financial crisis: omens of a Greek tragedy. Lancet. 2011;378(9801):1457-8. doi: 10.1016/S0140-6736(11)61556-0.
65. Kotsiou OS, Zouridis S, Kosmopoulos M, et al. Impact of the financial crisis on COPD burden: Greece as a case study. Eur Respir Rev. 2018;27(147):170106. doi: 10.1183/16000617.0106-2017.
66. Eurostat. Statistics on rural areas in the EU – European Union, 2017. Available from: https://ec.europa.eu/eurostat/statisticsexplained/index.php?title=Statistics_on_rural_areas_in_the_EU&oldid=391832
67. Oikonomou N, Tountas Y. Insufficient primary care services to the rural population of Greece. Rural Remote Health 2011;11(1): 1661.
68. Tsiligianni IG. COPD patients trapped in the financial crisis in rural Crete. Lancet Respir Med. 2013 Dec;1(10):e31-2. doi: 10.1016/S2213-2600(13)70227-3.
69. Gibson GJ, Loddenkemper R, Sibille Y, Lundbäck B. The European Lung White Book. Sheffield, European Respiratory Society, 2013.
70. Tsiligianni I, Anastasiou F, Antonopoulou M, et al. Greek rural GPs' opinions on how financial crisis influences health, quality of care and health equity. Rural Remote Health. 2013;13(2):2528.
71. Lionis C, Symvoulakis EK, Markaki A, et al. Integrated people-centred primary health care in Greece: unravelling Ariadne's thread. Prim Health Care Res Dev. 2019;20:e113. doi: 10.1017/S1463423619000446.
72. Soriano JB, Kendrick PJ, Paulson KR et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.Lancet Respir Med. 2020; 8: 585-596
73. Brakema EA, van der Kleij RM, Vermond D, et al. Let's stop dumping cookstoves in local communities. It's time to get implementation right. NPJ Prim Care Respir Med. 2020;30(1):3. doi:10.1038/s41533-019-0160-8
74. Mendis, S. et al. Gaps in capacity in primary care in low-resource settings for implementation of essential noncommunicable disease interventions. Int. J. Hypertens. 2012, 584041 (2012).
75. Nilsen, P. & Bernhardsson, S. Context matters in implementation science: a scoping review of determinant frameworks that describe contextual determinants for implementation outcomes. BMC Health Serv. Res. 2019;19:189.

76. Brakema EA, Vermond D, Pinnock H, et al. Implementing lung health interventions in low- and middle-income countries: a FRESH AIR systematic review and meta-synthesis. Eur Respir J. 2020;56(1):2000127. doi: 10.1183/13993003.00127-2020.
77. van Gemert F, Chavannes N, Nabadda N, et al. Impact of chronic respiratory symptoms in a rural area of sub-Saharan Africa: an in-depth qualitative study in the Masindi district of Uganda. Prim Care Respir J 2013;22(3):300-305.
78. Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respir Res. 2017;18:67.
79. Eurostat. Statistics on rural areas in the EU – European Union, 2017. Available from: https://ec.europa.eu/eurostat/statisticsexplained/index.php?title=Statistics_on_rural_areas_in_the_EU&oldid=391832
80. Oikonomou N, Tountas Y. Insufficient primary care services to the rural population of Greece. Rural Remote Health 2011; 11(1): 1661.
81. Oikonomou N, Tountas Y. The Greek economic crisis: a primary health-care perspective. Lancet. 2011;377(9759):28-9. doi: 10.1016/S0140-6736(10)62336-7.
82. Economou C et al The impact of the financial crisis on the health system and health in Greece. 2014. Available from: https://www.euro.who.int/__data/assets/pdf_file/0007/266380/The-impact-of-the-financial-crisis-on-the-health-system-and-health-in-Greece.pdf
83. Tsiligianni, I. Respiratory health in Greece. Lancet Respir. Med. 2020, 8, e65–e66
84. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328(7455):1519-1527.
85. Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD000165. DOI: 10.1002/14651858.CD000165.pub4.
86. Aveyard P, Begh R, Farley Aet al.. Brief opportunistic smoking cessation interventions: a systematic review and meta-analysis to compare advice to quit and offer of assistance. Addiction. 2011;107(6): 1066-0173.
87. West R, Fidler J. Smoking and smooking cessation in England 2010. London, 2011.
88. NHS Future Forum. The NHS's Role in the Public's Health: A Report from the NHS Future Forum. 2012.
89. Girvalaki C, Papadakis S, Vardavas C, et al. Training General Practitioners in Evidence-Based Tobacco Treatment: An Evaluation of the Tobacco Treatment Training Network in Crete (TiTAN-Crete) Intervention. Health Educ Behav. 2018;45(6):888-897. doi: 10.1177/1090198118775481.
90. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2018.
91. Levy MR, Quanjer, PH, Booker R, et al. Standards Document: Diagnostic Spirometry in Primary Care: Proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society Recommendations. Primary Care Respiratory Journal. 2009; 18(3): 130-147

92. Stout JW, Smith K, Zhou C, et al. Learning from a distance: Effectiveness of online spirometry training in improving asthma care. Acad. Pediatr. 2012;12(2):88-95. doi:10.1016/j.acap.2011.11.006.
93. Dombkowski KJ, Hassan F, Wasilevich EA, Clark SJ. Spirometry use among pediatric primary care physicians. Pediatrics 2010;126(4): 682-687.
94. Pleasants RA, Riley IL, Mannino DM. Defining and targeting health disparities in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2016;11:2475–2496. doi: 10.2147/COPD.S79077.
95. Kyriopoulos II, Zavras D, Skroumpelos A, et al. Barriers in access to healthcare services for chronic patients in times of austerity: an empirical approach in Greece. Int J Equity Health 2014; 13: 54. 15
96. Zavras D, Zavras AI, Kyriopoulos I-I, et al. Economic crisis, austerity and unmet healthcare needs: the case of Greece. BMC Health Serv Res 2016; 16: 309.
97. Kostikas K, Loefroth E, Fogel R, et al. Clinical consequences of late Chronic Obstructive Pulmonary Disease (COPD) diagnosis compared to early diagnosis in UK primary care. Eur Res J 2019 54: PA2497; DOI: 10.1183/13993003.congress-2019.PA2497
98. National Clinical Guideline Centre (UK). Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London, UK: Royal College of Physicians, 2010.
99. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011; 155(3): 179.
100. Jones R, Kirenga B, Pooler J, et al. A development study of pulmonary rehabilitation for patients with chronic lung disease in Uganda. Eur Respir J 2016; 48: PA858.
101. Bolton CE, Bevan-Smith EF, Blakey JD, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. Thorax 2013; 68(Suppl 2): ii1–ii30.
102. Jones R, Kirenga BJ, Katagira W, et al. A pre–post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. Int J Chron Obstruct Pulmon Dis 2017; 12: 3533–3599.
103. Pooler J, Muyinda H, Nyakoojo G, et al. A qualitative study on the development of pulmonary rehabilitation for patients with chronic lung disease in Kampala, Uganda. Eur Respir J 2016; 48: PA3964.
104. Jones R, Muyinda H, Nyakoojo G, et al. Does pulmonary rehabilitation alter patients' experiences of living with chronic respiratory disease? A qualitative study. Int J Chron Obstruct Pulmon Dis 2018; 13: 2375–2385.
105. Tsiligianni IG, Papadokostakis P, Prokopiadou D, et al. Impact of the financial crisis on adherence to treatment of a rural population in Crete, Greece. Qual Prim Care 2014; 22(5): 238–244.

106. Implementation Research Toolkit, World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases 2014
107. Pinnock H, Thomas M, Tsiligianni I, et al.The International Primary Care Respiratory Group (IPCRG) Research Needs Statement 2010. Prim Care Respir J 2010; 19(Suppl 1): S1-S21.
108. Pinnock H, Østrem A, Rodriguez MR, et al. Prioritising the respiratory research needs of primary care: the International Primary Care Respiratory Group (IPCRG) e-Delphi exercise. Prim Care Respir J 2012; 21: 19–27.
109. Kunzil N. The public health relevance of air pollution abatement. Eur Respir J 2002; 20(1): 198–209.
110. Ahmad N, Boutron I, Dechartres A, et al. Geographical Representativeness of published and ongoing randomized controlled trials. The example of: tobacco consumption and HIV infection. PLoS One. 2011; 6(2): e16878
111. Cragg L, Williams S, Chavannes NH. FRESH AIR: an implementation research project funded through Horizon 2020 exploring the prevention, diagnosis and treatment of chronic respiratory diseases in low-resource settings. NPJ Prim Care Respir Med. 2016;26:16035. doi: 10.1038/npjpcrm.2016.35.
112. van der Molen T, Willemse BW, Schokker S, et al. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health Qual Life Outcomes. 2003; 1:13.
113. Zhou Z, Zhou A, Zhao Y, et al. Evaluating the Clinical COPD Questionnaire: A systematic review. Respirology. 2017;22(2):251-262. doi: 10.1111/resp.12970.
114. Kocks JW, Tuinenga MG, Uil SM, et al. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. Respir Res. 2006; 7:62.
115. Kon SS, Dilaver D, Mittal M, et al. The Clinical COPD Questionnaire: response to pulmonary rehabilitation and minimal clinically important difference. Thorax. 2014;69(9):793-8. doi: 10.1136/thoraxjnl-2013-204119.
116. Gupta N, Pinto LM, Morogan A, et al. The COPD assessment test: a systematic review. Eur Respir J 2014; 44(4): 873–884.
117. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009, 34: 648–654.
118. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J 2009, 34: 648–654.
119. Kon SSC, Canavan JL, Jones SE, et al. Minimum clinically important difference for the COPD assessment test: a prospective analysis. Lancet Respir Med 2014; 2(3): 195–203.
120. Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. Respir Med 1991; 85(Suppl B): 25–31; discussion 33–37.
121. Barr JT, Schumacher GE, Freeman S, et al. American translation, modification, and validation of the St. George's Respiratory Questionnaire. Clin Ther. 2000 Sep, 22(9):1121-45.

122. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. Am Rev Respir Dis 1992, 145: 1321-1327;
123. Jones PW. St. George's respiratory questionnaire: MCID. COPD. 2005; 2(1): 75–79
124. Nelsen LM, Vernon M, Ortega H, et al. Evaluation of the psychometric properties of the St George's Respiratory Questionnaire in patients with severe asthma. Respir Med. 2017;128:42-49. doi: 10.1016/j.rmed.2017.04.015.
125. Lo C, Liang WM, Hang LW, et al. A psychometric assessment of the St. George's respiratory questionnaire in patients with COPD using rasch model analysis. Health Qual Life Outcomes. 2015;131. doi.org/10.1186/s12955-015-0320-7
126. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-65. doi: 10.2165/00019053-199304050-00006.
127. Chen H, Blanc PD, Chawla A, et al. Assessing Productivity Impairment in Patients with Severe or Difficult-to-Treat Asthma: Validation of the Work Productivity Activity Impairment - Asthma Questionnaire. J All Clin Immunol. 2006;17(2):S81. doi: https://doi.org/10.1016/j.jaci.2005.12.721.
128. Chen H, Blanc PD, Hayden ML, et al. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. Value Health. 2008;11(2):231-9. doi: 10.1111/j.1524-4733.2007.00229.x.
129. Fletcher MJ, Upton J, Taylor-Fishwick J, Buist SA, et al. COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. BMC Public Health. 2011;11:612. doi: 10.1186/1471-2458-11-612.
130. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x
131. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999;282(18):1737-44. doi: 10.1001/jama.282.18.1737.
132. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16(9):606-13.
133. Schuler M, Strohmayer M, Mühlig Set al. Assessment of depression before and after inpatient rehabilitation in COPD patients: Psychometric properties of the German version of the Patient Health Questionnaire (PHQ-9/PHQ-2). J Affect Disord. 2018;232:268-275. doi: 10.1016/j.jad.2018.02.037.
134. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012;185(4):435-452. doi:10.1164/rccm.201111-2042ST
135. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581-586.

136. Wedzicha JA, Bestall JC, Garrod R, Get al. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. Eur Respir J 1998;12:363–369
137. Crisafulli E, Clini EM. Measures of dyspnea in pulmonary rehabilitation. Multidiscip Respir Med. 2010; 5(3):202-10.
138. Chida M, Inase N, Ichioka M, et al. Ratings of perceived exertion in chronic obstructive pulmonary disease--a possible indicator for exercise training in patients with this disease. Eur J Appl Physiol Occup Physiol. 1991; 62(6):390-3.
139. Mador MJ, Rodis A, Magalang UJ. Reproducibility of Borg scale measurements of dyspnea during exercise in patients with COPD. Chest. 1995;107(6):1590-7. doi: 10.1378/chest.107.6.1590.
140. Rampulla C, Baiocchi S, Dacosto E, et al. Dyspnea on exercise. Chest 1992; 101: 248s–252s
141. Karnofsky DA, Burchenal JH. In: Evaluation of chemotherapeutic agents. MacLeod CM, editor. New York: Columbia University Press; 1949. The clinical evaluation of chemotherapeutic agents in cancer; pp. 191–205.
142. Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. BMC Med Inform Decis Mak. 2013;13:72. doi:10.1186/1472-6947-13-72
143. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984;2(3):187-93. doi: 10.1200/JCO.1984.2.3.187.
144. Crooks, V, Waller S, et al. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: M139-M144.
145. Hollen PJ, Gralla RJ, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Cancer. 1994; 73: 2087-2098.
146. Singh SJ, Morgan MD, Scott S, et al. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax. 1992;47(12):1019-24. doi: 10.1136/thx.47.12.1019.
147. Dyer CA, Singh SJ, Stockley RA, et al. The incremental shuttle walking test in elderly people with chronic airflow limitation. Thorax. 2002;57(1):34-8. doi: 10.1136/thorax.57.1.34.
148. Singh S, Moiz JA, Ali MS, et al. Validity, and Responsiveness of the Incremental Shuttle Walk Test in Patients With Interstitial Lung Disease. J Cardiopulm Rehabil Prev. 2018;38(6):425-429. doi: 10.1097/HCR.0000000000000327.
149. Singh SJ, Jones PW, Evans R, et al. Minimum clinically important improvement for the incremental shuttle walking test. Thorax. 2008; 63(9):775-7.
150. Vaidya T, Chambellan A, de Bisschop C. Sit-to-stand tests for COPD: A literature review. Respir Med. 2017;128:70-77. doi: 10.1016/j.rmed.2017.05.003.
151. Meretta, BM, Whitney, SL, Marchetti, GF, et al. The five times sit to stand test: responsiveness to change and concurrent validity in adults undergoing vestibular rehabilitation. J Vestib Res 2006; 16(4–5): 233–243.

152. Langley GL, Nolan KM, Nolan TW, et al. The Improvement Guide: A Practical Approach to Enhancing Organizational Performance (2nd edition). San Francisco: Jossey-Bass Publishers; 2009.
153. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7. doi: 10.1016/S0140-6736(07)61602-X.
154. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349-357.
155. Pinnock H, Barwick M, Carpenter CR, et al. Standards for reporting implementation studies (StaRI) statement. BMJ 2017; 356: i6795.
156. Brakema EA, Tabyshova A, van der Kleij et al. The socioeconomic burden of chronic lung disease in low-resource settings across the globe - an observational FRESH AIR study. Respir Res. 2019 Dec 21;20(1):291. doi: 10.1186/s12931-019-1255-z.
157. Colquhoun HL, Levac D, et al. Scoping reviews: Time for clarity in definition, methods and reporting. J Clin Epidemiol. 2014;(12):1291–4.
158. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. Int J Soc Res Methodol Theory Pract. 2005;8(1):19–32.
159. Munari AB, Gulart AA, Dos Santos K, et al. Modified Medical Research Council Dyspnea Scale in GOLD Classification Better Reflects Physical Activities of Daily Living. Respir Care. 2018;63(1):77-85. doi: 10.4187/respcare.05636.
160. Brakema EA, van der Kleij RMJJ, Poot CC, et al. Mapping low-resource contexts to prepare for lung health interventions in four countries (FRESH AIR): a mixed-method study. Lancet Glob Health. 2022;10(1):e63-e76. doi: 10.1016/S2214-109X(21)00456-3.
161. Brakema EA, van der Kleij RM, Poot CC, et al. A systematic approach to context-mapping to prepare for health interventions: development and validation of the SETTING-tool in four countries. BMJ Glob Health. 2021;6(1):e003221. doi: 10.1136/bmjgh-2020-003221. PMID: 33436446.
162. Bennett S, Woods T, Liyanage WM, et al. A simplified general method for cluster-sample surveys of health in developing countries. World Health Statistics Quarterly. 1991;44:98–106.
163. Anastasaki M, Tsiligianni I, Sifaki-Pistolla D, et al. Household Air Pollution and Respiratory Health in Rural Crete, Greece: A Cross-Sectional FRESH AIR Study. Atmosphere 2021;12:1369. doi: 10.3390/atmos12111369.
164. van Gemert F, de Jong C, Kirenga B, et al. Effects and acceptability of implementing improved cookstoves and heaters to reduce household air pollution: a FRESH AIR study. NPJ Prim Care Respir Med. 2019;29(1):32. doi: 10.1038/s41533-019-0144-8.
165. McEwen A, Pooler J, Lionis C, et al. Adapting Very Brief Advice (VBA) on smoking for use in low resource settings: Experience from the FRESH AIR project. J Smok Cessat. 2019;14:3. doi: https://doi.org/10.1017/jsc.2019.4.

166. Billingham SAM., Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. BMC Med Res Meth. 2013;13:104. doi.org/10.1186/1471-2288-13-104
167. West R. Theory of Addiction. Oxford, Blackwells. 2006.
168. Aveyard P, Begh R, Parsons A., et al. Brief opportunistic smoking cessation interventions: a systematic review and meta-analysis to compare advice to quit and offer of assistance. Addiction. 2006. doi: 10.1111/j.1360-0443.2011.03770.x.
169. Michie S, van Stralen MM., West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6: 42.
170. Michie S, Churchill S, West R. Identifying Evidence-Based Competences Required to Deliver Behavioural Support for Smoking Cessation. Ann Behav Med. 2011; 41:59-70
171. West R, Fidler J. Smoking and Smoking Cessation in England 2010. London: Vasco-Graphics. 2011.
172. Wagner EH, Austin BT, Davis C, et al. Improving chronic illness care: translating evidence into action. Health Aff (Millwood). 2001;20(6):64–78.
173. Coleman K, Austin BT, Brach C, et al. Evidence on the Chronic Care Model in the new millennium. Health Aff (Millwood). 2009;28(1):75-85. doi:10.1377/hlthaff.28.1.75
174. Smidth M, Christensen MB, Olesen F, et al. Developing an active implementation model for a chronic disease management program. Int J Integr Care. 2013;13:e020. doi:10.5334/ijic.994
175. Siminerio LM, Piatt G, Zgibor JC. Implementing the chronic care model for improvements in diabetes care and education in a rural primary care practice. Diabetes Educ. 2005;31(2):225-34. doi: 10.1177/0145721705275325.
176. Lionis CD, Duijker G, Angelaki A, et al Practice- Based Research Network in Primary Care: a lacking story and learning points from an empirical model on Crete. 1st Joint Meeting of EGPRN and the EURIPA. Attard-Malta, 2013.
177. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006; 3:77-101.
178. Anastasaki M, Trigoni M, Pantouvaki A, et al. Establishing a pulmonary rehabilitation programme in primary care in Greece: A FRESH AIR implementation study. Chron Respir Dis. 2019;16:1479973119882939. doi:10.1177/1479973119882939.
179. Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the health belief model. Health Educ Q. 1988; 15(2): 175–183.
180. Rochester CL, Vogiatzis I, Holland AE, et al. An official American Thoracic Society/European Respiratory Society policy statement: enhancing implementation, use, and delivery of pulmonary rehabilitation. Am J Respir Crit Care Med. 2015; 192(11): 1373–1386.
181. Morgan M, Singh S. Practical pulmonary rehabilitation. London, UK: Taylor & Francis, 1998.
182. van Dam van Isselt EF, Spruit M, et al. Health status measured by the clinical COPD questionnaire (CCQ) improves following post-acute pulmonary rehabilitation in patients with advanced COPD: a prospective observational study. NPJ Prim care Respir Med. 2014; 24: 14007.

183. Kroenke K, Spitzer RL, Williams JB, et al. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review.Gen Hosp Psychiatry. 2010; 32(4):345-59.
184. Whitney SL, Wrisley DM, Marchetti GF, et al. Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the five-times-sit-to-stand test. Phys Ther. 2005; 85(10): 1034–1045.
185. Sichletidis L, Tsiotsios I, Gavriilidis A, et al. Prevalence of chronic obstructive pulmonary disease and rhinitis in northern Greece. Respiration. 2005;72(3):270-7. doi: 10.1159/000085368.
186. Stafyla E, Kotsiou OS, Deskata K, et al. Missed diagnosis and overtreatment of COPD among smoking primary care population in Central Greece: old problems persist. Int J Chron Obstruct Pulmon Dis. 2018;13:487-498. doi: 10.2147/COPD.S147628.
187. World Health Organization. Country profiles of Environmental Burden of Disease, 2009. Available from: http://www.who.int/quantifying_ehimpacts/national/countryprofile/greece.pdf
188. Ierodiakonou D, Sifaki-Pistolla D, Kampouraki M, et al. Adherence to inhalers and comorbidities in COPD patients. A cross-sectional primary care study from Greece. BMC Pulm Med. 2020;20(1):253. doi:10.1186/s12890-020-01296-3
189. Carvounis CP, Nikas N, Panitti E. Epidemiological survey in primary care patients with chronic obstructive pulmonary disease in Greece; the EPIPTOSI study. Pneumon. 2012; 25: 386– 94
190. Papaporfyriou A, Tseliou E, Mizi E, et al. Depression Levels Influence the Rate of Asthma Exacerbations in Females. J Pers Med. 2021;11(6):586. doi:10.3390/jpm11060586
191. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available from: http://www.goldcopd.org/
192. European Centre for Disease Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe. Stockholm, Sweden: ECDC, 2017.
193. Katsoulas TA, Skordilis EK, Myrianthefs P, et al. Validity of St. George's respiratory questionnaire for Greek patients with chronic obstructive pulmonary disease. Percept Mot Skills. 2010; 110(3): 772–788.
194. Tsiligianni IG, Van der Molen T, Moraitaki D, et al. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). BMC Pulm Med. 2012; 12(1): 20.
195. Mohammadnezhad M, Tsourtos G, Wilson C, et al. Understanding socio-cultural influences on smoking among older Greek-Australian smokers aged 50 and over: facilitators or barriers? A qualitative study. Int J Environ Res Public Health. 2015;12(3):2718-34. doi: 10.3390/ijerph120302718.
196. Karademas EC, Peppa N, Fotiou A, et al. Family, school and health in children and adolescents: findings from the 2006 HBSC study in Greece. J Health Psychol. 2008;13(8):1012-20. doi: 10.1177/1359105308097965.

197. Michaelson V, Pilato KA, Davison CM. Family as a health promotion setting: A scoping review of conceptual models of the health-promoting family. PLoS One. 2021;16(4):e0249707. doi: 10.1371/journal.pone.0249707.
198. Saraga DE, Tolis EI, Maggos T, et al. PM2.5 source apportionment for the port city of Thessaloniki, Greece. Sci. Total. Environ. 2019;650 Pt 2, 2337–2354.
199. Assimakopoulos VD, Bekiari T, Pateraki S, et al Assessing personal exposure to PM using data from an integrated indoor-outdoor experiment in Athens-Greece. Sci. Total. Environ. 2018;636, 1303–1320.
200. Santamouris M, Alevizos S, Aslanoglou L, et al. Freezing the poor—Indoor environmental quality in low and very low income households during the winter period in Athens. Energy Build. 2014;70, 61–70.
201. Brakema EA, van Gemer FA, Williams S, et al. Implementing a context-driven awareness programme addressing HAP and tobacco: A FRESH AIR study. NPJ Prim. Care Respir. Med. 2020;30, 42.
202. Wändell PE, Waard AM, Holzmann MJ, et al. Barriers and facilitators among health professionals in primary care to prevention of cardiometabolic diseases: A systematic review. Fam Pract. 2018;35(4)383-398. doi.org/10.1093/fampra/cmx137
203. Chavannes N, Schermer T, Akkermans R, et al. Impact of spirometry on GPs' diagnostic differentiation and decision-making. Respir Med. 2004;98(11):1124-30. doi: 10.1016/j.rmed.2004.04.004. PMID: 15526814.
204. McCarthy B, Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015; 23(2): CD003793.
205. Smid DE, Franssen FME, Houben-Wilke S, et al. Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: a prospective analysis. J Am Med Dir Assoc. 2017; 18(1): 53–58.
206. Sciriha A, Lungaro-Mifsud S, Scerri J, et al. Health status of COPD patients undergoing pulmonary rehabilitation: a comparative responsiveness of the CAT and SGRQ. Chron Respir Dis. 2017; 14(4): 352–359.
207. Barakat S, Michele G, George P, et al. Outpatient pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. Int J Chron Obs Pulmon Dis. 2008; 3(1): 155–162.
208. Puhan MA, Guyatt GH, Goldstein R, et al. Relative responsiveness of the chronic respiratory questionnaire, St. George's respiratory questionnaire and four other health-related quality of life instruments for patients with chronic lung disease. Respir Med. 2007; 101(2): 308–316.
209. Green, CA, Duan N, Gibbons RD, et al. Approaches to mixed methods dissemination and implementation research: methods, strengths, caveats, and opportunities. Adm Policy Ment Health. 2014; 1-16.

210. Johnson KM, Bryan S, Ghanbarian S, et al. Characterizing undiagnosed chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Res. 2018;19:26. doi: 10.1186/s12931-018-0731-1.
211. Papadakis S, Anastasaki M, Papadakaki M, et al. 'Very brief advice' (VBA) on smoking in family practice: a qualitative evaluation of the tobacco user's perspective. BMC Fam Pract. 2020;21(1):121. doi: 10.1186/s12875-020-01195-w.
212. Patelarou E, Tzanakis N, Kelly FJ. Exposure to indoor pollutants and Wheeze and asthma development during early childhood. Int. J. Environ. Res. Public Health. 2015;12, 3993–4017.
213. Bentayeb M, Norback D, Bednarek M, et al. GERIE Study. Indoor air quality, ventilation and respiratory health in elderly residents living in nursing homes in Europe. Eur. Respir. J. 2015;45, 1228–1238.
214. Landrigan PJ, Fuller R, Acosta J, et al. The Lancet Commission on pollution and health. Lancet 2018;391, 462–512.
215. Thomas E, Wickramasinghe K, Mendis S, et al. Improved stove interventions to reduce household air pollution in low and middle income countries: A descriptive systematic review. BMC Public Health 2015;15, 650.
216. Quansah R, Semple S, Ochieng CA, et al. Effectiveness of interventions to reduce household air pollution and/or improve health in homes using solid fuel in low-and-middle income countries: A systematic review and meta-analysis. Environ. Int. 2017;103, 73–90.
217. Pope, D, Bruce N, Dherani M, et al. Real-life effectiveness of 'improved' stoves and clean fuels in reducing PM2.5 and CO: Systematic review and meta-analysis. Environ. Int. 2017; 101, 7–18.
218. EU Energy Poverty Observatory. Diagnosis of Causes and Consequences of Fuel Poverty in Belgium, France, Italy, Spain and United Kingdom. 2009. Available online: http://www.powerhouseeurope.eu/uploads/tx_phecasestudies/Analysis_report_epee_3_2_EN.pdf
219. Kollias P, Kantiranis N, Pytharoulis I, et al. Seasonal Variations of the Mineralogical Composition and the Organic Matter Content of Falling Dust in Thessaloniki During 2012-13; Springer: Cham, Switzerland, 2017; pp. 949–956.
220. Brunner KM, Spitzer M, Christanell A. Experiencing fuel poverty. Coping strategies of low-income households in Vienna/Austria. Energy Policy. 2012;49, 53–59.
221. Kolokotsa D, Santamouris M. Review of the indoor environmental quality and energy consumption studies for low income households in Europe. Sci. Total. Environ. 2015;536, 316–330.
222. World Health Organization. 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases; WHO: Geneva, Switzerland, 2009.
223. Schäfer W, Boerma W, Murante A, et al. Assessing the potential for improvement of primary care in 34 countries: a cross-sectional survey. Bull World Heal Organ 2015; 93(3): 161–168.

224. Lionis C, Papadakis S, Tatsi C, et al. Informing primary care reform in Greece: patient expectations and experiences (the QUALICOPC study). BMC Health Serv Res 2017; 17(1): 255.
225. Karamanoli E. Financial crisis harms respiratory health in Greece. Lancet Respir Med 2013; 1(7): 511–512.
226. World Health Organization. 2008-2013 action plan for the global strategy for the prevention and control of noncommunicable diseases, 2009.
227. Chavannes NH, Grijsen M, Den Akker MV, et al. Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. Prim Care Respir J 2009; 18(3): 171–176.
228. Kruis AL, Chavannes NH. Potential benefits of integrated COPD management in primary care. Monaldi Arch Chest Dis 2016; 73(3): 130–134.
229. Kruis AL, Boland MRS, Assendelft WJJ, et al. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. BMJ 2014; 349: g5392.
230. World Health Organization. Greek Health Reform: Opening of New Primary Health Care Units. 2017. Available from: https://www.euro.who.int/en/countries/greece/news/news/2017/12/greek-health-reform-opening-of-new-primary-health-care-units
231. Kieny, M.P.; Bekedam, H.; Dovlo, D.; Fitzgerald, J.; Habicht, J.; Harrison, G.; Kluge, H.; Lin, V.; Menabde, N.; Mirza, Z.; et al. Strengthening health systems for universal health coverage and sustainable development. Bull. World Health Organ. 2017;95, 537–539.

Appendix 1. Declarations

A1.1. General acknowledgements

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FRESH AIR was funded by European Commission's Research and Innovation program Horizon 2020 under grand agreement no. 680997 (trial registration number NTR5759). Funders had no role in any aspect of any study including design, data collection, analysis and interpretation, or writing of reports.

A1.3. Ethics

As part of FRESH AIR, this thesis was approved by the 7th Health Region of Crete under protocol number 6951, 27/05/2016 (approval attached in the next page). All participants (patients, healthcare professionals, community members and/or other stakeholders) were provided with an information sheet, explaining the aim and all activities of the respective study they were takin part to. Explicit information was always provided verbally by the research team, along with the opportunity to ask any questions. All participants signed an informed consent document prior to their enrolment. Studies were conducted according to the Helsinki Declaration and research complied with the local ethical regulations that were active during the time of conduction.

GREEK REPUBLIC
MINISTRY OF HEALTH
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Heraklion, 26/05/2016

Protocol number: 6951 / 27/05/16
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TO:
Mr. Christos Lionis,
Professor of General Practice and Primary Health Care,
Director of Clinic of Social and Family Medicine,
School of Medicine University of Crete

SUBJECT: Approval to conduct research project entitled "Free Respiratory Evaluation and Smoke- exposure reduction by primary Health cAre Integrated gRoups (FRESH-AIR)"

IN CONCERN TO: Your letters with dates 31st of March and 16th of May 2016.

Honorable Mr. Lionis,

Following your relevant letters, we inform you regarding the decision of the 7th Health Region of Crete to **approve the conduct of the program** *"Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH-AIR)"* in the Primary Health Care units under its supervision.
The implementation of the program will contribute to the further scientific and professional training of health staff and to the upgrade the of the health services provided by the Primary Health Care units.
Furthermore, we consider valuable your intention to provide for use the equipment and diagnostic tools which will be used in this program, but also the enhancement of our services, through the conclusion of staff contracts, always in the context of this project.

Yours sincerely,

The Director
of the 7th Health Region of Crete

Eleni E. Mavrommati

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Appendix 2. Supplementary tables

Supplementary Table 1. Epidemiological features, healthcare utilization and costs of COPD in Greece

	Value	Source
Prevalence, %	1) 8.4 (overall) – 9.1 (rural areas) 2) 5.6 3)7.06 4) 10.6 5) 17.8 6) 7.63 **Range: 5.6-17.8**	1) Tzanakis et al. 2004 2) Sichletidis et al. 2005 3) Minas M et al. 2010 4) Kourlaba et al. 2016 5) Stafyla et al. 2018a 6) GBD Chronic Respiratory Disease, 2019
Incidence	-	-
Mortality	1) 10.9 per 100.000 2) 3029 / 120291 (for chronic diseases of the lower respiratory system)	1) Atsou et al. 2011 2) Hellenic Statistical Authority, 2018
DALYs	0.2 per 1000 capita per year	WHO, 2009
QoL		
EQ-VAS	66. (4.4) in the mild/moderate vs 56.7 (14.9) in severe/very severe (p<0.01)	Mitsiki et al. 2015b
CCQ	1.87 (1)	Carvounis et al. 2012
Symptoms, %		
Cough	1) 49.5 2) 76.6 3) 37.9 **Range: 37.9-49.5**	1) Stafyla et al. 2018a 2) Karvounis et al. 2012 3) Tsiligianni, et al. 2019
Dyspnoea	1)56.5 2) 57.8 3) 53.4 **Range:53.4-57.8**	
Sputum	1) 58.1 2) 66.8	
Wheezing	1) 45.7 2) 46.0	
Symptom severity, %		
Mild	22	Carvounis et al. 2012
Moderate	52	
Severe	26	
CAT≥ 10, %	1) 91 2) 84 3) 30.6 **Range: 30.6-91**	1) Ierodiakonou et al. 2020 2) Kourlaba et al. 2016
mMRC≥ 2, %	1) 61 2) 50 3) 22% **Range: 50-61**	1) Ierodiakonou et al. 2020 a 2) Kourlaba et al. 2016 3) Stafyla et al. 2018a
Exacerbations in past year		
At least one, %	1) 51.7 2) 37 (≥2)	1) Kourlaba et al 2016 2) Tsiligianni 2019
Mean number (range)	2 (0.-3) 1 (0-4)	1) Mitsiki et al 2015 2) Tsiligianni et al. 2019

GOLD		
A	14.7 19.3 14.2 23.3 5.4 **Range: 5.4-23.3**	Perlikos F et al. 2017 Mitsiki et al. 2015 Kourlaba et al. 2016 Stafyla, et al. 2018b Tsiligianni et al. 2019
B	8 35.4 34.1 15.5 56.4 **Range: 8-56.4**	
C	33.6 25.6 1.8 22.9 1.5 **Range: 1.8-33.6**	
D	43.7 19.6 49.9 38.4 36.8 **Range: 19.6-49.9**	
Health care utilization		
Emergency care unit visits	85.2	Carvounis et al. 2012
Hospitalization	97.1	
Intensive care unit admissions	97.1	
Hospital discharges		
J44.0	3783 / 1484485	Hellenic Statistical Authority, 2015
J44.1	3195 / 1484485	
J44.8	354 / 1484485	
J44.9	1228 / 1484485	
Comorbidity		
Obesity	1) 82.2 2)21.8 3) 29.3 **Range: 21.8-82.2**	1) Ierodiakonou et al. 2020 b 2) Perlikos F et al. 2017 3) Mitsiki et al. 2015 4) Stafyla et al. 2018b
Hypertension	1) 72.9 2) 75.6 3) 55.3 4) 44.6 **Range: 44.6-75.6**	
Diabetes Mellitus	1) 58 2) 31 3) 20.6 4) 21.2 **Range: 20.6-58**	
≥ 2 comorbidities	1) 77.1% 2) 86.5	
Managing physician, %		
GP/pathologist (hospital outpatient)	19.1	Souliotis et al. 2016a
Pulmonologist (hospital outpatient)	23.2	
GP/pathologist (private)	12.8	
Pulmonologist (private)	24.2	

GP/pathologist (home)	8	
Pulmonologist (home)	12.8	
Medications, %		
LABA	1) 23.5 10	1) Tsiligianni 2019 2) Souliotis et al. 2016a
LAMA	1)0.8 2)63	
LAMA+LABA	1) 2.0 2) 23	
LABA + ICS	1) 54.9 2) 13	
LAMA+LABA+ICS	1) 8.0	
Others	1) 10.8	
Prescribing patterns		
LABA+ICS	53.2	Souliotis et all. 2016b
ICS	34.5	
LAMA	33.7	
LABA	25.7	
SAMA	15.2	
SABA+SAMA	18.7	
Total costs of COPD management (annual), *euros*		
Direct	1) 2896 2) 2955.8 (medical and non-medical) 3) 1034.55 (222.94 out-of-pocket) **Range: 1034.55-2955.8**	1) Rehman et al. 2018 2) Souliotis et al.2016a 3) Stafyla et. Al. 2018b
Indirect (work productivity loss)	1) 998 2) 17741	
Work days lost, *mean (SD)*	10 (23)	Kourlaba et al. 2016
Types of costs of COPD management		
Exacerbations	1512.4	Souliotis et al. 2016a
Maintenance phase	835.0	
Additional resources	462.3	
Patients' time	146.1	
Work loss days	968	
Cost of functional/imaging tests, (annual), *euros*		
Spirometry	44	Souliotis et al. 2016a
Electrocardiography	4.1	
Chest computed tomography	45	
Chest radiography	4.1	

Populations
Atsou *et al. 2011: systematic literature review, Europe*
Ierodiakonou *et al. 2020a and b: N=257, COPD, primary care, across Greece*
Kourlaba *et al. 2016: N=351, >40 years, self-reported, nationwide*
Minas *M 2010: N= 20299, >14yo, primary care, central Greece*
Mitsiki *et al. 2015a: N=6125, COPD, nationwide*
Mitsiki *et al. 2015b: N=490, COPD, > 40 years, northern Greece*
Perlikos *et al. 2017: N=5978, COPD*
Rehman *et al. 2018: systematic literature review, Europe*
Sichletidis *et al. 2005, N=8151, 21-80 years, northern Greece*
Souliotis *et al. 2016a: Delphi panel of pulmonologists*
Souliotis *et al. 2016b: prescription data from social insurance fund*
Stafyla *2018a: N=186, >40 years, current/ex-smokers, primary care, central Greece*
Stafyla *2018b: N= 245, COPD patients, one hospital, central Greece*
Tsiligianni *et al. 2019: N= N=257, COPD, primary care across Greece*
Tzanakis *et al. 2004: N=888, >35 years, smokers, nationwide*

Abbreviations are defined in the list presented in the beginning of the thesis

Supplementary Table 2. Epidemiological features, healthcare utilisation and costs of asthma in Greece.

	Value	Source
Prevalence, %	1) 9 (8.5 in rural areas) 2) 4.33 3) 9.1 4) 8.6 **Range: 4.33-9.1**	1) Zervas et al 2012 2) GBD Chronic Respiratory Disease, 2019 3) Kourlaba et al. 2019 4) Asthma Team of the Hellenic Thoracic Society
Prevalence by age group, %		
0-9	3.79	Asthma Team of the Hellenic Thoracic Society
10-18	7.89	
18-44	8.80	
45-69	9.12	
>70	11.76	
Incidence	16 per 1000 people	Zervas et al 2012
Mortality		
DALYs	0.4 per 1000 capita per year	WHO, 2009
QoL	0.65 (not-well controlled) vs 0.86 (well-controlled)	Kourlaba et al. 2019
Hospital Anxiety Depression Scale (HADS)	8.00 (7.00)	Papaporfyriou et al. 2021
Health care utilization		
Emergency care unit visits	0.2 (0.7)	Vellopoulou et al. 2009
Hospitalization	1.6 (1.4)	
Hospital discharges		
J45	2171 / 148448	Hellenic Statistical Authority, 2015
Medications		
Antibiotics	31	Vellopooulou et al 2009
Oral corticosteroids	33	
ICS/LABA	57	
SABA	25	
Leuko-RA	16	
Total costs of asthma management (annual), *euros*		
Direct	1622.1	Souliotis et al. 2017
Direct-societal	895 (696–1105)	Vellopooulou et al 2009
Direct-payer	673(497–861)	
Direct-patient (out-of-pocket)	151 (119–188)	
Indirect (work productivity loss)	1) 659.7	1) Souliotis et al. 2017
Work days lost, *mean (SD)*	10.5	Souliotis et al. 2017
Types of annual costs of asthma management		
Exacerbations vs maintenance phase	273.1 vs 1100.2	
Medication	939.8 (42% of total cost)	Souliotis et al. 2017
Medical treatment	75.4	
Hospitalisation and intensive care unit	188.3	
Lab/imaging tests	169.7	
Additional resources	96.6	
Work loss days	602.6	
Cost of functional/imaging tests, (annual), *euros*		
Spirometry	64	Souliotis et al. 2017
Electrocardiography	20	
Chest computed tomography	12	
Chest radiography	37	
Populations		

Asthma Team of the Hellenic Thoracic Society*: N=2632, nationwide*
Kourlaba *et al. 2011: N=3946, ≥18 years*
Papaporfyriouet *al. 2021: N=100, asthma, ≥18 years*
Souliotis *et al. 2017: Delphi panel of pulmonologists*
Vellopoulou *et al. 2011: N=353, >18 years, nationwide*
Zervas *et al. 2012: N=2191, > 18 years, nationwide*

Abbreviations are defined in the list presented in the beginning of the thesis

Appendix 3. List of publications

Two publications in international peer -reviewed journals have been produced as a direct result of this thesis. Additional publications have been co-authored by the PhD candidate as part of FRESH AIR, including one publication in Lancet Global Health. Thesis findings have also been presented by the PhD candidate at local and international scientific meetings.

Authorship and reporting of manuscripts resulting from this thesis have been guided by the Recommendations for the Conduct, Reporting, Editing and publication follow the Disclosure of Potential Conflicts of Interest of the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org/).

A3.1. List of thesis publications

1. *Anastasaki M*, Trigoni M, Pantouvaki A, et al. **Establishing a pulmonary rehabilitation programme in primary care in Greece: A FRESH AIR implementation study**. Chron Respir Dis. 2019;16:1479973119882939. doi:10.1177/1479973119882939

2. *Anastasaki M*, Tsiligianni I, Sifaki-Pistolla D, Chatzea VE, Karelis A, Bertsias A, et al. **Household Air Pollution and Respiratory Health in Rural Crete, Greece: A Cross-Sectional FRESH AIR Study**. Atmosphere 2021;12:1369. doi: 10.3390/atmos12111369.

A3.2. Co-authorship in FRESH AIR publications

1. McEwen A, Pooler J, Lionis C, Papadakis S, Tsiligianni I, *Anastasaki M*, et al. **Adapting Very Brief Advice (VBA) on smoking for use in low resource settings: Experience from the FRESH AIR project**. J Smok Cessat. 2019;14:3. doi: https://doi.org/10.1017/jsc.2019.4

2. Kjærgaard J, *Anastasaki M*, Østergaard MS, Isaeva E, Akylbekov A, Nguyen NQ, et al. **Diagnosis and treatment of acute respiratory illness in children under five in primary care in low-, middle-, and high-income countries: A descriptive FRESH AIR study**. Plos One. 2019;14(11):e0221389. doi: 10.1371/journal.pone.0221389

3. Brakema EA, Tabyshova A, van der Kleij MJJ, Sooronbaev T, Lionis C, *Anastasaki M* et al. **The socioeconomic burden of chronic lung disease in low-resource settings across the globe – an observational FRESH AIR study**. Respir Res. 2019;20(1):291. doi: 10.1186/s12931-019-1255-z

4. Brakema EA, van der Kleij RMJJ, Poot CC, An PL, *Anastasaki M*, Crone MR, et al. **Mapping low-resource contexts to prepare for lung health interventions in four countries (FRESH AIR): a mixed-method study**. Lancet Glob Health. 2022;10(1):e63-e76. doi: 10.1016/S2214-109X(21)00456-3

A3.3. Group authorship in FRESH AIR publications

1. van Gemert F, de Jong C, Kirenga B, et al. **Effects and acceptability of implementing improved cookstoves and heaters to reduce household air pollution: a FRESH AIR study**. NPJ Prim Care Respir Med. 2019;29(1):32. 2019. doi:10.1038/s41533-019-0144-8

2. Brakema EA, van Gemert FA, van der Kleij RMJJ, et al. **COPD's early origins in low-and-middle income countries: what are the implications of a false start?.** NPJ Prim Care Respir Med. 2019;29(1):6. doi:10.1038/s41533-019-0117-y

3. Kjærgaard J, Nissen TN, Isaeva E, et al. **No time for change? Impact of contextual factors on the effect of training primary care healthcare workers in Kyrgyzstan and Vietnam on how to manage asthma in children - A FRESH AIR implementation study.** BMC Health Serv Res. 2020;20(1):1137. doi:10.1186/s12913-020-05984-y

4. Brakema EA, van Gemert FA, Williams S, et al. **Implementing a context-driven awareness programme addressing household air pollution and tobacco: a FRESH AIR study.** NPJ Prim Care Respir Med. 2020;30(1):42. doi:10.1038/s41533-020-00201-z

A3.4. Participation in international conferences

1. **84th EGPRN meeting, Riga, Latvia, 2017**
   Oral presentation: Preventing chronic respiratory diseases by implementing awareness-raising interventions to reduce smoking and household air pollution in rural Crete, Greece.

2. **22nd WONCA Europe Conference, Prague, Czech Republic, 2017**
   Oral presentation: Beliefs, perceptions and behaviors towards chronic lung diseases in a Roma population in Greece: experience from the ‘FRESH AIR’ project

3. **2nd International Congress on Controversies in Primary and Outpatient Care (COPOC), Zagreb, 2017**

Poster presentation: FRESH-AIR - a collaborative European research programme: interpreting results and exploring the benefits for Greek primary care

4. **7th EURIPA Rural Health Forum, Crete, 2017**

   Oral presentation: Beliefs, perceptions and behaviors towards chronic lung diseases in rural populations of Crete: A 'FRESH AIR' study

   Round table: Participative research on reducing exposure to household air pollution in rural Crete, Greece: A 'FRESH AIR' study

   Round table: Free Respiratory Evaluation and Smoke exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR)

5. **9th IPCRG World Conference, Porto, 2018**

   Oral presentation: Training general practitioners in Greece in 'Very Brief Advice' on smoking: The FRESH AIR Project

   Oral presentation: Terms, concepts, barriers and treatment practices towards childhood cough and asthma in rural Greece: a qualitative FRESH AIR study

6. **European Forum for Primary Care (EFPC) Conference, Crete, 2018**

   Oral presentation: Pulmonary Rehabilitation (PR) in the Greek primary care setting: lessons learnt from a FRESH AIR study

7. **10th IPCRG World Conference, 2021 (virtually)**

   e-Poster: Household air pollution and respiratory health in rural Crete, Greece: A cross-sectional FRESH AIR study.

   e-Poster: Implementation and evaluation of a lung health awareness programme in primary care in Crete, Greece: a FRESH AIR study.

A3.5. Participation in national conferences

1. **12ο Πανελλήνιο Συνέδριο για τη διοίκηση τα Οικονομικά και τις Πολιτικές της Υγείας, Αθήνα, 2016**

   Παρουσίαση: Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR)

   Παρουσίαση: Πεποιθήσεις, αντιλήψεις και συμπεριφορές για τα Χρόνια Αναπνευστικά Νοσήματα σε αγροτικές περιοχές και τον πληθυσμό των Ρομά στην Κρήτη: Τοπικές ανισότητες, εμπόδια και παράγοντες διευκόλυνσης

2. **6ο Πανελλήνιο Συνέδριο του Φόρουμ Δημόσιας Υγείας & Κοινωνικής Ιατρικής, Αθήνα, 2016**

   Παρουσίαση: Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR)

3. **10ο Πανελλήνιο και 9ο Πανευρωπαϊκό Νοσηλευτικό Συνέδριο, Ηράκλειο, 2017**

   Παρουσίαση: Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR)

A3.6. Copy of first thesis publication

DOI: 10.1177/1479973119882939

Original paper

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Establishing a pulmonary rehabilitation programme in primary care in Greece: A FRESH AIR implementation study

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Abstract

Pulmonary rehabilitation (PR) is an evidence-based, low-cost, non-medical treatment approach for patients with chronic respiratory diseases. This study aimed to start and assess the feasibility, acceptability and impact of a PR programme on health and quality of life of respiratory patients, for the first time in primary care in Crete, Greece and, particularly, in a low-resource rural setting. This was an implementation study with before–after outcome evaluation and qualitative interviews with patients and stakeholders. In a rural primary healthcare centre, patients with chronic obstructive pulmonary disease (COPD) and/or asthma were recruited. The implementation strategy included adaptation of a PR programme previously developed in United Kingdom and Uganda and training of clinical staff in programme delivery. The intervention comprised of 6 weeks of exercise and education sessions, supervised by physiotherapists, nurse and general practitioner. Patient outcomes (Clinical COPD Questionnaire (CCQ), COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), Patient Health Questionnaire-9 (PHQ-9), Incremental Shuttle Walking Test (ISWT)) were analysed descriptively. Qualitative outcomes (feasibility, acceptability) were analysed using thematic content analysis. With minor adaptations to the original programme, 40 patients initiated (24 with COPD and 16 with asthma) and 31 completed PR (19 with COPD and 12 with asthma). Clinically important improvements in all outcomes were documented (mean differences (95% CIs) for CCQ: −0.53 (−0.81, −0.24), CAT: −5.93 (−8.27, −3.60), SGRQ: −23.00 (−29.42, −16.58), PHQ-9: −1.10 (−2.32, 0.12), ISWT: 87.39 (59.37, 115.40)). The direct PR benefits and the necessity of implementing similar initiatives in remote areas were highlighted. This study provided evidence about the multiple impacts of a PR programme, indicating that it could be both feasible and acceptable in low-resource, primary care settings.

Keywords

Pulmonary rehabilitation, primary care, low-resource settings, COPD, asthma

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Introduction

Background of the problem

The burden of chronic respiratory diseases (CRDs) in Greece is significant. Namely, the prevalence of chronic obstructive pulmonary disease (COPD) is estimated at 8.4%, with higher rates being observed in semi-urban and rural areas.[1] The prevalence of asthma in the adult population reaches 9%.[2] At the same time, exposure to risk factors is high, with the country having one of the highest rates of tobacco consumption in the European Union.[3]

CRDs are also responsible for substantial costs for Greek patients and the healthcare system, with the total annual costs of managing COPD and asthma (including medications and hospitalizations) reaching 4730 and 2281 euros per patient, respectively.[4,5] Further to their economic impact, CRDs constitute an important issue for the quality of life and work productivity of patients in Greece. Specifically, annual per patient productivity losses exceed 900 euros for COPD[4] and 600 euros for asthma,[5] while disability adjusted life years are estimated at 0.2 for COPD and 0.4 for asthma per 1000 capita per year.[6]

Despite the above, integrated services for patients with CRDs, including pulmonary rehabilitation (PR), are largely absent in the country, especially at the primary care setting. While the World Health Organization (WHO) places increasing emphasis on chronic diseases, integrating primary and secondary care in the management of long-term conditions remains a neglected area in the current health agenda.[7] The situation has been aggravated during the last decade due to the economic crisis experienced in the country, leading to even more severe restrictions for patients with CRDs.[8,9]

Rationale for the implementation strategy

In 2015, a development study was conducted in Uganda aiming to assess the feasibility of a culturally adapted PR programme,[10] developed based on UK standards.[11] This was not a substitution of hospital-based PR, but rather a low-cost and locally tailored approach (e.g. PR training equipment was substituted by practical, everyday objects, while recruitment, referral and learning processes were based on local cultural demands).

Experience gained from this programme was used to inform content, design and delivery of PR programmes for roll-out in other resource-limited settings. This particular study was part of the European Horizon 2020 FRESH AIR project.[12]

Rationale for the intervention

PR is an evidence-based, non-medical, low-cost treatment intervention, proven effective in amending the systemic effects of lung disease, including breathlessness, inactivity and deconditioning.[13] PR is recommended by international guidelines for patients with COPD.[13–15] The pilot PR programme of Uganda resulted in substantial improvements in patient symptoms, exercise capacity[10,16] and quality of life.[17,18] To this direction, improving functional status with limited cost may significantly benefit people with CRDs and their families also in Greece, especially during the ongoing period of austerity.

Aims and objectives

This study aimed to adapt, implement and evaluate a PR programme for patients with CRDs, in a rural primary care setting in Crete, Greece. Specific objectives were:

- To determine the programme content (e.g. exercise and educational activities);
- To adapt existing manuals and educational materials;
- To define suitable outcome measures for evaluating the programme's impact on patients, including general- and disease-specific indicators;
- To evaluate process outcomes (i.e. recruitment, response and engagement rates); and
- To assess the programme feasibility and acceptability through qualitative research.

Methods

Study design

A pre–post implementation study of a community-based PR programme was conducted using quantitative and qualitative research. The quantitative component assessed recruitment, concordance, attrition and patient outcome indicators. Qualitative research explored feasibility and acceptability of the PR programme. The study followed the Standards for Reporting Implementation Studies.[19]

Context

The Greek healthcare system combines elements from both the public and the private sector.[20] Primary care is mainly represented by vocationally trained general practitioners (GPs), typically serving in healthcare centres and rural practices with limited inter-professional support.

Respiratory care is organized at three levels: (i) GPs and private practice doctors offering primary care; (ii) hospitals providing secondary care; and (iii) tertiary hospitals offering specialized services. Respiratory services mainly focus on acute care with much lower emphasis on long-term management and preventive services. Integration and coordination within primary care and between primary and secondary care still requires extensive efforts.

The economic crisis has, additionally, meant reductions to healthcare budgets, resulting in cuts to several public services. PR is offered at a very limited scale, remaining restricted to few tertiary hospitals. PR programmes are not available in the rural periphery, where the burden of CRDs is substantial[1] while the population is more deprived in terms of both income and healthcare provision.[21,22]

Study population

The study population consisted of patients with a diagnosis of a clinically stable CRD, including COPD and asthma. Patients were recruited and referred by GPs serving the study site who also performed an initial medical review to confirm diagnosis.

Suitable patients were invited to undertake a baseline assessment performed by a PR supervising team to determine eligibility for entry into the study. This included screening and tests to determine physical capacity and respiratory status.

Inclusion criteria were:

- Definite diagnosis of COPD and/or chronic asthma;
- Medical Research Council (MRC) dyspnoea score of two or higher.

Exclusion criteria were:

- Within 4 weeks of an acute exacerbation;
- Unwilling or unable to attend the programme;
- Unstable cardiovascular disease or locomotor difficulties precluding exercise; and
- Unable to provide informed consent.

Since this was a development study, sample size estimation was not performed. Based on previous studies suggesting that a sample of 30 patients is sufficient to measure before and after changes in the main outcome measures (Incremental Shuttle and Walking Test (ISWT) distance and Clinical COPD Questionnaire (CCQ) total score), assessing at least 40 patients was set as the recruitment goal.[16]

Sites

A public primary healthcare centre located at a rural area of Heraklion on the island of Crete, Greece was selected to host the PR programme due to its representativeness, capacity, safety and quality standards (basic diagnostic tools, brief inpatient treatment, ambulance service, comfortable spaces), affordable distance from the university and focal position (serving a population of 48,855 people with 13 rural practices belonging to its operational responsibility). PR sessions were performed in a spacious room and the grounds of the building.

Two physiotherapists and one nurse were posted at the study site to conduct PR. Their selection was based on their professional experience and availability from official duties. A GP serving the centre completed the PR team. Supervising team members had over 15 years of practice in public healthcare facilities, with lifelong experience with respiratory patients.

Implementation strategy

The implementation strategy consisted of stakeholder meetings, adaptation of PR context and educational materials, training of the supervising team and programme delivery and assessment. Groundwork was conducted in 2016 in Crete. Meetings were held with regional health authorities, healthcare and administrative staff, patients, academicians and researchers to determine suitable locations, processes of patient recruitment and the team required to assess patients and conduct the programme. Key messages delivered by groundwork activities established that:

- Patients were interested and available in sufficient numbers in primary care.
- Patients were able to access the study site.
- GPs were able to refer to PR.
- There was sufficient space and facilities in the site to run the programme.

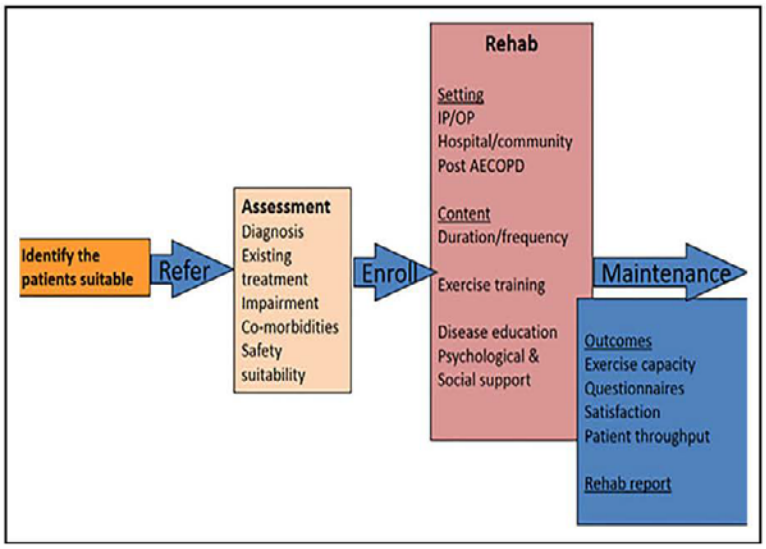

Figure 1. Components of the programme of Crete, Greece.

In March 2016, the research teams from United Kingdom and Crete met in Crete to adapt PR content, design and delivery and train the local healthcare professionals. The training of the PR team was provided face-to-face by the UK team during a one-week period and was supported by previously developed educational materials and videos.[10] It included introduction to PR and its benefits, interactive demonstration and explanation of exercises, train-the-trainer sessions on risk factor education, motivational techniques, assessment of patient eligibility and data collection procedures. These activities were also tested in field prior to programme initiation. Several distant sessions were also held online to support the local team. Data collection procedures were also established and visits to the study site were performed to ensure appropriateness of space and procedures.

Intervention

PR consists of a programme of exercises and health education based on international guidance.[11,23] Following the structure of the original programme (Figure 1), PR in Crete was delivered as a 6-week programme, with twice-a-week sessions of approximately 2 hours. After baseline assessment, patients were assigned to one pilot (June–July 2016) and two main groups (September–October 2016) of 10–12 participants each. Programme completion was defined as attendance of 75% of classes. There were no differences in the design, implementation or evaluation between the pilot and main groups. The distinction served only with identifying unexpected procedural barriers that could have hampered programme conduction. Since no such barriers were encountered, we report our results on the overall sample rather than on each group individually.

Each PR session included half an hour of walking in the yard and 1 hour of resistance and strength exercising (bands and weights for upper and lower limbs, sit-to-stand, steps) and static bicycle. PR equipment was kept minimal, while practical solutions were provided to patients to maintain PR exercises at home (e.g. weights as bottles of water). Everyone followed the same exercise regime; however, its level of difficulty was adjusted for each individual and monitored as programme progressed. Specifically, walking and exercise intensity and duration were based on Borg rating. If patients graded 4 or lower, exercise intensity was increased in the next session. In case Borg score was between 4 and 6, intensity was kept the same, until exercise became easy. In case of disagreement between heart rate and Borg score, heart rate guided the progression of exercise intensity in the following session.

Seven educational sessions of 1 hour were delivered per group by the trained PR team (GP, physiotherapists, nurse). Their contents were based on existing materials, adapted during groundwork.[16,24] They covered causes of breathlessness, coping and relaxation techniques, secretion disposal, risk factor (tobacco and biomass smoke) avoidance, behaviour

and lifestyle modifications (e.g. nutrition), medication intake (e.g. using inhalers), handling the CRD psychological impacts and understanding the importance of exercising and maintaining PR benefits. Written materials reminding the exercises and education were developed and provided to participants to encourage PR continuation and sharing with other community members.

Outcomes of the implementation strategy

Implementation strategy outcomes included the production of a culturally adapted and affordable PR programme, training of healthcare staff and programme implementation. Adaptation of procedures was summarized from stakeholder meeting reports, field notes and patient comments. Barriers and facilitators were recorded throughout the project to inform the implementation process and were summarized in discussions between the two research teams. Costs associated with purchasing PR equipment not routinely available in primary care were also documented to keep track of the direct extra expenditure.

Outcomes of the intervention

Patient socio-demographic characteristics, medical history, health habits and outcomes were assessed by the PR supervising team at baseline and at the end of PR using an adapted Case Report Form.[10,16] Outcomes included:

- Respiratory health status using the CCQ,[25] COPD Assessment Test (CAT)[26] and Saint George Respiratory Questionnaire (SGRQ)[27];
- Dyspnoea using the MRC and Borg Dyspnoea Scales[28];
- Functional impairment using the Karnofsky Score[29];
- Depression using the Patient Health Questionnaire-9 (PHQ-9)[30];
- Biometric indicators (height, weight, limb circumference);
- Functional measures using the sit-to-stand time[31]; and
- Exercise capacity using the ISWT[32] with before and after pulse oximetry.

Process evaluation

Adoption and reach of the programme were evaluated by reporting the number of sites implementing PR, the numbers and types of healthcare staff trained and delivering PR and the number of patients assessed, entered and completing the programme.

Feasibility and acceptability of the PR programme were examined through qualitative research, using theoretical input from the health belief model.[33] Semi-structured interviews were performed by local researchers before and after the PR programme with a sample of purposively selected patients. A focus group with stakeholders (site healthcare and administrative staff, community leaders, PR team members, specialized doctors) led by a local qualitative expert was also conducted at the end of the programme. In summary, qualitative activities assessed programme's practicality (e.g. how easy was it to attend and follow the programme), implementation (e.g. what went wrong or well, recruitment, retain, achievement of expectations), barriers/facilitators (e.g. to attendance, implementation) and sustainability (e.g. maintenance of benefits, programme scaling up).

Analysis

Patient outcomes were summarized using descriptive statistics; 95% confidence intervals (95% CIs) were estimated for quantitative variables. Fishers' exact test was used to compare proportions, with significance set at $a = 0.05$. Analysis was performed using SPSS (Version 23.0. Armonk, NY: IBM Corp). Published Minimal Clinically Important Differences (MCIDs) are reported in relation to observed changes in clinical outcomes.

All qualitative activities were audio-taped, transcribed and analysed using thematic content analysis by a local qualitative expert. The majority of qualitative data was translated into English and a qualitative scientist from the UK team cross-checked results. Conclusions were based on consensus between the two teams.

Ethics

The study was approved by the 7th Health Region of Crete (Pr. No.: 6951, 27 May 2016). During baseline assessment, eligible patients were provided with an information sheet, explaining the study aim and all activities. Explicit information was provided verbally by the supervising team, along with the opportunity to ask any questions. All participating patients signed an informed consent document. Signed informed consent was also obtained by stakeholders for participation in the focus group.

Results

Developing the implementation strategy and intervention

Relatively minimal adaptation to the PR programme of Uganda was performed. Adaptations were mainly cultural and included:

- Translation of documents into Greek and
- Exclusion of post-TB patients due to very low TB notification rates in Greece.[34]

Replacement of the EuroQoL (EQ-5D) questionnaire with the SGRQ and CAT as disease-specific health status tools, validated and used widely in the Greek context[35,36]:

- Delivery of walking exercises outdoors due to suitable weather;
- Purchase of training equipment instead of using practical objects due to higher capacity;
- Discarding of the follow-up data collection at 6 weeks post-rehabilitation; and
- Development of patient diaries to record symptoms, medications and exercises.

Delivering the intervention

A total of four healthcare professionals were trained and delivered the PR programme in one primary healthcare centre. Patient flow in the study is illustrated in Figure 2. Overall, 63 patients underwent baseline assessment and 46 were found eligible. In total, 40 patients started PR (participation rate: 87%), with 31 completing the programme (completion rate: 77.5%). Lack of time and reluctance due to unfamiliarity with PR procedures were mentioned as main reasons for not engaging with the programme. Medical issues and lack of time were reported as main reasons for dropping out the programme.

The total cost of purchasing PR equipment (weights, digital chronometers, bands, step aerobics, stationary bicycles and printouts) was 1602.66 euros.

Patient health outcomes

Table 1 presents the main baseline characteristics of the original sample of patients, along with differences among individuals who dropped out and those who completed the programme. Overall, slightly more than half of patients were females (55.0%), with a mean age of 67.2 years (95% CI: 63.9, 70.5). COPD was the main diagnosis for 60.0%, while 65.0% had ever smoked. With the exception of education ($p = 0.019$), no differences were observed between people completing and dropping out of PR with respect to socio-demographic characteristics.

In addition, mean BMI of the total sample was 31.24 kg/m^2 (95% CI: 29.63, 32.84), namely 33.79 (95% CI: 31.17, 36.41) for patients dropping out and 30.58 (28.69, 32.47) for those completing the programme. Patients who dropped out also had lower ISWT than their counterparts (mean difference: −53.84, 95% CI: −134.26, 26.59), with the mean value for the overall sample being 244.36 m (95% CI: 211.21, 277.51). Total CCQ score was 1.86 (95% CI: 1.51, 2.21) with a difference of 1.04 (95%CI: −0.41, 2.49) between individuals dropping out and completing PR.

Data on pre- and post-PR outcomes are presented in Table 2, for patients who completed the programme. Mean dyspnoea levels as measured by the MRC scale was reduced by 1.03 points, reaching the MCID of 1.[37] Functional and exercise capacity measurements were improved by the end of PR. The mean sit-to-stand time was reduced by 2.41 seconds, a change close to the MCID of 2.3 seconds.[38] The mean ISWT increased by 87.39 m greatly exceeding the MCID of 47.5 m.[39] The mean dyspnoea levels after performing ISWT, as measured by the Borg scale, decreased by 0.94 units.

Substantial improvements were also documented in all health status indicators. The mean CCQ total score was reduced by 0.53 units, a difference above the MCID of 0.4.[40] Mean CAT score dropped by almost 6 units, exceeding the MCID of 2.[41] The mean SGRQ total score decreased by 23 units, a difference higher than the MCID of 4.[42] The mean Karnofsky score was improved by 9.67 units. PHQ-9 scores were low already from baseline, yet a reduction of 1.10 points was observed.

Feasibility and acceptability

Interviews were conducted with a total of 8 patients (4 males, mean age: 64.5 years) pre- and post-PR. Seven stakeholders attended the focus group, including the PR physiotherapists and nurse, one GP facilitating patient recruitment, the site director (also a GP), the community vice-mayor and a pulmonologist from a public hospital of the city.

The main themes of qualitative interviews and focus groups are presented in Table 3. A detailed

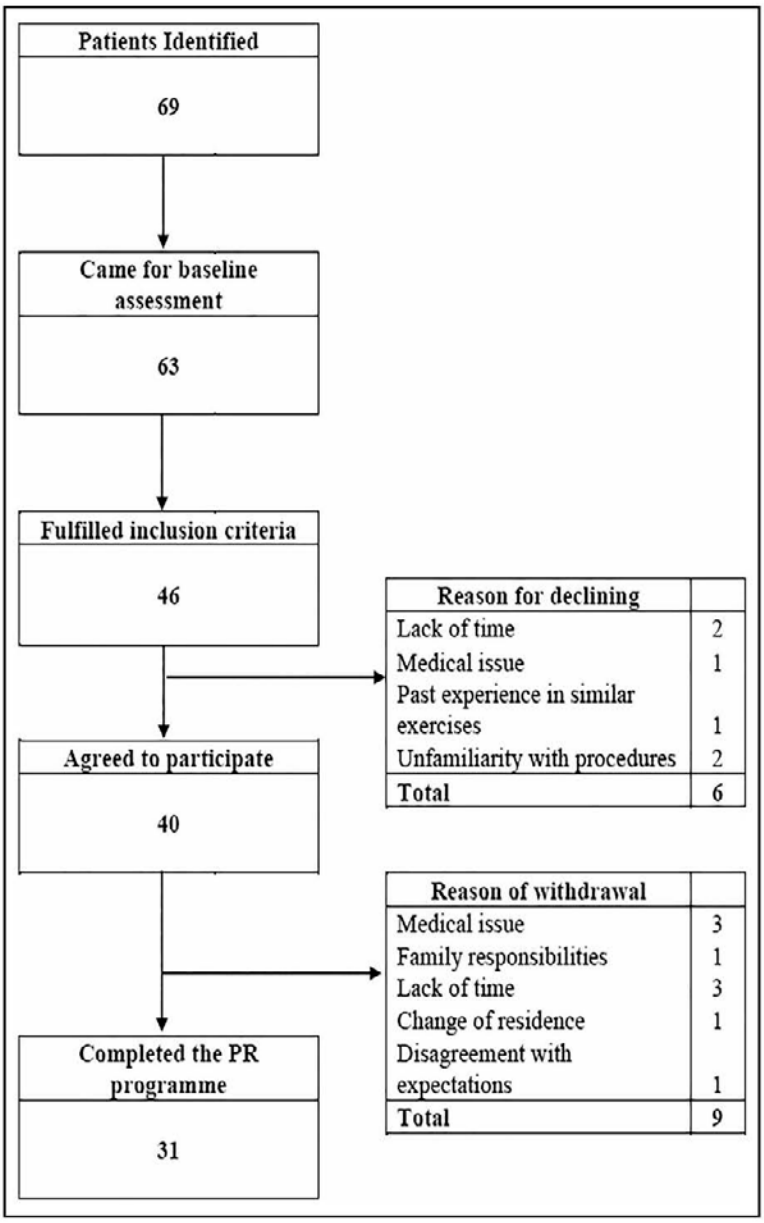

Figure 2. Recruitment flow diagram of COPD and asthma patients of the PR programme in Crete, Greece.
PR: pulmonary rehabilitation; COPD: chronic obstructive pulmonary disease.

description will follow in a separate report. In summary, patients' expectations included an overall health improvement and less medication dependence, partly to alleviate the financial burden of drugs. At the end of PR, both patients and stakeholders positively assessed the programme, noting the significant symptoms' reduction, the improvement and increase of physical activity and the benefits of received education on disease self-management. Patients and stakeholders recommended that the PR programme should be sustained and similar actions should be implemented in remote areas.

Table 1. Baseline characteristics of the original sample of COPD and asthma patients ($N = 40$) and differences between patients dropping out and completing the PR programme in Crete.

Outcomes	Total sample ($N = 40$)	Dropped out ($N = 9$)	Completed ($N = 31$)	Difference
Socio-demographics, *n* (%)				
Gender				
Male	18 (45.0)	2 (22.2)	16 (51.6)	$p = 0.15$[a]
Female	22 (55.0)	7 (77.8)	15 (48.4)	
Age (years), mean (95% CI)	67.2 (63.9, 70.5)	67.6 (59.5, 75.6)	67.1 (63.3, 70.9)	0.43 (−7.51, 8.37)
Diagnosis, *n* (%)				
COPD	24 (60.0)	5 (55.6)	19 (61.3)	$p = 1.0$[a]
Chronic asthma	16 (40.0)	4 (44.4)	12 (38.7)	
Education, *n* (%)				
None	1 (2.5)	1 (11.1)	0 (0.0)	$p = 0.019$[a]
Incomplete primary (<6 years)	1 (9.1)	3 (33.3)	2 (6.5)	
Complete primary (all 6 years)	8 (72.7)	3 (33.3)	25 (80.6)	
Incomplete secondary (<6 years)	1 (9.1)	1 (11.1)	2 (6.5)	
Complete secondary (all 6 years)	1 (9.1)	1 (11.1)	2 (6.5)	
Income (euros), mean (95% CI)	460.8 (385.3, 536.4)	420.0 (139.1, 700.9)	472.6 (398.9, 546.6)	−52.75 (−235.69, 130.19)
Smoking, *n* (%)				
Yes, currently	6 (15.0)	1 (11.1)	5 (16.1)	$p = 1.0$[a]
Yes, in the past	20 (50.0)	5 (55.6)	15 (48.4)	
No	14 (35.0)	3 (33.3)	11 (35.5)	
Biometrics, mean (95% CI)				
BMI (kg/m^2)	31.24 (29.63, 32.84)	33.79 (31.17, 36.41)	30.58 (28.69, 32.47)	3.21 (−0.68, 7.10)
Symptoms, mean (95% CI)				
MRC dyspnoea scale	3.23 (2.91, 3.55)	3.50 (0.34, 4.68)	3.16 (2.85, 3.48)	0.28 (−0.77, 1.33)
Exercise capacity, mean (95% CI)				
ISWT (m)	244.36 (211.21, 277.51)	117.50 (97.47, 257.53)	261.61 (225.66, 297.56)	−53.84 (−134.26, 26.59)
Health status, mean (95% CI)				
CCQ total score	1.86 (1.51, 2.21)	2.85 (1.26, 4.44)	1.61 (1.39, 1.82)	1.04 (−0.41, 2.49)
CAT total score	16.97 (14.32, 19.62)	19.38 (11.18, 27.57)	16.35 (13.51, 19.20)	3.02 (−3.56, 9.60)

CI: confidence interval; BMI: body mass index; ISWT: Incremental Shuttle Walking Test; CCQ: Clinical COPD Questionnaire; CAT: COPD Assessment Test.
[a]*p* Value based on Fischer's Exact Test.

Barriers and facilitators of implementation

Key barriers and facilitators identified by patients and stakeholders are summarized in Table 4. According to patients, barriers mainly concerned caring responsibilities, while few were related to accessing the programme. A key facilitator enhancing participation as perceived by both patients and stakeholders included the opportunity offered to patients by the programme to socialize while improving their health. Additionally, stakeholders identified timely information and comprehensive GPs' referral as core elements facilitating optimal recruitment. In contrast to patients, barriers to attending PR according to stakeholders' concerned transportation and an initial hesitation of patients attributed to lack of experience with such initiatives.

Discussion

Summary of findings

Our results suggested substantial and clinically important improvements in patient outcomes including symptoms (MRC dyspnoea scale), exercise (ISWT, sit-to-stand test) and quality of life (CCQ, CAT, SGRQ). The feasibility potential, along with a request for sustaining and expanding similar initiatives for remote populations, was also highlighted.

Discussion of the study's findings in the light of international literature should be performed with

Table 2. Outcomes of patients at baseline and at the end of the PR programme in Crete.

Outcomes	Baseline, mean (95% CI)	End of PR, mean (95% CI)	Difference, mean (95% CI)
Biometrics ($N = 30$)			
BMI (kg/m^2)	30.56 (28.69, 32.47)	30.44 (28.50, 32.38)	−0.12 (−0.31, 0.08)
Mid-upper arm circumference (cm)	29.63 (28.41, 30.86)	29.80 (28.63, 30.97)	0.17 (−0.16, 0.49)
Thigh (cm)	45.45 (43.33, 47.57)	46.75 (44.67, 48.83)	1.30 (0.34, 2.26)
Symptoms ($N = 30$)			
MRC dyspnoea scale	3.17 (2.84, 3.49)	2.13 (1.88, 2.39)	−1.03 (−1.45, −0.61)
Functionality ($N = 31$)			
Sit-to-stand time (seconds)	14.49 (12.97, 16.01)	12.08 (10.98, 13.18)	−2.41 (−3.58, −1.23)
Exercise capacity ($N = 31$)			
ISWT (m)	261.61 (228.66, 297.57)	349.00 (301.19, 396.81)	87.39 (59.37, 115.40)
Borg score (before ISWT)	1.15 (0.54, 1.75)	0.97 (0.41, 1.52)	−0.18 (−0.78, 0.43)
Pulse oximetry (before ISWT)	95.39 (94.52, 96.25)	95.35 (94.40, 96.31)	−0.03 (−0.90, 0.84)
Borg score (after ISWT)	4.90 (4.16, 5.65)	3.97 (3.23, 4.70)	−0.94 (−1.55, −0.32)
Pulse oximetry (immediately after ISWT)	95.13 (93.62, 96.64)	94.13 (92.48, 95.77)	−1.00 (−2.34, 0.34)
Pulse oximetry (2 minutes after ISWT)	96.61 (95.87, 97.36)	96.61 (95.98, 97.24)	0.00 (−0.66, 0.66)
Health status ($N = 30$)			
CCQ total score	1.59 (1.37, 1.81)	1.06 (0.79, 1.33)	−0.53 (−0.81, −0.24)
CCQ symptom score	1.50 (1.10, 1.89)	1.08 (0.71, 1.44)	−0.43 (−0.94, 0.09)
CCQ mental state score	2.10 (1.61, 1.59)	1.10 (0.63, 1.57)	−1.00 (−1.50, −0.49)
CCQ functional state score	1.43 (1.11, 1.74)	1.03 (0.68, 1.39)	−0.39 (−0.77, −0.02)
CAT total score	16.13 (13.22, 19.05)	10.20 (8.17, 12.23)	−5.93 (−8.27, −3.60)
SGRQ total score	43.20 (36.86, 49.54)	20.20 (15.15, 25.25)	−23.00 (−29.42, −16.58)
SGRQ symptoms score	46.96 (37.68, 56.24)	19.76 (14.39, 25.14)	−27.20 (−37.16, −17.23)
SGRQ activity score	55.02 (47.33, 62.72)	23.69 (15.83, 31.54)	−31.34 (−40.55, −22.12)
SGRQ impacts score	35.19 (28.61, 41.77)	18.31 (13.10, 23.65)	−16.82 (−23.31, −10.32)
Karnofsky score	77.67 (74.78, 80.56)	87.33 (84.09, 90.58)	9.67 (7.37, 11.96)
PHQ-9 total score	4.70 (2.92, 6.48)	3.60 (2.31, 4.89)	−1.10 (−2.32, 0.12)

CI: confidence interval; BMI: body mass index; MRC: Medical Research Council; ISWT: Incremental Shuttle Walking Test; CCQ: Clinical COPD Questionnaire; CAT: COPD Assessment Test; SGRQ: Saint George Respiratory Questionnaire; PHQ-9: Patient Health Questionnaire-9; PR: pulmonary rehabilitation; COPD: chronic obstructive pulmonary disease.

Table 3. Main themes emerging from patient interviews and stakeholders' focus group about the PR programme in Crete.

Themes	Patient interview	Stakeholder focus groups
Expectations of the programme	• Overall health improvement • Less medication dependence	–
Assessment of the programme	• Respiratory symptoms' reduction • Improvement and increase of physical activity	• Significant reduction in respiratory symptoms
Benefits of education	• Dyspnoea control • Appropriate exercise performance • Overall health education	• Disease self-management • Panic avoidance during exacerbation
Sustainability	• Importance of implementing similar programmes in remote areas	• Implementation in primary care for remote populations • Expansion in all healthcare facilities including hospitals • Central funding for continuation

caution due to considerable diversities in settings, patient characteristics and programme designs. Yet, pre- and post-PR differences in main clinical outcomes (CCQ and ISWT) were generally close to those observed in the development study of Uganda.[16]

Table 4. Key barriers and facilitators to implement the PR programme in Crete, according to patients and stakeholders.

Key barriers	Key facilitators
Caring responsibilities	Opportunity for socializing while improving health
Convincing patients to initiate this novel programme	Timely information of stakeholders
Transportation	Comprehensive GPs' referral

PR: pulmonary rehabilitation; GP: general practitioner.

By reading other studies, differences in ISWT and CCQ recorded in this one were generally higher. In a comparative review, the change in ISWT was found 39.77 m higher in COPD patients receiving PR versus usual care, a result much lower than the pre-/post-ISWT difference documented in this study (87.39 m).[43] Similarly, in a prospective study of 419 COPD patients, CCQ improved by 0.6 points after PR, a change close the one observed in this study (−0.53).[44] Changes in SGRQ total score (−23.00) were also higher than in other studies (−21.07 and −12.3, respectively).[45,46]

Improvements observed in SGRQ scores were impressive. This may explained by the fact that, as disease-specific questionnaire, the SGRQ is more likely to be responsive to changes after PR and more sensitive to specific respiratory issues.[47] Additionally, the fact that the programme served patients in a holistic manner, including medical, psychological and social support, may have increased their overall positive response and assessment.

Interestingly, the completion rate documented in our study (77.5%) was similar or higher than other reports. In a study assessing a community-based PR programme, less than 57% of patients completed the full regime.[48] In an assessment of over 200 PR programmes in the United Kingdom, the completion rate was lower than this study (60%).[49] In other studies, adherence or completion rates ranged around 70%.[50,51]

Strengths and limitations

To the best of our knowledge, this is the first attempt to establish and assess a community-based PR programme in rural primary care areas in Greece. Yet, our study is prone to certain limitations. Firstly, this was a development study with small sample size and without adequate statistical power to perform significance testing. Its design does not also allow for any type of comparisons or causality determination. We are also unable to report on patient lung function characteristics. Spirometry is not available in Greek primary care and our efforts in overcoming this by using a portable spirometer did not provide quality results (most frequent errors: reduced expiration time, obstruction of the spirometer mouthpiece, poor patient collaboration and reduced peak expiratory flow). Additionally, we did not capture an overview of the long-term effects of the PR programme; however, this does not affect our before and after indicators. Furthermore, the local setting and population as well as the primary care context and organizational culture may significantly differ from Western or other low-resource settings, raising implications regarding generalizability. Interpretation of results also requires caution due to two sources of potential bias which may have influenced the provided self-reported information: the free-for-service nature of the present PR programme and the close relationships established over time between patients and healthcare professionals. As implementation research, our results may, however, offer valuable insights in terms of PR delivery for local and other low-resource settings.

Implications of the study

This study is in accordance with international literature documenting the beneficial effects of PR for patients with CRDs.[14,52] The experience and novel evidence gained through the PR programme of Crete may provide ground for future research to elicit precise estimates about the effectiveness and cost-effectiveness of PR and to ensure the optimal implementation of similar efforts addressing respiratory as well as other non-communicable diseases.

The PR programme achieved to bring together a group of diverse healthcare professionals and engage patients in an interactive procedure of education and health improvement. This is particularly relevant for informing clinical practice and service delivery in a country which is missing high performance in several aspects of quality-based care, including proactive involvement of patients in their therapeutic process, use of multidisciplinary teams and focus on disease prevention and health promotion.[53,54] Creating the health and social environments to support patients' participatory engagement and motivation to act for their health, along with exploring how medical curricula could be adjusted to include education on PR and

other team-based approaches, seem to be important messages of this study.

The PR programme of Crete was implemented in times of an economic recession which has significantly affected the size, structure and quality of provided health care services, with particular evidence capturing these unfavourable effects on patients.[9,55,56] Primary care is the most sustainable, accessible and cost-effective setting to tackle non-communicable diseases according to the WHO.[57] Additionally, it provides the ground for multidisciplinary collaboration, patient empowerment and community reactivation, which are all core components of PR. Instigating integrated disease management programmes such as PR in primary care may assist not only with improving patient outcomes and quality of life[58,59] but also with increasing the overall level of care integration[60] with positive effects on systems and communities.

The findings of this study, supported by the already reported health and financial benefits of PR,[52,61,62] speak to the need to work with policymakers to advocate for integration of PR programmes in primary care, provision of universal coverage through social insurance and investigation potential synergies with existing services to offer high-quality and affordable respiratory care for all. Taking into consideration the Primary Healthcare Reform and the changes of the curriculum of General Practice currently unfolding in Greece,[63] this study comes as timely as ever to provide further space for constructive discussion.

Conclusions

In a period of economic recession, these results highlight that evidence-based and low-cost PR programmes may constitute a promising in terms of improving patient outcomes, feasible and acceptable approach towards CRDs in low-resource, primary care settings.

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Author contributions

MA participated in the local coordination of the project, analysed the quantitative data, interpreted all results with the co-authors and wrote the first version of the manuscript. MT conducted the qualitative research and analysed the data, participated in the writing of this manuscript. AP, MT and MM participated in the local adaptation procedures were trained and delivered this programme and contributed to the finalization of this article. NC is the principal investigator of the overall FRESH AIR project, an original author of the FRESH AIR protocol and participated in the finalization of this manuscript. RJ and JP contributed to the design, conduct of the study, data interpretation and manuscript writing. SvK contributed to the analysis of data and writing of the article. CL was the country leader for the FRESH AIR project and participated in the design, study conduct, data interpretation and writing of the manuscript. IT participated in all steps of this programme by designing, coordinating, assessing and evaluating patients, being the GPs responsible for this programme and writing of this article. All authors have read and approved the final version of this manuscript.

Declaration of conflicting interests

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References

1. Tzanakis N, Anagnostopoulou U, Filaditaki V, et al. Prevalence of COPD in Greece. *Chest* 2004; 125(3): 892–900.
2. Zervas E, Loukides S, Kostikas K, et al. Asthma and asthma-like symptoms in Greece. The Greece asthma national prevalence survey. *Eur Respir J* 2012; 40(Suppl_56): P3936.
3. European Commission. *Special Eurobarometer 458*: Attitudes of Europeans towards tobacco and electronic cigarettes. Geneva, Switzerland: European Union, 2017.
4. Souliotis K, Kousoulakou H, Hillas G, et al. The direct and indirect costs of managing chronic obstructive pulmonary disease in Greece. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 1395–1400.
5. Souliotis K, Kousoulakou H, Hillas G, et al. Direct and indirect costs of asthma management in Greece: an expert panel approach. *Front public Heal* 2017; 5: 67.
6. World Health Organization. *Country profiles on Environmental Burden of Disease (Greece)*. Geneva, Switzerland: Public Health and the Environment, 2009.
7. Lionis C, Symvoulakis EK, Markaki A, et al. Integrated primary health care in Greece, a missing issue in the current health policy agenda: a systematic review. *Int J Integr Care* 2009; 9: e88.
8. Tsiligianni IG, Papadokostakis P, Prokopiadou D, et al. Impact of the financial crisis on adherence to treatment of a rural population in Crete, Greece. *Qual Prim Care* 2014; 22(5): 238–244.
9. Tsiligianni IG. COPD patients trapped in the financial crisis in rural Crete. *Lancet Respir Med* 2013; 1(10): e31–e32.
10. Jones R, Kirenga B, Pooler J, et al. A development study of pulmonary rehabilitation for patients with chronic lung disease in Uganda. *Eur Respir J* 2016; 48: PA858.
11. Bolton CE, Bevan-Smith EF, Blakey JD, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. *Thorax* 2013; 68(Suppl 2): ii1–ii30.
12. Cragg L, Williams S and Chavannes NH. FRESH AIR: an implementation research project funded through Horizon 2020 exploring the prevention, diagnosis and treatment of chronic respiratory diseases in low-resource settings. *NPJ Prim care Respir Med* 2016; 26: 16035.
13. Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease*, 2018.
14. Guideline National Clinical Guideline Centre (UK). *Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care*. London, UK: Royal College of Physicians, 2010.
15. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med* 2011; 155(3): 179.
16. Jones R, Kirenga BJ, Katagira W, et al. A pre–post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 3533–3599.
17. Pooler J, Muyinda H, Nyakoojo G, et al. A qualitative study on the development of pulmonary rehabilitation for patients with chronic lung disease in Kampala, Uganda. *Eur Respir J* 2016; 48: PA3964.
18. Jones R, Muyinda H, Nyakoojo G, et al. Does pulmonary rehabilitation alter patients' experiences of living with chronic respiratory disease? A qualitative study. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 2375–2385.
19. Pinnock H, Barwick M, Carpenter CR, et al. Standards for reporting implementation studies (StaRI) statement. *BMJ* 2017; 356: i6795.
20. Economou C, Kaitelidou D, Karanikolos M, et al. Greece: health system review. *Health Syst Transit* 2017; 19(5): 1–166.
21. Eurostat. *Statistics on rural areas in the EU – European Union*, 2017.
22. Oikonomou N and Tountas Y. Insufficient primary care services to the rural population of Greece. *Rural Remote Health* 2011; 11(1): 1661.
23. Rochester CL, Vogiatzis I, Holland AE, et al. An official American Thoracic Society/European Respiratory Society policy statement: enhancing implementation, use, and delivery of pulmonary rehabilitation. *Am J Respir Crit Care Med* 2015; 192(11): 1373–1386.
24. Morgan M and Singh S. *Practical pulmonary rehabilitation*. London, UK: Taylor & Francis, 1998.

25. van Dam van Isselt EF, Spruit M, Groenewegen-Sipkema KH, et al. Health status measured by the clinical COPD questionnaire (CCQ) improves following post-acute pulmonary rehabilitation in patients with advanced COPD: a prospective observational study. *NPJ Prim care Respir Med* 2014; 24: 14007.
26. Gupta N, Pinto LM, Morogan A, et al. The COPD assessment test: a systematic review. *Eur Respir J* 2014; 44(4): 873–884.
27. Jones PW, Quirk FH and Baveystock CM. The St George's respiratory questionnaire. *Respir Med* 1991; 85(Suppl B): 25–31; discussion 33–37.
28. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; 54(7): 581–586.
29. Karnofsky DA, Abelmann WH, Craver LF, et al. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. *Cancer* 1948; 1(4): 634–656.
30. Kroenke K, Spitzer RL, Williams JBW, et al. The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry* 2010; 32: 345–359.
31. Whitney SL, Wrisley DM, Marchetti GF, et al. Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the five-times-sit-to-stand test. *Phys Ther* 2005; 85(10): 1034–1045.
32. Singh SJ, Morgan MD, Scott S, et al. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992; 47(12): 1019–1024.
33. Rosenstock IM, Strecher VJ and Becker MH. Social learning theory and the health belief model. *Health Educ Q* 1988; 15(2): 175–183.
34. European Centre for Disease Control/WHO Regional Office for Europe. *Tuberculosis surveillance and monitoring in Europe*. Stockholm, Sweden: ECDC, 2017.
35. Katsoulas TA, Skordilis EK, Myrianthefs P, et al. Validity of St. George's respiratory questionnaire for Greek patients with chronic obstructive pulmonary disease. *Percept Mot Skills* 2010; 110(3): 772–788.
36. Tsiligianni IG, Van der Molen T, Moraitaki D, et al. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). *BMC Pulm Med* 2012; 12(1): 20.
37. Crisafulli E and Clini EM. Measures of dyspnea in pulmonary rehabilitation. *Multidiscip Respir Med* 2010; 5(3): 202.
38. Meretta BM, Whitney SL, Marchetti GF, et al. The five times sit to stand test: responsiveness to change and concurrent validity in adults undergoing vestibular rehabilitation. *J Vestib Res* 2006; 16(4–5): 233–243.
39. Singh SJ, Jones PW, Evans R, et al. Minimum clinically important improvement for the incremental shuttle walking test. *Thorax* 2008; 63(9): 775–777.
40. Kocks J, Tuinenga M, Uil S, et al. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. *Respir Res* 2006; 7(1): 62.
41. Kon SSC, Canavan JL, Jones SE, et al. Minimum clinically important difference for the COPD assessment test: a prospective analysis. *Lancet Respir Med* 2014; 2(3): 195–203.
42. Jones PW. St. George's respiratory questionnaire: MCID. *COPD* 2005; 2(1): 75–79.
43. McCarthy B, Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; 23(2): CD003793.
44. Smid DE, Franssen FME, Houben-Wilke S, et al. Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: a prospective analysis. *J Am Med Dir Assoc* 2017; 18(1): 53–58.
45. Sciriha A, Lungaro-Mifsud S, Scerri J, et al. Health status of COPD patients undergoing pulmonary rehabilitation: a comparative responsiveness of the CAT and SGRQ. *Chron Respir Dis* 2017; 14(4): 352–359.
46. Barakat S, Michele G, George P, et al. Outpatient pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. *Int J Chron Obs Pulmon Dis* 2008; 3(1): 155–162.
47. Puhan MA, Guyatt GH, Goldstein R, et al. Relative responsiveness of the chronic respiratory questionnaire, St. George's respiratory questionnaire and four other health-related quality of life instruments for patients with chronic lung disease. *Respir Med* 2007; 101(2): 308–316.
48. Zakrisson AB, Engfeldt P, Hägglund D, et al. Nurse-led multidisciplinary programme for patients with COPD in primary health care: a controlled trial. *Prim Care Respir J* 2011; 20(4): 427–433.
49. National COPD Audit Programme: pulmonary rehabilitation workstream 2013–2018. *Pulmonary rehabilitation: steps to breathe better*. London, UK: Royal College of Physicians, 2016.
50. Sohanpal R, Hooper R, Hames R, et al. S112 estimating participation rates of COPD patients in pulmonary

rehabilitation and self-management programmes: the importance of defining participation. *Thorax* 2012; 67: A55.
51. Hayton C, Clark A, Olive S, et al. Barriers to pulmonary rehabilitation: characteristics that predict patient attendance and adherence. *Respir Med* 2013; 107(3): 401–407.
52. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; 188(8): e13–e64.
53. Schäfer W, Boerma W, Murante A, et al. Assessing the potential for improvement of primary care in 34 countries: a cross-sectional survey. *Bull World Heal Organ* 2015; 93(3): 161–168.
54. Lionis C, Papadakis S, Tatsi C, et al. Informing primary care reform in Greece: patient expectations and experiences (the QUALICOPC study). *BMC Health Serv Res* 2017; 17(1): 255.
55. Kentikelenis A, Karanikolos M, Papanicolas I, et al. Health effects of financial crisis: omens of a Greek tragedy. *Lancet* 2011; 378(9801): 1457–1458.
56. Karamanoli E. Financial crisis harms respiratory health in Greece. *Lancet Respir Med* 2013; 1(7): 511–512.
57. World Health Organization. *2008-2013 action plan for the global strategy for the prevention and control of noncommunicable diseases*, 2009.
58. Chavannesa NH, Grijsen M, Den Akker MV, et al. Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim Care Respir J* 2009; 18(3): 171–176.
59. Kruis AL and Chavannes NH. Potential benefits of integrated COPD management in primary care. *Monaldi Arch Chest Dis* 2016; 73(3): 130–134.
60. Kruis AL, Boland MRS, Assendelft WJJ, et al. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. *BMJ* 2014; 349: g5392.
61. Griffiths TL, Phillips CJ, Davies S, et al. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001; 56(10): 779–784.
62. Golmohammadi K, Jacobs P and Sin DD. Economic evaluation of a community-based pulmonary rehabilitation program for chronic obstructive pulmonary disease. *Lung* 2004; 182(3): 187–196.
63. World Health Organization. *Greek health reform: opening of new primary health care units*, 2017. http://www.euro.who.int/en/countries/greece/news/news/2017/12/greek-health-reform-opening-of-new-primary-health-care-units.

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Household Air Pollution and Respiratory Health in Rural Crete, Greece: A Cross-Sectional FRESH AIR Study

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Abstract: Breathing polluted air is a risk to respiratory conditions. During the Greek financial crisis, the use of household fireplaces/wood stoves shifted from mostly decorative to actual domestic heating, resulting in increased indoor smoke production. We aimed to evaluate household air pollution (HAP), fuel use and respiratory symptoms in rural Crete, Greece. $PM_{2.5}$ and CO were measured in 32 purposively selected rural households (cross-sectional study) at periods reflecting lesser (baseline) versus extensive (follow-up) heating. Clinical outcomes were assessed using questionnaires. Mean $PM_{2.5}$ were not significantly different between measurements (36.34 μg/m^3 vs. 54.38 μg/m^3, $p = 0.60$) but exceeded the WHO air quality guidelines. Mean and maximal CO levels were below the WHO cut-offs (0.56 ppm vs. 0.34 ppm, $p = 0.414$ and 26.1 ppm vs. 9.72 ppm, $p = 0.007$, respectively). In total, 90.6% of households were using wood stoves or fireplaces for heating, but half also owned clean fuel devices. The differences between devices that were owned versus those that were used were attributed to financial reasons. In both cases, the most frequent respiratory symptoms were phlegm (27.3% vs. 15.2%; $p = 0.34$) and cough (24.2% vs. 12.1%; $p = 0.22$). Our findings demonstrate the magnitude of HAP and confirm the return to harmful practices during Greece's austerity. Upon validation, these results can support strategies for fighting fuel poverty, empowering communities and strengthening local health systems.

Keywords: household air pollution; $PM_{2.5}$; CO; respiratory health; fuel poverty; economic crisis; Greece

1. Introduction

Breathing polluted air is a risk factor to most respiratory conditions [1]. Improving air quality and reducing exposure to any kind of smoke are important steps towards promoting respiratory health [2]. In many low-resource settings, however, smoke produced by burning biomass inside households for heating and/or cooking is an important source of household air pollution (HAP) [3], the levels of which may often exceed the internationally established air quality standards [4,5].

In such settings, indoor biomass burning is mainly attributed to financial and awareness reasons, which impede the availability and purchase of clean fuels and the adoption of preventive measures [6]. Yet, accumulating evidence suggests that exposure to HAP can substantially increase the burden and risk of chronic obstructive pulmonary disease (COPD) and can affect lung health in childhood [7–10]. Specifically for Greece, about

1838 deaths and 31,611 disability-adjusted life years (DALYs) have been attributed to HAP (age-standardized rates of deaths and DALYs per 100,000 capita: 6 and 136.7, respectively) [11]. Worldwide, biomass fuels are approximately used by 50% of households, exposing more than three billion people to the adverse effects of indoor air pollution [4].

In Greece, the issue of air quality deterioration received prominence during the peak of the recent financial crisis, which substantially affected the country. Outdoor air quality data from urban settings suggested a dramatic rise in the concentration of airborne particulate matters during the winter period, which, apart from morning traffic hours, also peaked at noon [12–14]. Additionally, measurements of carbon monoxide during the night time suggested that emissions from biomass combustion contributed increasingly to the atmospheric pollution of urban areas [15]. The phenomenon was attributed to an increased use of fireplaces which, due to the significant increases in the price of conventionally-used fuel oil, shifted from mostly decorative reasons to actual domestic heating [16,17]. A survey of 598 Greek households showcased the impact of the economic crisis on energy consumption, highlighting that low-income households were even more vulnerable to being "fuel poor" [18].

Comparative figures demonstrate that biomass fuel use in Greece has increased between the pre- and post-financial recession periods. Namely, in 2005, slightly more than 2% of the total energy use in the household sector was attributed to biomass burning. In 2030, it is estimated that the respective share will reach almost 4%. These estimates exceed the European Unions' overall use, where, in 2005, biomass combustion in the residential sector accounted for 1.9% of total energy use, while the respective estimate for 2030 is approximately 3% [19].

Despite the above evidence, little is known about the magnitude and health effects of HAP in Greek households. Data are even scarcer for rural areas, which, despite being more deprived than urban areas, have been equally affected by austerity [20]. Households in Greek remote and mountainous areas are even more prone to fuel poverty than urban areas due to their increased heating needs, accessibility and economic restrictions [21]. The economic recession also seems to have had a particular impact on disease management for patients with chronic respiratory diseases [22], as well as on the general respiratory health of the rural population of Crete [23].

This study aims to assess HAP levels, heating activity and residents' respiratory symptoms and awareness between periods of differing biomass use intensity in rural Crete, Greece, to reflect on the generalized impact of the country's economic recession on health-related practices and outcomes.

2. Methods

2.1. Design, Setting and Participants

A cross-sectional study was conducted as part of the European, Horizon 2020 programme "FRESH AIR" [24]. In eight purposively selected rural and remote villages in the county of Heraklion, Crete, Greece, households using biomass fuels for heating were identified for the measurement of indoor air pollution. In each house, a household survey was completed by the person most responsible for domestic issues and an individual questionnaire was administered to all adult residents. Both tools included a combination of open- and closed-ended questions and were administered by the researchers to the participants during a face-to-face interview.

2.2. Environmental Outcomes

Environmental outcomes of HAP were assessed by measuring carbon monoxide (CO) and particulate matter smaller than 2.5 μg ($PM_{2.5}$). Measurements were conducted by trained researchers who visited the participating households at two time points reflecting periods of lesser (baseline: November–December 2017) versus extensive heating (follow-up: January–March 2018). Normally, these periods should reflect the verge of change between the seasons that influence the intensity of fuel use. CO and $PM_{2.5}$ levels were recorded

for 48 h each time. A stationary monitoring was performed. Namely, researchers visited households and placed the CO and $PM_{2.5}$ monitors above the central fireplace/stove, usually located in the central living room or kitchen. Researchers returned two days later to collect the monitors. Both at baseline and follow-up, all households of the same village were generally measured simultaneously, although measurements between different villages were performed on different days (due to a limited number of monitors available for this study). In cases where fast monitor battery discharge was identified during the monitor collection visit, the measurement was repeated on another day.

2.3. $PM_{2.5}$ Monitoring

$PM_{2.5}$ levels were measured using the RTI MicroPEM Sensor (https://www.rti.org/impact/micropem-sensor-measuring-exposure-air-pollution, accessed on 1 October 2021). The MicroPEM provides fully representative personal exposure characterizations by simultaneously defining the integrated exposure (filter based) as well as the patterns of exposure (real-time) in a wearable, lightweight, quiet, low-burden monitor. Due to limitations in device availability, in this study, the MicroPEM was placed above the central fireplace/stove of the household rather than worn personally. The MicroPEM collects up to 500 micrograms of PM on a 25 mm PTFE filter for gravimetric and speciation analyses. The laser-based light scattering nephelometer collects real-time PM concentration data at up to 3 s resolution over a range from 3 to 15,000 g/m^3. The 3-axis accelerometer monitors the frequency and intensity of movement for protocol compliance determination. The nephelometer and accelerometer data can be combined to calculate the potential inhaled dose. For this study, this calculation was performed by RTI experts in the USA.

Quality control metrics continuously monitored are temperature, relative humidity, pressure drop across the filter, battery voltage and sample flow rate. The comparability of MicroPEM PM and accelerometer data to a known "referee" standard defines its accuracy. The MicroPEM achieves the US EPA criteria for $PM_{2.5}$ and PM_{10} impactor cut-points, ± 0.5 µm. Collocated laboratory testing has shown the calibration slope is within $\pm 15\%$ and the intercept is within $\pm 10\%$ of the standard. The accelerometer standard is the downward 1.0 G value when at rest and the MicroPEM performs within $\pm 5\%$ of this value. Filter mass and nephelometer mass concentration precision are within $\pm 15\%$ over the full concentration range. The minimum valid data capture rate, also known as completeness, should exceed 95% when the MicroPEMs are properly maintained and correctly programmed for sample collection.

After 48 h sampling, the MicroPEM devices were taken to a central location to undergo filters' change, calibration and flow checking for next use. Measurement data were downloaded using the MicroPEM Docking Station software. The Docking Station is also the interface for calibrating the pump flow, performing nephelometer calibration, programming system cycling and customizing data validity parameters. The data download process retrieves the logged nephelometer, accelerometer, pump flow and other quality control data. Filters from the MicroPEM measurements were sent to RTI in the USA for analysis.

2.4. CO Monitoring

CO levels were measured using the Lascar EasyLog USB (https://www.lascarelectronics.com/software/easylog-software/easylog-usb, accessed on 1 October 2021). This standalone data logger measures and stores up to 32,510 Carbon Monoxide (CO) readings over a 0 to 1000 ppm measurement range and −10 to +40 °C (14 to +104 °F) operating temperature range. The user can easily set up the logging rate and start time, and download the stored data by plugging the data logger into a PC's USB port and running the purpose designed software. The data can then be graphed, printed and exported to other applications. Data is stored in non-volatile memory and is retained when the battery is empty. In this study, conduction of CO monitoring was also stationary rather than personal.

2.5. Household Survey

In addition to the above, a household survey was administered at both visits. This assessed housing characteristics (dwelling condition and age) and space heating activity, namely, duration of heating, type of heaters owned and type of heaters used (multiple-choice questions), reasons for differences between heaters owned vs. used (open-ended question), type of fuels used (multiple-choice question) and presence of other respiratory exposures (tobacco smoking indoors and type of smoking products as multiple-choice questions). This questionnaire was designed by the research team and adapted to the local context. At each time point we also kept track of the weather conditions by recording temperature and wind speed, according to the official weather forecast that was issued on the date of each household visit by the national meteorological service.

2.6. Clinical Outcomes

Respiratory health outcomes were assessed through an individual questionnaire, which was completed by all adult household members who were in the house during baseline and follow-up visits. This questionnaire was formed by the research team and adapted to the local context, but it also included typical, standardized scales for measuring respiratory symptoms. Data were collected on sociodemographic characteristics (age, gender) and symptoms experienced in general during each of the time points (cough, phlegm, wheezing, breathlessness, the Clinical COPD Questionnaire (CCQ), Medical Research Council (MRC) dyspnea scale). Presence of each symptom was recorded as a yes/no question. The CCQ total score was calculated as the sum of all items divided by ten, with higher value indicating lower health status [25]. The MRC dyspnea scale consists of five items grading a person's perceived breathlessness, with higher grades indicating higher perceived respiratory disability [26]. Similarly, symptoms experienced specifically when the heater was on (cough, phlegm, wheezing, breathlessness, headache, irritated eyes, nasal congestion, running nose, irritated throat, chest tightness, nausea, fatigue, dizziness, irritability), diagnosis of lung diseases (asthma, COPD, tuberculosis, pneumonia, lung cancer) and diagnosis of comorbidities (diabetes, heart disease, stroke, eye disease/cataract) were also recorded. Awareness (knowledge on the harmful effects of biomass burning for adults and children with sources of respective information) was finally added as three closed-ended survey questions as an important health-related outcome.

2.7. Study Size

The study size was based on resource considerations, namely the availability of CO and $PM_{2.5}$ measuring devices along with the time and costs associated with performing the measurements. Household recruitment and engagement were facilitated by four general practitioners (GPs) serving the targeted population, who identified eligible households from their medical records and performed the initial invitation via a face-to-face or telephone communication. Each GP identified two villages from the catchment area of their practice and invited four eligible households from each village. Subsequently, a convenience sample of 32 households was recruited.

2.8. Statistical Analysis

Data were summarized descriptively. Changes between baseline and follow-up measurements were explored using McNemar's tests for categorical variables and Wilcoxon signed rank test for continuous variables. Critical p-value was set at the 0.05 level. Analyses were performed using IBM SPSS v23.

2.9. Ethics

The study was approved by the 7th Health Region of Crete (Pr. No: 6951). All participants provided signed informed consent prior to their participation.

3. Results

3.1. Environmental Exposures

Baseline measurements and household surveys were completed by all 32 identified households. Two households were lost to follow-up due to family issues. The average weather temperature was 14.4 °C (min: 12 °C, max: 16 °C) at baseline and 14.8 °C (min: 10 °C, max: 18 °C) at follow-up.

Median (interquartile range, IQR) values of household $PM_{2.5}$ levels between measurements were 27.4 (30) $\mu g/m^3$ at baseline and 27.5 (40) $\mu g/m^3$ at follow-up. This difference was not statistically significant ($p = 0.607$). However, these values are above the safe air quality cut-off points (25 $\mu g/m^3$ for 24 h mean) indicated by the WHO [5].

At baseline, the overall median (IQR) value of CO levels was 0.02 (1) parts per million (ppm), while the median of maximal values was 12.3 (32) ppm. At follow-up, the overall median of CO values was 0.01 (0.4) ppm and the median of maximal CO values was 4.3 (12) ppm. The difference between the overall levels was not statistically significant ($p = 0.414$), in contrast to the difference between the maximal CO values ($p = 0.007$). Still, these CO levels are below the WHO air quality guidelines (26.6 ppm for 1 h and 6.1 ppm for 24 h mean) [5].

3.2. Heating Activity, Fuel Use and Other Respiratory Exposures

Table 1 presents data on household characteristics, heating activity and air pollution sources between the two assessments. Household questionnaires were collected from all 32 houses at baseline and from 30 houses at follow-up. Dwelling condition was considered good by most households (n = 15 or 48.4%), although most were traditional residencies constructed before 1940 (n = 21 or 34.4%). The vast majority of households owned local heating devices (n = 29 or 90.6%), most of which were stand-alone wood-burning stoves (n = 17 or 53.1%) and fireplaces (n = 13 or 40.6%).

Table 1. Household conditions, heating activity and air pollution sources at baseline and follow-up in rural Crete, Greece.

Outcomes, N (%)	Baseline (N = 32)	Follow-Up (N = 30)
Housing characteristics		
Condition of dwelling		
excellent	5 (16.1)	
good	15 (48.4)	
average	9 (29)	
poor	1 (3.2)	
very poor	1 (3.2)	
Year of construction		
after 1991	3 (9.4)	
1969–1990	8 (25.0)	
1940–1968	6 (18.8)	
before 1939	5 (15.6)	
I don't know	10 (31.3)	
Space heating activity		
Number of months requiring heating, *mean (SD)*	5.2 (0.9)	
What do you have to heat the rooms?		
purpose-built heater	32 (100)	
central heating	14 (43.8)	
petroleum radiators	9 (28.1)	
olive cores radiators	2 (6.3)	
unspecified	3 (9.4)	
local heating	29 (90.6)	

Table 1. *Cont.*

Outcomes, N (%)	Baseline (N = 32)	Follow-Up (N = 30)
stand-alone stoves	17 (53.1)	
fireplace	13 (40.6)	
portable electric heater	5 (15.6)	
air conditioner	2 (6.3)	
What do you use to heat the rooms?		
purpose-built heater	31 (96.9)	28 (93.3)
central heating	9 (28.1)	1 (3.3)
petroleum radiators	4 (12.5)	0 (0)
olive cores radiators	2 (6.3)	0 (0)
unspecified	3 (9.4)	1 (3.3)
local heating	28 (87.5)	27 (90.0)
stand-alone stoves	16 (50.0)	15 (50.0)
fireplace	13 (40.6)	12 (40.0)
portable electric heater	4 (12.5)	0 (0)
air conditioner	0 (0)	0 (0)
Reason of difference between what you have and what you use? (N = 9)		
financial reasons	9 (100)	
Type of fuel for heating		
wood	32 (100)	29 (96.7)
petroleum	8 (25.0)	1 (3.3)
olive cores	3 (9.4)	1 (3.3)
electricity	9 (28.1)	0 (0)
Other exposures		
Indoor tobacco smoking (yes)	10 (31.3)	6 (20.0)
Type of tobacco product		
manufactured cigarettes	10 (31.3)	5 (16.7)
rolled cigarettes	0 (0)	1 (3.3)

Non-biomass heaters including petroleum radiators, portable electric devices and air-conditioners were owned by 9 (28.1%), 5 (15.6%) and 2 (6.3%) houses, respectively. When asked what devices are actually used for heating at baseline, most households still reported using stand-alone stoves (n = 16 or 50%) and fireplaces (n = 13 or 40.6%). Petroleum radiators and electric heaters were only used in 4 (12.5%) households, while none were using the air-conditioner. Among nine households reporting reasons for differences between devices owned versus those used, all were attributed to financial restrictions. At follow-up, trends regarding the use of stand-alone stoves and fireplaces were similar to baseline.

At baseline, all households were using wood as a biomass fuel and, to a lesser extent, olive cores (n = 3 or 9.4%). Petroleum was used by 8 (25%) households and electricity by 9 (28.1%). Wood remained the main fuel used at follow-up (n = 29 or 96.7%), while non-biomass fuels were reported less frequently (petroleum: n = 1 or 3.3%, electricity: n = 0). Smoking tobacco indoors was reported by 10 (31.3%) households at baseline and 6 (20%) at follow-up. There were no statistically significant differences in PM2.5 and CO levels between households that reported indoor tobacco smoking versus those that did not, either at baseline or follow-up (Supplementary Table S1).

3.3. Clinical Respiratory Outcomes

Table 2 presents residents' symptoms and health-related outcomes, in combination with the exposure data described previously. There were 43 adult questionnaires completed at baseline and 42 at follow-up. In total, 33 individuals had paired data for both assessments and are included in the present analysis. Their mean age was 66.8 years (SD = 14.9), while 24 participants (72.7%) were women.

Table 2. Respiratory health-related outcomes in combination with exposure data of residents with paired data in rural households using biomass fuels in Crete, Greece (N = 33).

Outcomes N (%)	Baseline	Follow-Up	*p*-Value *
Socio-demographics			
Age (years), *mean (SD)*	66.8 (14.9)	-	-
Gender (women)	24 (72.7)	-	-
General symptoms			
Cough (yes)	8 (24.2)	4 (12.1)	0.34
Phlegm (yes)	9 (27.3)	5 (15.2)	0.22
Wheezing (yes)	1 (3)	1 (3)	1
Breathlessness (yes)	4 (12.1)	4 (12.1)	1
MRC dyspnea scale, *median (IQR)*	2.0 (3)	2.0 (1)	0.07
CCQ total score, *median (IQR)*	0.2 (5)	0.2 (10)	0.82
Symptoms during heating			
Cough	5 (15.2)	3 (9.1)	0.69
Phlegm	0 (0)	0 (0)	N/A
Wheezing	1 (3)	0 (0)	1
Breathlessness	3 (9.1)	2 (6.1)	1
Headache	12 (36.4)	6 (18.2)	0.70
Irritated eyes	6 (18.2)	6(18.2)	1
Nasal congestion	3 (9.1)	1 (3)	0.63
Running nose	2 (6.1)	1 (3)	1
Irritated throat	3 (9.1)	1 (3)	0.5
Chest tightness	2 (6.1)	1 (3)	1
Nausea	6 (18.2)	0 (0.0)	**0.03**
Fatigue	14 (42.4)	5 (15.2)	**0.004**
Dizziness	9 (27.3)	1 (3)	**0.02**
Irritability	8 (24.2)	0 (0)	**0.008**
Exposures			
$PM_{2.5}$ ($\mu g/m^3$), *median (IQR)*	27.4 (30)	27.5 (40)	0.607
CO (ppm), *median (IQR)*	0.02 (1)	0.01 (0.4)	0.414
CO max (ppm), *median (IQR)*	12.3 (32)	4.3 (12)	0.007
Lung health			
Asthma (yes)	0 (0)		
COPD (yes)	2 (6.1)		
Tuberculosis (yes)	1 (3.0)		
Pneumonia (yes)	5 (15.2)		
Lung cancer (yes)	0 (0)		
Comorbidities			
Diabetes (yes)	9 (27.3)		
Heart disease (yes)	12 (36.4)		
Stroke (yes)	4 (12.1)		
Eye disease/cataract (yes)	11 (33.3)		
Awareness			
Did you know that biomass burning may harm your health? (yes)	16 (48.5)		
Source of information			
Healthcare professional	2 (12.5)		
Physician	2 (12.5)		
Media (radio, newspaper, TV)	12 (75.0)		
Family	2 (12.5)		
Villagers	0 (0)		
Own experience	1 (6.3)		
Did you know that biomass burning may harm your children's health? (yes)	17 (51.5)		

* McNemar's test for categorical variables and Wilcoxon Signed Ranks test for continuous variables. Abbreviations: SD: Standard Deviation, IQR: Interquartile range, MRC: Medical Research Council, CCQ: Clinical COPD Questionnaire, CI: Confidence Interval, $PM_{2.5}$: Particulate matter smaller than 2.5 μg, CO: Carbon monoxide, ppm: Parts per million.

The most frequently reported general respiratory symptom at both time points was phlegm (n = 9 or 27.3% vs. n = 5 or 15.2%), followed by cough (n = 8 or 24.2% vs. n = 4 or 12.1%). Differences in all general respiratory symptoms including cough, phlegm, wheezing and breathlessness were not significant between assessments.

At baseline, fatigue was the most common symptom experienced specifically when the heater was on (n = 12 or 42.4%), followed by headache (n = 12 or 36.4%). At follow-up, the respective symptoms were headache and irritated eyes (n = 6 or 18.2% for both). Among symptoms experienced specifically when the heater was on, nausea, fatigue, dizziness and irritability were reported at significantly higher rates during baseline compared to follow-up (n = 6 or 18.2% vs. n = 0, $p = 0.03$; n = 14 or 42.4% vs. n = 5 or 15.2%, $p = 0.004$; n = 9 or 27.3% vs. n = 1 or 3%, $p = 0.02$ and n = 8 or 24.2% vs. n = 0; $p = 0.008$, respectively). The occurrence and frequencies of symptoms reported specifically when the heater was on are in line with the CO exposure data and contrary to $PM_{2.5}$ concentrations. However, differences between baseline and follow-up levels are not statistically significant.

No participant reported having asthma. COPD was reported by 2 (6.1%) participants, while 5 (15.2%) reported having experienced pneumonia. Heart disease was the most common comorbidity (n = 12 or 36.4%), followed by eye disease (n = 11 or 33.3%). There were no meaningful statistically significant differences in the most common symptoms between people with any comorbidities versus without, either at baseline or follow-up (Supplementary Table S2).

Less than half of participants (n = 16 or 48.5%) knew that indoor biomass burning for heating could harm their health, of which the majority (n = 12 or 75%) had heard so from media, followed by a healthcare professional/physician (n = 4 or 25%).

4. Discussion

4.1. Summary of Findings and Comparison with the Literature

To the best of our knowledge, this study is among the first to provide insights about the levels of HAP and relevant health-related practices and outcomes during a period of economic recession in Greece. Our results revealed levels of household $PM_{2.5}$ exceeding the WHO air quality guidelines. These values are lower than those reported in a similar FRESH AIR study conducted in global low-resource settings [27], and further investigation is warranted to determine whether this can suggest a public health issue in rural Crete. Still, although direct comparisons cannot be performed, a recent study including outdoor data from the second largest Greek city showed that biomass burning during winter comprised the second largest $PM_{2.5}$ source, indicating an important health-related issue deserving prompt attention [28]. Additionally, another study assessing personal PM exposure through an indoor–outdoor experiment in Athens showed that, in general, 24 hours averaged $PM_{2.5}$ concentrations frequently exceeded the limits set by the European Union [29].

Interestingly, although clean fuel devices were owned by a considerable proportion of households in our study, they were used at substantially lower rates, with disparities being attributed to financial limitations. This is in accordance with previous evidence highlighting the negative impact of the economic crisis on heating practices in Greece [16]. In another study exploring indoor environmental conditions in low-income, urban households during the Greek recession, temperatures in participating houses were found to be much lower than the appropriate thresholds for comfort and health, suggesting that the significant barriers to buying energy had placed the population under serious environmental and health-related risks [30].

Cough and phlegm were the most frequent general symptoms, reported by approximately one fourth of participants in both baseline and follow-up measurements. This is in line with the most frequent symptoms recorded in a similar study conducted by members of our group in low-resource settings [27]. In terms of symptoms experienced specifically during heating, we observed an unexpected decline in the frequency of nausea, fatigue, dizziness and irritability at follow-up. This finding could be partially explained by the weather conditions, which were unexpectedly similar and relatively good between the

two measurements—a fact that may have hindered the true effect of heating practices on respiratory symptoms. Still, this result requires cautious interpretation under the study limitations.

Last but not least, we report on what seems to be an awareness gap for our study population. Namely, less than half of our participants knew that burning biomass inside the household may be harmful for their or their children's health (48.5% and 51.5% respectively). For those who knew, the media (including radio, newspaper, TV) was the main source of information (75%). This result agrees with previously published literature in low resource settings, where awareness on the respective issue was found at similarly low levels [31].

4.2. Strengths and Limitations

The study is prone to certain limitations. Firstly, its descriptive design and small sample does not allow for adequate statistical inference. Moreover, it should not be neglected that the particularities of the local setting and population may differentiate them from Western or other low-resource settings, raising issues of generalizability. Additionally, all provided information was self-reported while different investigators performed the baseline and follow-up evaluations, facts that may have had an impact on the results. The purposive recruitment of households by the facilitating GPs may further introduce bias in terms of selection practices. However, due to the nature of their practice (that also includes household consultations apart from office practice), GPs were able to identify a quite diverse sample in terms of household income and residents' economic and health vulnerability. Still, we did not collect data on residents' educational level, a factor that may influence knowledge regarding smoke and HAP.

Other challenges faced during implementation were related to the function of measuring devices, including recording duration due to fast battery discharge and device calibration. Although these were tackled immediately during field work, there is a chance that they may have affected the measurements' quality.

Furthermore, the presence of a control group of households that do not use biomass fuels would have allowed for more comprehensive comparisons of HAP. However, our primary intention was to reflect on outcomes between periods of diverse biomass use intensity, rather than between "exposed" versus "non-exposed" households. It should, however, not be neglected that the ingress of outdoor pollutants indoors may have influenced our observed measurements, while the lack of data on ventilation may also impact the interpretation of findings. The limited availability of data before the economic crisis does not further allow for the comprehensive interpretation of the observed health outcomes with respect to the noted levels of HAP.

Finally, although we intended to reflect on outcomes between periods of lesser versus extensive heating, weather conditions encountered during the two data collection periods were unusually similar, a fact that may have hampered the identification of meaningful differences.

Still, despite the resource restrictions and the complex nature of data collection, this study is among the first to attempt the measurement of HAP attributed to indoor biomass-burning, offering valuable lessons regarding measuring practices and implementation design within the local context.

4.3. Study Implications and Suggestions for Future Actions

During the last decade, the economic recession of Greece has meant changes in health-related practices, including the switch to biomass burning for domestic heating. The impact of the subsequent indoor air pollution on respiratory health has been studied in several settings (including Greece) and the particular susceptibility of both young children and older adults has been recognised [32,33]. Our study adds to the literature by demonstrating indications that HAP ($PM_{2.5}$) levels exceed the internationally established standards. Although further research is necessary to overcome our study's limitations and confirm our findings, several implications are raised for both healthcare and policy actions.

As in the case of Greece, HAP is generally linked to poverty. The inability of households to cover their heating needs—described as "fuel poverty"—constitutes a growing problem in Europe. Energy and fuel poverty for low-income households is a complex issue, which has a strong societal and economic aspect. It, thus, demands a multidisciplinary approach for which the strong collaboration and engagement of diverse stakeholders at both the governmental and the international partnerships' level is necessary [8,34]. Understanding local cultural and socio-economic backgrounds and enabling the active involvement of local communities in decision making is, also, crucial for the successful implementation of any intervention aiming to reduce HAP and improve health [35].

Such interventions have been implemented in several countries and their positive effects have been well-documented [36–38]. In a FRESH AIR study with similar aims and methods, a community-oriented intervention of implementing clean cooking/heating stoves was associated with lower exposures and improved short-term health benefits. Local adaptation of the intervention and vigorous inclusion of the community in the selection and installation of clean alternatives was, indeed, central to the success of implementation [27]. In the long-term, experience can also be drawn from other European countries that have developed concrete policies for tackling low-income household problems, including the provision of incentives to improve housing stock, replace heating systems and raise households' energy awareness [39].

The European Fuel Poverty and Energy Efficiency Project [37] has also identified key interventions for fighting energy poverty including the reduction of energy prices and the improvement of energy efficiency of buildings with vulnerable households, the education of households in rational use of energy and the improvement of low incomes. Other proposed actions suggest the implementation of the WHO indoor air quality guidelines on household fuel combustion, the formation of country alliances for the dissemination of improved devices and the investment in renewable energy [40]. Specifically for Greece, discussed strategies include the distribution of natural gas, the development of catalytic domestic wood stoves and the upgrade of buildings' energy efficiency [16,29,41]. Although national action plans integrating the above measures are necessary [42], a European response setting common criteria for energy poverty should be examined for the development of sustainable actions [40].

Last but not least, raising public and professional awareness on HAP is an area deserving special attention when considering interventions for preventing respiratory disease, which, in fact, constitutes the most affordable and effective way to reduce the burden [1]. In a FRESH AIR study conducted in global low-resource settings, the researcher and local stakeholders co-created a train-the-trainer awareness programme empowering communities to take action against biomass and tobacco smoke. They showed significant increases in lung health awareness and the damaging effects of HAP, while the high compatibility of the programme with local contexts was key to its acceptability and eventual success [43].

To close, in our study, general practitioners were central for the information about people, their recruitment and their engagement in the project. For the community to commit to positive action, long-term support from primary care is critical. Primary care is also essential for the effective and equitable combat of respiratory and other non-communicable diseases [31], including cardiovascular disease, for which HAP seems to be holding an emerging role [44]. Trained primary care providers can hold a key role in awareness raising, community motivation and behaviour change with regards to HAP and health [31]. Taking into consideration the Primary Healthcare Reform and the changes in the curriculum of General Practice unfolding in Greece in the last few years [45], this study may serve as a starting-point for exploring organizational issues to strengthen the health system and support local communities in agreement with the agenda of the Sustainable Development Goals [46].

5. Conclusions

The study described the levels of indoor air pollution and residents' respiratory health characteristics in rural households during the Greek economic crisis. Further research is necessary to overcome our limitations and validate our findings. However, this study could provide baseline information for expanding exposure reduction strategies and enhancing the prevention of both respiratory and other relevant non-communicable diseases.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/atmos12111369/s1, Table S1: Differences in environmental outcomes between smoking and non-smoking households at baseline and follow-up in Crete, Greece, Table S2: Differences in selected symptoms between people with any comorbidities versus without, at baseline and follow-up in Crete, Greece.

Author Contributions: M.A. participated in local study development, coordinated and contributed to data collection, analysed the data and wrote the first and subsequent versions of the manuscript. I.T. participated in the writing of the original FRESH AIR proposal and provided scientific input for local study development, implementation and results' interpretation. D.S.-P., V.E.C. and A.K. participated in local study development, data collection and results' interpretation. A.B. participated in local study development, coordination of data collection and results' interpretation. N.H.C. was the principal investigator of the overall FRESH AIR project, an original author of the FRESH AIR proposal and contributed to the development of the study protocol. F.v.G. designed the study, trained the local researcher and gave input throughout the data collection, analysis and report. C.L. was the country lead for the FRESH AIR project, providing overall supervision and scientific input for study design, implementation and results' interpretation. All authors have read and agreed to the published version of the manuscript. The FRESH AIR Collaborators participated in the overall FRESH AIR project, contributing to the success of each sub-study.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the 7th Health Region of Crete (Pr. No: 6951).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to data privacy and safety agreement.

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References

1. Forum of International Respiratory Societies. *The Global Impact of Respiratory Disease*, 2nd ed.; Forum of International Respiratory Societies: Sheffield, UK, 2017.
2. van Gemert, F.; van der Molen, T.; Jones, R.; Chavannes, N. The impact of asthma and COPD in sub-Saharan Africa. *Prim. Care Respir. J.* **2011**, *20*, 240–248. [CrossRef]
3. World Health Organization. *Indoor Air Pollution—The Killer in the Kitchen*; WHO: Geneva, Switzerland, 2010.
4. World Health Organization. *Household Air Pollution and Health*; WHO: Geneva, Switzerland, 2018.
5. World Health Organization. *WHO Guidelines for Indoor Air Quality: Household Fuel Combustion*; WHO: Geneva, Switzerland, 2018.
6. Fullerton, D.G.; Bruce, N.; Gordon, S.B. Indoor air pollution from biomass fuel smoke is a major health concern in the developing world. *Trans. R. Soc. Trop. Med. Hyg.* **2008**, *102*, 843–851. [CrossRef]
7. Gordon, S.B.; Bruce, N.G.; Grigg, J.; Hibberd, P.L.; Kurmi, O.P.; Lam, K.B.H.; Mortimer, K.; Asante, K.P.; Balakrishnan, K.; Balmes, J.; et al. Respiratory risks from household air pollution in low and middle income countries. *Lancet Respir. Med.* **2014**, *2*, 823–860. [CrossRef]
8. Thurston, G.D.; Kipen, H.; Annesi-Maesano, I.; Balmes, J.; Brook, R.D.; Cromar, K.; De Matteis, S.; Forastiere, F.; Forsberg, B.; Frampton, M.W.; et al. A joint ERS/ATS policy statement: What constitutes an adverse health effect of air pollution? An analytical framework. *Eur. Respir. J.* **2017**, *49*, 1600419. [CrossRef]
9. Kurmi, O.P.; Lam, K.B.; Ayres, J.G. Indoor air pollution and the lung in low- and medium-income countries. *Eur. Respir. J.* **2012**, *40*, 239–254. [CrossRef]
10. Rennard, S.I.; Drummond, M.B. Early chronic obstructive pulmonary disease: Definition, assessment, and prevention. *Lancet* **2015**, *385*, 1778–1788. [CrossRef]
11. World Health Organization. Household Air Pollution: Burden of Disease. 2016. Available online: https://www.who.int/data/gho/data/themes/air-pollution/household-air-pollution# (accessed on 28 September 2021).
12. Manoli, E.; Kouras, A.; Karagkiozidou, O.; Argyropoulos, G.; Voutsa, D.; Samara, C. Polycyclic aromatic hydrocarbons (PAHs) at traffic and urban background sites of northern Greece: Source apportionment of ambient PAH levels and PAH-induced lung cancer risk. *Environ. Sci. Pollut. Res. Int.* **2016**, *23*, 3556–3568. [CrossRef] [PubMed]
13. Argyropoulos, G.; Besis, A.; Voutsa, D.; Samara, C.; Sowlat, M.H.; Hasheminassab, S.; Sioutas, C. Source apportionment of the redox activity of urban quasi-ultrafine particles (PM0.49) in Thessaloniki following the increased biomass burning due to the economic crisis in Greece. *Sci. Total. Environ.* **2016**, *568*, 124–136. [CrossRef] [PubMed]
14. Vouitsis, I.; Amanatidis, S.; Ntziachristos, L.; Kelessis, A.; Petrakakis, M.; Stamos, I.; Mitsakis, E.; Samaras, Z. Daily and seasonal variation of traffic related aerosol pollution in Thessaloniki, Greece, during the financial crisis. *Atmos. Environ.* **2015**, *122*, 577–587. [CrossRef]
15. Gratsea, M.; Liakakou, E.; Mihalopoulos, N.; Adamopoulos, A.; Tsilibari, E.; Gerasopoulos, E. The combined effect of reduced fossil fuel consumption and increasing biomass combustion on Athens' air quality, as inferred from long term CO measurements. *Sci. Total. Environ.* **2017**, *592*, 115–123. [CrossRef]
16. Saffari, A.; Daher, N.; Samara, C.; Voutsa, D.; Kouras, A.; Manoli, E.; Karagkiozidou, O.; Vlachokostas, C.; Moussiopoulos, N.; Shafer, M.M.; et al. Increased biomass burning due to the economic crisis in Greece and its adverse impact on wintertime air quality in Thessaloniki. *Environ. Sci. Technol.* **2013**, *47*, 13313–13320. [CrossRef]
17. Sindosi, O.; Hatzianastassiou, N.; Markozannes, G.; Rizos, E.C.; Ntzani, E.; Bartzokas, A. PM10 Concentrations in a Provincial City of Inland Greece in the Times of Austerity and Their Relationship with Meteorological and Socioeconomic Conditions. *Water Air Soil Pollut.* **2021**, *232*, 1–19. [CrossRef]
18. Santamouris, M.; Paravantis, J.A.; Founda, D.; Kolokotsa, D.; Michalakakou, P.; Papadopoulos, A.M.; Kontoulis, N.; Tzavali, A.; Stigka, E.K.; Ioannidis, Z.; et al. Financial crisis and energy consumption: A household survey in Greece. *Energy Build.* **2013**, *65*, 477–487. [CrossRef]
19. Amann, M.; Cofala, J.; Klimont, Z.; Nagl, C.; Schieder, W. Measures to address air pollution from small combustion sources. *IIASA* **2018**, 8–10. Available online: https://ec.europa.eu/environment/air/pdf/clean_air_outlook_combustion_sources_report.pdf (accessed on 1 October 2021).
20. Oikonomidou, E.; Anastasiou, F.; Dervas, D.; Patri, F.; Karaklidis, D.; Moustakas, P.; Andreadou, N.; Mantzanas, E.; Merkouris, B. Rural primary care in Greece: Working under limited resources. *Int. J. Qual. Health Care* **2010**, *22*, 333–337. [CrossRef]
21. Katsoulakos, N.M.; Kaliampakos, D.C. The energy identity of mountainous areas: The example of Greece. *J. Mt. Sci.* **2018**, *15*, 1429–1445. [CrossRef]
22. Tsiligianni, I.G. COPD patients trapped in the financial crisis in rural Crete. *Lancet Respir. Med.* **2013**, *1*, e31–e32. [CrossRef]
23. Tsiligianni, I. Respiratory health in Greece. *Lancet Respir. Med.* **2020**, *8*, e65–e66. [CrossRef]
24. Cragg, L.; Williams, S.; Chavannes, N.H. FRESH AIR: An implementation research project funded through Horizon 2020 exploring the prevention, diagnosis and treatment of chronic respiratory diseases in low-resource settings. *NPJ Prim. Care Respir. Med.* **2016**, *26*, 16035. [CrossRef]
25. van der Molen, T.; Willemse, B.W.; Schokker, S.; ten Hacken, N.H.; Postma, D.S.; Juniper, E.F. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual. Life Out* **2003**, *1*, 13. [CrossRef]

26. Bestall, J.C.; Paul, E.A.; Garrod, R.; Garnham, R.; Jones, P.W.; Wedzicha, J.A. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* **1999**, *54*, 581–586. [CrossRef] [PubMed]
27. van Gemert, F.; de Jong, C.; Kirenga, B.; Musinguzi, P.; Buteme, S.; Sooronbaev, T.; Tabyshova, A.; Emilov, B.; Mademilov, M.; An, P.L.; et al. Effects and acceptability of implementing improved cookstoves and heaters to reduce HAP: A FRESH AIR study. *NPJ Prim. Care Respir. Med.* **2019**, *29*, 1–9. [CrossRef]
28. Saraga, D.E.; Tolis, E.I.; Maggos, T.; Vasilakos, C.; Bartzis, J.G. PM2.5 source apportionment for the port city of Thessaloniki, Greece. *Sci. Total. Environ.* **2019**, *650 Pt 2*, 2337–2354. [CrossRef]
29. Assimakopoulos, V.D.; Bekiari, T.; Pateraki, S.; Maggos, T.; Stamatis, P.; Nicolopoulou, P.; Assimakopoulos, M. Assessing personal exposure to PM using data from an integrated indoor-outdoor experiment in Athens-Greece. *Sci. Total. Environ.* **2018**, *636*, 1303–1320. [CrossRef]
30. Santamouris, M.; Alevizos, S.; Aslanoglou, L.; Mantzios, D.; Milonas, P.; Sarelli, I.; Karatasou, S.; Cartalis, K.; Paravantis, J. Freezing the poor—Indoor environmental quality in low and very low income households during the winter period in Athens. *Energy Build.* **2014**, *70*, 61–70. [CrossRef]
31. Brakema, E.A.; van Gemert, F.A.; Williams, S.; Sooronbaev, T.; Emilov, B.; Mademilov, M.; Tabyshova, A.; An, P.L.; Quynh, N.N.; Hong, L.H.T.C.; et al. Implementing a context-driven awareness programme addressing HAP and tobacco: A FRESH AIR study. *NPJ Prim. Care Respir. Med.* **2020**, *30*, 42. [CrossRef]
32. Patelarou, E.; Tzanakis, N.; Kelly, F.J. Exposure to indoor pollutants and Wheeze and asthma development during early childhood. *Int. J. Environ. Res. Public Health* **2015**, *12*, 3993–4017. [CrossRef]
33. Bentayeb, M.; Norback, D.; Bednarek, M.; Bernard, A.; Cai, G.; Cerrai, S.; Eleftheriou, K.K.; Gratziou, C.; Holst, G.J.; Lavaud, F.; et al. GERIE Study. Indoor air quality, ventilation and respiratory health in elderly residents living in nursing homes in Europe. *Eur. Respir. J.* **2015**, *45*, 1228–1238. [CrossRef]
34. Landrigan, P.J.; Fuller, R.; Acosta, N.J.R.; Adeyi, O.; Arnold, R.; Basu, N.; Baldé, A.B.; Bertollini, R.; Bose-O'Reilly, S.; Boufford, J.I.; et al. The Lancet Commission on pollution and health. *Lancet* **2018**, *391*, 462–512. [CrossRef]
35. Brakema, E.A.; van der Kleij, R.M.; Vermond, D.; van Gemert, F.A.; Kirenga, B.; Chavannes, N.H. Let's stop dumping cookstoves in local communities. It's time to get implementation right. *NPJ Prim. Care Respir. Med.* **2020**, *30*, 1–3. [CrossRef] [PubMed]
36. Thomas, E.; Wickramasinghe, K.; Mendis, S.; Roberts, N.; Foster, C. Improved stove interventions to reduce household air pollution in low and middle income countries: A descriptive systematic review. *BMC Public Health* **2015**, *15*, 650. [CrossRef]
37. Quansah, R.; Semple, S.; Ochieng, C.A.; Juvekar, S.; Armah, F.A.; Luginaah, I.; Emina, J. Effectiveness of interventions to reduce household air pollution and/or improve health in homes using solid fuel in low-and-middle income countries: A systematic review and meta-analysis. *Environ. Int.* **2017**, *103*, 73–90. [CrossRef] [PubMed]
38. Pope, D.; Bruce, N.; Dherani, M.; Jagoe, K.; Rehfuess, E. Real-life effectiveness of 'improved' stoves and clean fuels in reducing PM2.5 and CO: Systematic review and meta-analysis. *Environ. Int.* **2017**, *101*, 7–18. [CrossRef] [PubMed]
39. EU Energy Poverty Observatory. Diagnosis of Causes and Consequences of Fuel Poverty in Belgium, France, Italy, Spain and United Kingdom. 2009. Available online: http://www.powerhouseeurope.eu/uploads/tx_phecasestudies/Analysis_report_epee_3_2_EN.pdf (accessed on 1 October 2021).
40. Kolokotsa, D.; Santamouris, M. Review of the indoor environmental quality and energy consumption studies for low income households in Europe. *Sci. Total. Environ.* **2015**, *536*, 316–330. [CrossRef]
41. Kollias, P.; Kantiranis, N.; Pytharoulis, I.; Zanis, P. *Seasonal Variations of the Mineralogical Composition and the Organic Matter Content of Falling Dust in Thessaloniki During 2012-13*; Springer: Cham, Switzerland, 2017; pp. 949–956.
42. Brunner, K.M.; Spitzer, M.; Christanell, A. Experiencing fuel poverty. Coping strategies of low-income households in Vienna/Austria. *Energy Policy* **2012**, *49*, 53–59. [CrossRef]
43. World Health Organization. *2008–2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases*; WHO: Geneva, Switzerland, 2009.
44. Uzoigwe, J.C.; Prum, T.; Bresnahan, E.; Garelnabi, M. The emerging role of outdoor and indoor air pollution in cardiovascular disease. *N. Am. J. Med. Sci.* **2013**, *5*, 445–453.
45. World Health Organization. Greek Health Reform: Opening of New Primary Health Care Units. 2017. Available online: https://www.euro.who.int/en/countries/greece/news/news/2017/12/greek-health-reform-opening-of-new-primary-health-care-units (accessed on 28 September 2021).
46. Kieny, M.P.; Bekedam, H.; Dovlo, D.; Fitzgerald, J.; Habicht, J.; Harrison, G.; Kluge, H.; Lin, V.; Menabde, N.; Mirza, Z.; et al. Strengthening health systems for universal health coverage and sustainable development. *Bull. World Health Organ.* **2017**, *95*, 537–539. [CrossRef] [PubMed]

Appendix 4. List of tools

Tools or information about the tools (questionnaires and/or interview guides) used in this thesis are included in the following FRESH AIR publications:

Objective 1: The questionnaire was developed by the FRESH AIR team of University Medical Center Groningen and can be found in:

- Brakema EA, Tabyshova A, van der Kleij RMJJ, Sooronbaev T, Lionis C, Anastasaki M, An PL, Nguyen LT, Kirenga B, Walusimbi S, Postma MJ, Chavannes NH, van Boven JFM; FRESH AIR collaborators. The socioeconomic burden of chronic lung disease in low-resource settings across the globe - an observational FRESH AIR study. Respir Res. 2019 Dec 21;20(1):291. doi: 10.1186/s12931-019-1255-z.

Objective 2: The questionnaire was developed by the FRESH AIR team of Leiden University Medical Center and can be found in:

- Brakema EA, van der Kleij RM, Poot CC, Chavannes NH, Tsiligianni I, Walusimbi S, An PL, Sooronbaev T, Numans ME, Crone MR, Reis RR; FRESH AIR collaborators. A systematic approach to context-mapping to prepare for health interventions: development and validation of the SETTING-tool in four countries. BMJ Glob Health. 2021 Jan;6(1):e003221. doi: 10.1136/bmjgh-2020-003221.

Objective 3: The questionnaires were developed by the FRESH AIR team of University Medical Center Groningen and respective information can be found in:

- van Gemert F, de Jong C, Kirenga B, Musinguzi P, Buteme S, Sooronbaev T, Tabyshova A, Emilov B, Mademilov M, Le An P, Quynh NN, Dang TN, Hong LHTC, Chartier R, Brakema EA, van Boven JFM; FRESH AIR. Effects and acceptability of implementing improved cookstoves and heaters to reduce household air pollution: a FRESH AIR study. NPJ Prim Care Respir Med. 2019 Aug 15;29(1):32. doi: 10.1038/s41533-019-0144-8.

- Anastasaki M, Tsiligianni I, Sifaki-Pistolla D, Chatzea VE, Karelis A, Bertsias A, Chavannes NH, van Gemert F, Lionis C, the FRESH AIR Collaborators. Household Air Pollution and Respiratory Health in Rural Crete, Greece: A Cross-Sectional FRESH AIR Study. Atmosphere. 2021; 12(11):1369. https://doi.org/10.3390/atmos12111369

Objective 4: The questionnaires were developed by the National Center of Smoking Cessation and Training, UK and respective information can be found in:

- McEwen A, Pooler J, Lionis C, et al. Adapting Very Brief Advice (VBA) on smoking for use in low-resource settings: experience from the FRESH AIR project. Journal of Smoking Cessation. 2019;14(3):190-194. doi:10.1017/jsc.2019.4

Objective 5: The interview guide was developed by the FRESH AIR team of the University of Crete, however respective information has not yet been published.

Objective 3: The case report forms were developed by the FRESH AIR team of Plymouth University and respective information can be found in:

- Jones R, Kirenga BJ, Katagira W, et al. A pre-post intervention study of pulmonary rehabilitation for adults with post-tuberculosis lung disease in Uganda. Int J Chron Obstruct Pulmon Dis. 2017;12:3533-3539. Published 2017 Dec 11. doi:10.2147/COPD.S146659
- Anastasaki M, Trigoni M, Pantouvaki A, et al. Establishing a pulmonary rehabilitation programme in primary care in Greece: A FRESH AIR implementation study. Chron Respir Dis. 2019;16:1479973119882939. doi:10.1177/1479973119882939

Appendix 5. Curriculum vitae

Marilena Anastasaki (Crete, 1989) graduated from the Department of Mathematics (BSc) of the National and Kapodistrian University of Athens in 2012 and received her Master degree in Biostatistics (MSc) by the same University in 2015. Ever since she has been working as research associate of the Clinic of Social and Family Medicine (CSFM) of the School of Medicine at the University of Crete, starting her PhD in 2018. Her fields of interest are Public Health and Epidemiology, with particular focus on non-communicable diseases, socioeconomic determinants of health, behavioural change, implementation science, community empowerment, professional training and integrated care. Marilena has worked as main researcher in more than 10 international collaborative programmes (four Horizon2020) and in an equal number of locally funded projects. She has also received a Stipendium research scholarship from the Faculty of Medicine, Linkoping University, Sweden and is collaborating with the University of Crete Research Center for Humanities, Social and Education Sciences as a researcher of CSFM's affiliated Health Promotion Unit. Marilena is involved in the teaching of the courses of Research Methodology and Epidemiology in the Master of 'Public Health -Primary Health Care - Healthcare Services' of the University of Crete and in the Master of 'Community Heath Care' of Frederick University, Cyprus. Marilena received an Academic Fellowship for her teaching work by the School of Medicine of the University of Crete in 2021. She has co-authored 26 peer-reviewed publications and has participated as a speaker in more than 20 international conferences. She is an assistant editor in the journal of Rural and Remote Health and a member of three scientific societies. Marilena speaks English fluently and is an advanced user of statistical software, including SPSS and STATA.

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