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DESARROLLO DE UN PROGRAMA DE ESTUDIO DE CASOS DE ENFERMEDAD PULMONAR OBSTRUCTIVA CRÓNICA EN USUARIOS DE FARMACIA DE ALTO RIESGO

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La Dra. Mercedes Mayos Pérez, profesora asociada del departamento de Medicina de la Universitat Autònoma de Barcelona y el Dr. Pere Casan Clarà, catedrático de la facultad de Medicina de la Universidad de Oviedo,

CERTIFICAN:

Que la tesis doctoral titulada: DESARROLLO DE UN PROGRAMA DE ESTUDIO DE CASOS DE ENFERMEDAD PULMONAR OBSTRUCTIVA CRÓNICA EN USUARIOS DE FARMACIA DE ALTO RIESGO, presentada por Diego M. Castillo Villegas para optar al grado de Doctor en Medicina, ha sido realizada bajo su dirección y consideran que reúne los requisitos formales y científicos para proceder a su lectura y defensa pública.

Firmas,

Dra. Mercedes Mayos Perez **Dr. Pere Casan Clará** **Dr. Diego M. Castillo Villegas**

Toco esta mano al fin que comparte mi vida
y en ella me confirmo
y tiento cuanto amo,
lo levanto hacia el cielo
y aunque sea ceniza lo proclamo: ceniza.
Aunque sea ceniza cuanto tengo hasta ahora,
cuanto se me ha tendido a modo de esperanza.

José Ángel Valente

AGRADECIMIENTOS

A la manos que tiento cada día... *mi ceniza*,

a las manos amigas que siempre me sujetaron con fuerza,

a las manos sabias que guiaron esta tesis,

a las manos que alzan las copas en las noches del Barcino,

a las manos que realizaron todas estas espirometrías,

a las manos de los enfermos, para que tienten y encuentren...

… a modo de esperanza...

PRÓLOGO

La presente tesis doctoral forma parte de un proyecto que nació en laboratorio de función pulmonar del Hospital de la Santa Creu i Sant Pau bajo la dirección del Dr. Pere Casan y posteriormente la Dra. Mercedes Mayos. El objetivo era explorar nuevas estrategias diagnósticas para reducir el infradiagnóstico de la Enfermedad Pulmonar Obstructiva Crónica (EPOC). En concreto, el desarrollo de un programa pionero a nivel mundial de estudio de casos en usuarios de alto riesgo de farmacias comunitarias. Por ello el proyecto fue bautizado como "FARMAEPOC".

El proyecto estuvo vinculado desde sus inicios a las líneas de investigación del departamento de Medicina de la Universitat Autònoma de Barcelona con el objetivo de que el presente doctorando pudiera completar los estudios de doctorado. De hecho la primera fase del proyecto FARMAEPOC, el denominado "estudio piloto", fundamentó su suficiencia investigadora (anexo 1). En la introducción se han resumido los principales hallazgos del mismo dado que este estudio fue la base metodológica de las investigaciones posteriores, tanto nuestro grupo como de otros.

Los resultados del presente trabajo han sido publicados en las siguientes revistas científicas (anexos 2-3):

- **Castillo D**, Burgos F, Guayta R, Giner J, Lozano P, Estrada M, et al. Airflow limitation case finding in community-pharmacies: a novel strategy to reduce COPD underdiagnosis. Respir Med. 2015;109:475-482 (IP: 3,086).

- **Castillo D**, Burgos F, Gascon P. El papel de la farmacia comunitaria en el manejo de las enfermedades respiratorias crónicas. Arch Bronconeumol 2015;51:429-430. (IP: 1,83)

Los artículos han sido anexados a esta tesis doctoral con la previa autorización del editor correspondiente.

Por otro lado es importante mencionar también que una de las virtudes de este proyecto consistió en unir a diversos agentes de diferentes niveles asistenciales, todos ellos implicados en el manejo de la EPOC. La lista de entidades participantes en FARMAEPOC fue la siguiente:

- Servicio de Neumología.Hospital de la Santa Creu i Sant Pau. Barcelona
- Centro de diagnóstico respiratorio. Hospital Clinic. Barcelona.
- Fundació Caubet-Cimera. Bunyola. Illes Balears.
- Col·legi Oficial de Farmacèutics de Barcelona. Barcelona.
- Consell Catalá de Col·legis de Farmacèutics. Barcelona.
- Boehringer-Ingelheim. Sant Cugat del Valles. Barcelona.
- SonMedica S.A. Barcelona.
- Ndd Medical Technologies. Swiitzerland.
- Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Proyectos de investigación integrada (PII EPOC).
- Societat Catalana de Metges d'Atenció Primaria i Familiar (CAMFIC).

El comité científico estuvo compuesto por:

- Hospital Sant Creu i Sant Pau (Barcelona): D. Castillo, J. Giner, M. Mayos, M. Torrejon.
- Hospital Clinic i Provincial (Barcelona): F. Burgos, Y Torralba, A. Orquin.
- Hospital Universitario Central de Asturias (Oviedo, Asturias): P. Casan.
- Fundació Caubet-CIMERA (Illes Balears): J.B. Soriano.
- Col·legi Oficial Farmacèutics Barcelona (Barcelona): P. Lozano, M. Estrada, M. Barau, C. Capdevilla, Cristina Rodríguez-Caba.
- Consell Catala de Col·legis de Farmacèutics (Barcelona): R. Guayta.
- Boehringer-Ingelheim (Barcelona): E. Mas, E. Gobartt, X. Ribera.
- Son-Médica S.A. (Barcelona): J.M. Vázquez, A. Sanchez-Nieva.
- ndd Medical Technologies (Swiitzerland): J. Anderauer.
- Societat Catalana de Medicina Familiar i Comunitaria (CAMFIC) (Barcelona): X. Flor, J. Lozano.

Los estudios de esta tesis recibieron las siguientes subvenciones económicas:

- Sociedad Española de Neumología y Cirugía Torácica (SEPAR): Beca Ayuda Investigación SEPAR obtenida en la convocatoria 2008 con una duración de 3 años para el proyecto de investigación “Programa de estudio de casos de EPOC en farmacias mediante espirometría”. (IP: Diego M. Castillo Villegas).
- Boehringer-Ingelheim

Es importante clarificar que ninguno de ellos tuvo parte en la recogida, manejo, análisis o interpretación de los datos. Ni tampoco en la redacción, revisión o presentación de esta tesis doctoral.

Por último mencionar también que los resultados de este trabajo fueron presentados en los siguientes congresos nacionales e internacionales:

- **D. Castillo**, F. Burgos, J. Giner, M. Estrada , JB Soriano, X. Flor, et al. Cribado de EPOC: nuevas herramientas y circuitos sanitarios. Resultados preliminares del FARMAEPOC 2. Congreso SEPAR. Oviedo. 2011
- F. Burgos, B. Galdiz, C. Gallego, M. Vallverdú, P. Caminal, **D. Castillo**, et al. Novel strategies for quality control of forced spirometry. ERS Conference. Amsterdam. 2011
- F. Burgos, M. Vallverdu, B. Galdiz, C. Gallego, **D. Castillo**, J. Ayza, et al. High quality spirometry across the healthcare system. ATS Conference. Denver. 2011
- F. Burgos, B. Galdiz, **D. Castillo**, M. Vallverdú, J. Giner, C. Gallego, et al. Espirometría de calidad en el sistema sanitario. Congreso SEPAR. Madrid. 2012.
- M Barau; **D Castillo**; R Guayta-Escolies; F Burgos; J Giner; M Estrada-Campmany, et al. Cribado oportunista y manejo de EPOC en farmacias comunitarias en el marco de la estrategia GOLD (Global Initiative for Chronic Obstructive Lung Disease). Proyecto FarmaEpoc. Congreso SEFAC. Bilbao. 2013

Haber tenido la oportunidad de trabajar en un proyecto de estas características me ha permitido "saborear" el placer del trabajo multidisciplinar. A día de hoy hay demasiadas barreras entre farmacéuticos, atención primaria y atención especializada. Ojalá los ecos del proyecto FARMAEPOC sirvan para romper esas barreras ("caminando juntos, caminando más lejos ").

DEVELOPMENT OF A COPD CASE FINDING PROGRAM IN HIGH RISK CUSTOMERS OF COMMUNITY-PHARMACIES

TABLE OF CONTENTS

ABREVIATIONS

ACQ:	Asthma control questionnaire
ATS:	American Thoracic Society
BMI:	Body mass index
COFB:	Col·legi Oficial de Farmacèutics de Barcelona
COPD:	Chronic Obstructive Pulmonary Disease
DALY:	Disability-adjusted lost years
ERS:	European Respiratory Society
FEV_1:	Forced exhale volume in 1 second
FEV_6:	Forced exhale volume in 6 seconds
FVC:	Forced vital capacity
GB:	Great Britain
GP:	General Practitioner
HSE:	Health and Safety Executive
IIDB:	Industrial Injuries Disablement Benefit
NIOSH:	National institute of occupational safety and health
NND:	Number needed-to-screen
LLN:	Lower Limit of normality
PC:	Primary care
PEF:	Peak expiratory flow
pMDIs:	pressurized metered dose inhalers

GOLD: Global Initiative of Chronic Obstructive Lung Disease

SEPAR: Sociedad Española de Neumología y Cirugía Torácica

SEFAC: Sociedad Española de Farmacia Comunitaria

SPSS: Statistical Package for Social Sciences

THOR-SWORD: The Health and Occupation Research Network- Surveillance of work related and occupational respiratory disease.

USA: United States of America

YLD: Years lived with disease

WHO: World Health Organization

INTRODUCTION

Chronic Pulmonary Obstructive Disease

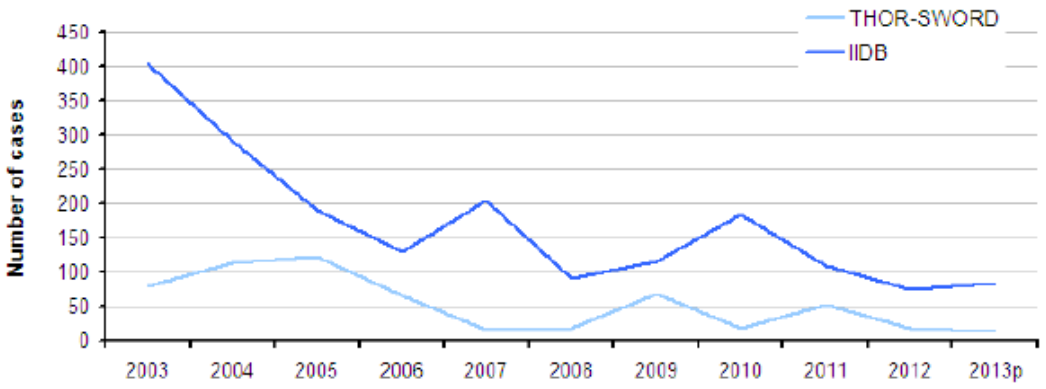
Definition

The Global Initiative for Obstructive Lung Disease (GOLD) defines Chronic Pulmonary Obstructive Disease (COPD) as "a common, preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases" (1). This definition is similar to the one from the Spanish or European Respiratory Society COPD guidelines (2, 3).

Smoking is the most frequent exposure related to COPD but there are several other exposures that can also increase the risk of suffering COPD as biomass fumes or working related (4).

Indeed, the Health and Safety Executive (HSE) report estimated in 2014 that in Great Britain (GB) around 15% of COPD cases are work-related (5). Based in the numbers of cases reported, there could be around 4.000 occupational COPD deaths currently each year in GB (**figure 1**).

Figure 1: Chronic bronchitis and emphysema in Great Britain, 2003-2013



THOR-SWORD: The Health and Occupation Research Network- Surveillance of work-related and occupational respiratory disease

IIDB: Industrial Injuries Disablement Benefit

Classification

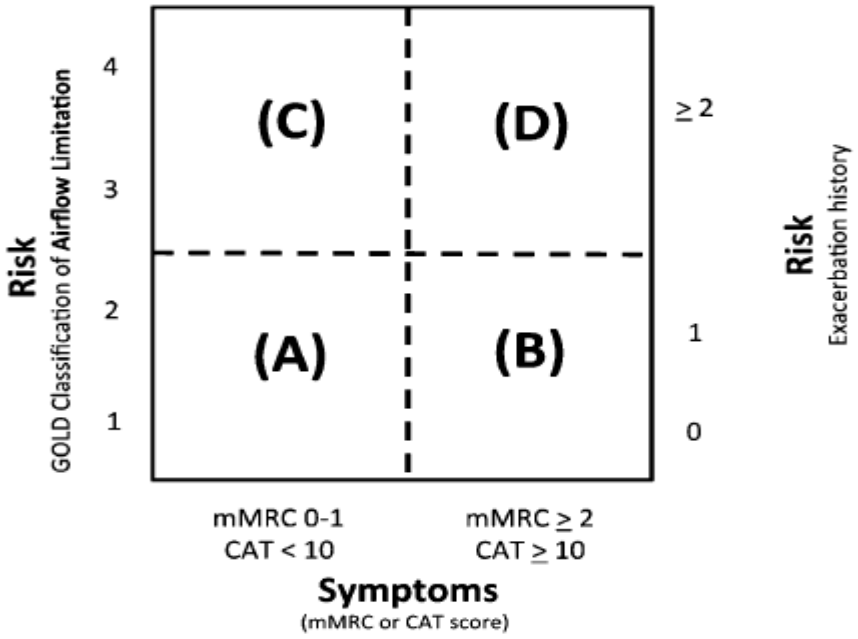
Lung function values and particularly forced exhale volume in 1 second (FEV_1) has been used classically to classify COPD. However, there was no consensus between guidelines. The GOLD proposes the following classification (**table 1**) (1):

Table 1. GRADING OF SEVERITY OF AIRFLOW LIMITATION IN COPD (BASED ON POST-BRONCHODILATOR FEV_1)

COPD severity	FEV_1/FVC %	FEV_1 (%)
Mild	< 70	≥ 80
Moderate	< 70	50–79
Severe	< 70	30-49
Very severe	< 70	< 30

But there are other factors aside lung function that impact in the disease evolution. The most recent guidelines have incorporated these domains to cover the full spectrum of COPD. For example, the GOLD guideline from 2013 has introduced exacerbations and symptoms to staging COPD. Patients are classified based on lung function capacity, number of exacerbations and intensity of symptoms (measured by the modified Medical Research Council (mMRC) dyspnea scale and the COPD assessment test (CAT)) (**figure 2**) (1).

Figure 2. COMBINED COPD ASSESMENT. GOLD 2013 GUIDELINES



Prevalence

COPD is a leading chronic disease. It is now estimated there are at least 328 million people with COPD in the World (6). In 2000, the "IBERPOC" study estimated that the prevalence of COPD in Spain was 9,1% (7). Later, *Miratvilles et al.* found three factors related with COPD prevalence in Spain: age, tobacco consumption and lower educational levels (8).

In 2000, the "Confronting COPD International Survey" studied the impact of COPD in the United States of America (USA) and six European countries (United Kingdom, Spain, Netherlands, Italy, France and Germany) (9) (**table 2**).

Table 2. Confronting COPD International

	TOTAL	USA	CAN	FRA	GER	ITA	NET	SPA	UK
Sample: n	3265	447	401	400	400	400	415	402	400
Age (%)									
45 - 54 years	25	22	28	34	31	23	31	21	23
55 – 64 years	29	29	29	26	32	24	31	22	35
65 - 74 years	29	30	25	25	22	35	25	34	27
≥ 75 years	18	19	18	16	14	18	13	24	15
Gender (M/F)	56/64	45/55	49/51	70/30	63/37	69/31	54/46	77/23	49/51
COPD/Emphysema diagnosis by GP (%)	49	69	45	33	29	45	42	30	39
Breathlessnees (%)	54	70	51	41	43	35	51	22	67
Hospitalizations (%)	15	20	16	11	10	11	18	14	11
Hospitalizations last year (%)	13	14	14	11	8	11	9	20	14
Emergency care last year (%)	29	38	30	27	15	16	21	29	33
Spirometry (%)	79	87	77	70	83	55	80	76	79
High satisfaction with COPD management (%)	83	86	85	82	83	73	90	81	83

USA: United States of America, CAN: Canada, FRA: France, GER: Germany, ITA: Italy, NET: Netherlands, SPA: Spain, UK: United Kingdom,

Prevalence of COPD was similar across countries. An update was published in 2014. The "Continuing to Confront COPD International Patient Survey" aimed to estimate the prevalence of COPD globally, and included twelve countries (10). Again, the prevalence of COPD was not significantly different between countries, ranging from 7 to 12%. A small rise in COPD prevalence was detected compared to the previous study.

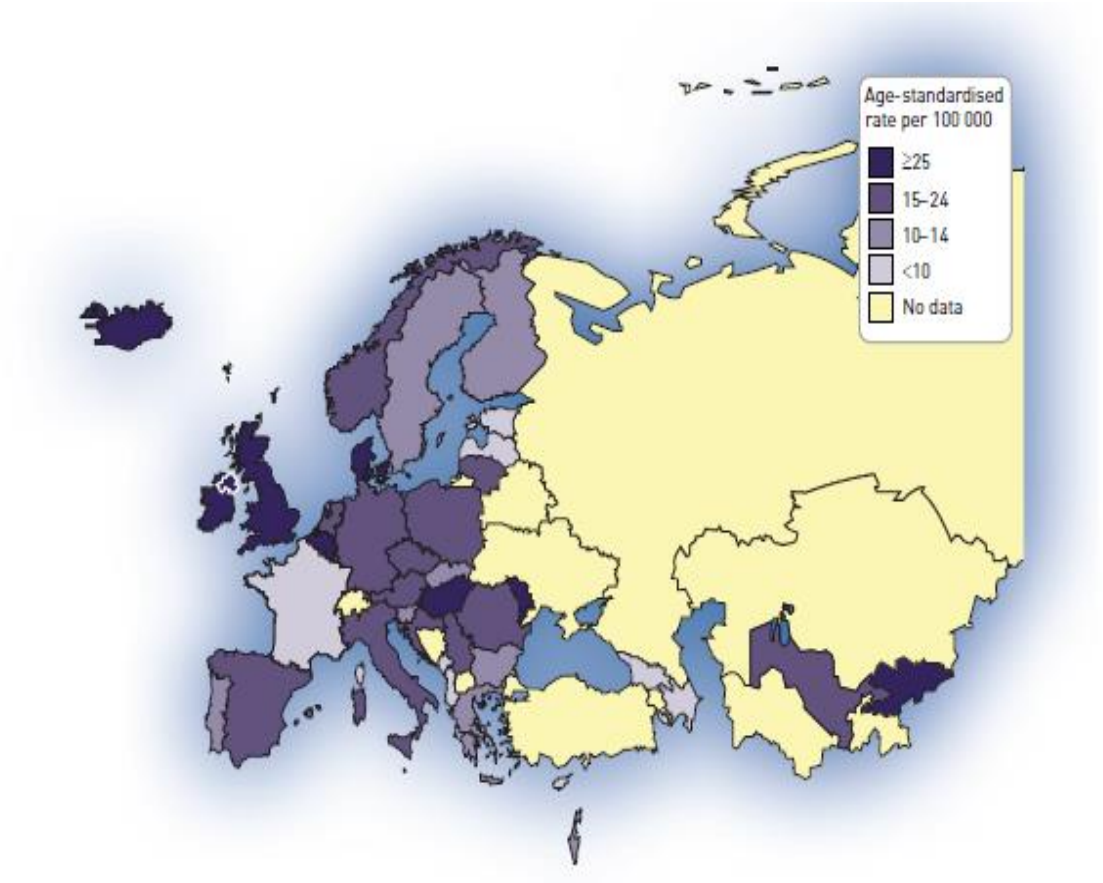
Morbility and mortality

COPD could progress significantly in some patients causing respiratory insufficiency and death. By 2020, is projected to be the third leading cause of death (11-14).

Overall, the COPD mortality rate for men and women in Europe, age-standardised to the European Standard Population, is about 18 per 100.000 inhabitants per year, based in the mortality data provided to the World Health Organization (WHO) and European Mortality Database (update 2011) (**figure 3**) (15).

However, as *Represas et al.* highlighted in a recent editorial published in *Archivos de Bronconeumología*, studies from cohorts in Europe and North America showed that there is a reduction in mortality related to COPD in those countries (16-19). Indeed, *Lopez Campos et al.* evaluation of mortality trends for COPD in 27 European countries between 1994-2010 confirmed a persistent decrease in mortality, especially within men.

Figure 3. Mortality rate for COPD across Europe.



Also COPD has a significant impact in patients' quality of life (8): 6,3% of total years lived with disease (YLD) worldwide are due to chronic lung diseases (20). COPD is the main contributor with 29,4 million YLD. Regarding disability-adjusted lost years (DALY), chronic lung diseases represents a 4,7% of total (6).

Costs

In Spain, in 1997 the estimated annual cost of COPD was 238,82 million (in Euros) (21). But later, as stated in the COPD national program, the National Health Service budget for COPD was estimated in 750-1000 million euros per year (22) Average pharmacological treatment costs in Spain was between 1.218 and 1.314 euros per patient per year (23). This means that COPD consumed a significant proportion of the National Health budget. But this could be even higher in future years (24).

Diagnosis

Spirometry is the cornerstone of COPD diagnosis because is the gold standard to measure airway limitation (25). However, it is important to point out that there is not a consensus about the definition of airway limitation. Although it's a serious matter; as *Celli et al.* showed, the definition used could result in variation in COPD prevalence (26). Currently, there is a debate regarding the use of a fix ratio (forced exhale volume in 1 second /forced volume capacity (FEV_1/FVC) lower than 0,7) or Lower Limit of Normality (LLN) (27, 28).

Nevertheless, spirometry alone is not enough: exposures, symptoms plus medical examination among other tests are needed to establish the diagnosis. Besides, other chronic obstructive respiratory diseases, like asthma or bronchiectasis, shall be ruled out.

Management

COPD management includes avoiding risk exposures, healthy life style habits (including regular exercise), vaccination (Influenza and Pneumococae) and pharmacological therapy (mainly bronchodilators in inhaled therapy) (29).

COPD clinical behavior is characterized by acute exacerbation episodes. These are commonly triggered by an infection (viral or bacterial) or pollution. COPD exacerbations have impact in the disease's progression and mortality. *Soler-Cataluña et al.* COPD cohort data showed that severe exacerbations have an independent negative impact on patient prognosis (30). Therefore, early treatment of these episodes is needed. Usually, optimizing the inhaled therapy plus oral steroids and/or antibiotics is required (31).

Value of early diagnosis

In the last years there has been a debate regarding early diagnosis in COPD. As *Decramer et al.* stated recently "early stage COPD carries a significant healthcare burden that is currently underrecognised, underdiagnosed and undertreated" (32). Even patients with undiagnosed mild COPD have impairment in quality of life (8).

However, early COPD diagnosis was initially interpreted as "a relatively fruitless effort", since treatments other than smoking-cessation efforts were unlikely to alter its course (33, 34).

But nowadays it is accepted that early diagnosis can impact in the four components of COPD management, as defined by GOLD ((1, 35-37)):

1) Disease's assessment and monitoring.

2) Risk factors exposures.

3) Stable disease management -through education and nonpharmacologic and pharmacologic treatments;

4) Management of exacerbations.

Because:

1. Patients with a known diagnosis are more likely to quit smoking, which is the main risk exposure (38). Specially, when their lung age is calculated based on forced spirometry results (39).
2. Patients with underdiagnosed COPD have usually symptoms and repeat exacerbations deteriorating their quality of life and disease evolution (8, 40).
3. Diagnosed patients could access to different treatments (pharmacological and non-pharmacological) that could avoid progression of their disease and improve their quality of life (1, 32, 36).
4. Recent studies suggested pharmacological therapies could be more effective in early disease´s stages (41, 42).

But early diagnosis is even more valuable in younger adults after the data published by *Lange et al.* in the *New England Journal of Medicine* (43). Until now, the prevailing paradigm of COPD pathogenesis was related with a decline in lung function in susceptible persons exposed to know risk factors (mainly tobacco smoke) (44). However, *Lange et al.* results point out that this paradigm is not an obligate feature of COPD and that a substantial proportion of COPD patients have a low FEV_1 level in early adulthood. So, this data support that is very important to know the lung function capacity in young adults in order to stablish the risk of developing lung diseases, especially if they have risk factors.

Underdiagnosis

Current problems

Although COPD is a prevalent disease, remains highly underdiagnosed. For example, the "IBERPOC" study showed that there was a lack of diagnosis in 78% of the patients with COPD (7). These results are similar to other published in Europe. In Poland, *Bednarek et al.* showed that in a primary care population only 18,6% of the COPD patients had previously been diagnosed.

Several reasons have been proposed to explain COPD underdiagnosis in Spain:

1. The lack of knowledge about COPD among general population. As a result, many individuals with respiratory symptoms do no request medical attention (45).

2. The attitude among general physicians has also been criticized, as they mainly consider a COPD diagnosis in men with severe disease (46). Furthermore, significant geographical variations have been observed in Spain regarding management and diagnosis of COPD (47).In Australia, *Walters et al.* identified a high rate of misclassification of COPD in primary care and therefore considerable inappropriate use of respiratory medications (48). That happened because general practitioners were relying in symptoms to do the diagnosis and spirometry was lack. Then, as *Soler et al.* suggested, the dissemination of the Spanish Respiratory Society (SEPAR) guidelines may improve management of COPD in primary care (49).

3. By contrast, the access of primary care physicians to quality forced spirometry has being pointed out as the main factor for COPD underdiagnosis (50, 51). A study by *Naveran et al.* published in 2006 identified that there was a very limited availability of spirometers in primary health centers in Spain. There was also a lack in spirometry technique training (52). Even when a spirometer was available, in 2006 *Hueto et al.* showed than in primary health centers in Navarra it was underused. Furthermore, there was little compliance with guidelines and the quality of the measurements was very low (53). This problem is not related only to Spain. In a Dutch study, only 38,8% of the spirometries done in a primary care setting met the acceptability as well as reproducibility criteria (54).

Quality of spirometry

As we mentioned previously, spirometry is the key diagnostic test in COPD. In this context, a policy of improving quality spirometry availability in primary care was developed by local and national health authorities (22).

One developing area was improving the numbers of primary care offices with spirometer. In 2011, the situation was not much different based on *Monteagudo et al.* results (55). However, a vast study about spirometry in Spain, published in 2013 by *Lopez-Campos et al* showed that only 19% of the screened primary or secondary care centers did not have a spirometer or were not using it (56). Inter-regional variability in performance and interpretation of spirometry was still observed (57).

Quality was the second developing area. Quality in spirometry is a feasible goal (58). But requires continuing education (59-61). Although we need to remember that around 15% of spirometries would not fulfil the quality criteria even in expert referral centers, in-house education significantly reduce spirometry errors (62, 63). A small study by *Carr et al.* indicates that a simple educational intervention is able to reduce referrals up to 50% as a consequence of less misdiagnosis (62).

Recently, telemedicine has appeared as a breakthrough factor to improve forced spirometry quality in primary care. *Burgos et al.* showed that using a web-based remote support platform forced spirometry quality was improved from 59,9% to 71,5% in a randomised clinical trial in 12 primary care offices in Spain (64). Later *Marina et al.* evaluated the cost-effectiveness of telespirometry in 51 primary care centers (65). The analysis concludes that telespirometry increased cost in 23% but was 46% more

effective. Avoiding poor quality spirometries generates savings that compensate for the increased costs of performing telespirometry.

Finding solutions

Therefore, as several experts have highlighted in recent editorials, improving diagnosis is key to improve COPD management (33, 36, 66). COPD strategies developed by National Health Departments have included early COPD diagnosis as a primary objective (22, 67). This has been translated in several programs over the past years. Unfortunately, this has improved COPD management but as *Soriano et al.* showed in a recent study it has not been successful in reducing underdiagnosis. The study evaluates the evolution of COPD management in Spain between 1997-2007. The percentage of COPD underdiagnosis in Spain, compared to the "IBERPOC" data, has only being reduced to 73% (5%) in 10 years (68). That means that the whole COPD diagnosis strategy should be revaluated because this could not be only limited to the spread of quality spirometry. There are other questions to be review, as when, how and where physicians diagnose COPD.

When?

After a thoughtful debate, case finding in primary care using forced spirometry is the most support strategy for COPD screening (69).

Screening general population for COPD has never been proposed as a useful strategy. Value spirometry requires good quality technique and proper interpretation

of the results, which are difficult to secure in population screening programs, where spirometry should be performed out doctor´s office. If spirometry is not used properly misdiagnosis could be increased. Besides it is not known the benefit of detecting a subject without risk factors or symptoms but with spirometric findings of airway limitation. Then it has been proposed that forced spirometry is used in high-risk populations as a case finding rather than a screening tool (70).

Zielinski et al. explored in Poland the option of screening high-risk COPD population through mass media advertisement using spirometry (71, 72). High-risk subjects were encouraged to contact one of the 12 participating centers to attend for a spirometry. The impressive data of eleven thousand twenty-seven subjects was achieved. Of whom 24,3% had spirometric evidence of airway limitation. Therefore, mass spirometry in high-risk subjects was proposed as an effective method for early detection of COPD. *Maio et al.* explored an opportunistic approach with the European Respiratory Society (ERS) tent. The results highlighted the usefulness of detecting airway obstruction in large numbers of city residents during large awareness initiatives (73).

By contrast, *Van Schayck et al.* investigated the effectiveness of case finding program in general practise (74). Their results showed that by testing one smoker a day, an average practice could identify one patient at risk a week with little cost to the practice. *Jordan et al.* studied an active approach to case finding rather than opportunistic. The systematic case-finding strategy can potentially identify 70% more new cases than opportunistic identification alone (75). In Greece, *Konstantikaki et al.* results were similar (76). The numberneeded-to-screen (NNS) for a new diagnosis of

COPD was 3.6 in the case-finding programme compared to 11.9 in the open spirometry programme. Furthermore the average cost for a new diagnosis of COPD was 173 euros in the open spirometry programme and 102 euros in the case-finding programme.

In conclusion, case finding is accepted as the adequate strategy in COPD early diagnosis programs but together with an active approach rather than opportunistic. This supports that every primary care center should develop a COPD case finding program.

How?

But, certainly, spirometry is a complex technique. That's why others tools, simpler and cheaper, has been proposed for COPD case finding. But, in any case, these tools could be used as a case-finding test prior to referral for diagnostic spirometry in order to confirm or refute a diagnosis of COPD (77). Alternatives like a functional model has been proposed as a surrogate of spirometry (78). But especially three have been proposed as useful:

- Microspirometry:

In 2000, *Swanney et al.* suggested that forced exhale volume in 6 seconds (FEV_6) was an acceptable surrogate for forced volume capacity (FVC) in detecting airway limitation using forced spirometry (79). FEV_6 manoeuvres are less physically demanding and more reproducible than FVC. Indeed, when *Perez-Padilla et al.* analysed the reliability of FEV_1/FEV_6 versus FEV_1/FVC for the detection of airway obstruction in the "PLATINO" study, they found the former

more reliable (80). In elderly population, the use of the FEV_1/FEV_6 ratio has been helpful to avoid strenuous manoeuvres in frail patients (81).

Later studies have supported the use in primary care of FEV_6 for COPD screening purposes in high-risk populations. *Vandevoorde et al.* analysed 11.616 spirometric examinations for diagnosis of airway limitation. The FEV_1/FEV_6 ratio sensitivity was 94% and specificity 93,1% (82). *Akpinar-Elci et al.* also proposed the use of FEV_6 at workplace. He found that interpretations (airway limitation or restriction) based on the FEV_6 had a high agreement rate with those based of the FVC ((Kappa 50.90; p,0.001) in a worker population (83).

A benefit of the FEV_1/FEV_6 ratio is the possibility of using simpler devices. The PIKo-6© is an expiratory flow meter that can measure the FEV_1/FEV_6 ratio. In theory, that would simplify the technique and help in the spreading of case finding. Two studies have showed that PIKo-6© has good sensitivity and specificity to detect airway limitation (84). But not enough to avoid referring a significant amount of subjects to a forced spirometry to confirm the diagnosis. In conclusion, FEV_1/FEV_6 ratio is an alternative that deserves further studies in COPD case finding but still is not back by current guidelines.

- Peak expiratory flow:

The same statement can be applied to peak expiratory flow (PEF). *Jithoo et al.* studied PEF as an initial COPD screening tool. For moderate/severe COPD only 19-22% (83-84% sensitivity) needed confirmatory spirometry and less than 9% for severe COPD (sensitivity 91-93%) (85). But other studies have shown significant weakness. *Nelson et al*. found that only 63,1% subjects with abnormal

PEF has a confirmed spirometry with airflow limitation. However, as is a cheap and fast tool, the roll of PEF in COPD case finding should be studied further (86).

- Questionnaires:

The following instrument to be considered is COPD questionnaires. Through a few questions we could be able to select high risk subjects, that later should be formally diagnosed. Studies have failed to demonstrate that COPD questionnaires alone can diagnose properly subjects with airway limitation (87). Symptoms could be not enough to confirm moderate/severe patients (88). Then questionnaires are always part of a 2-step case finding approach in which the questionnaire helps to determinate which subjects shall we tested (86, 89, 90). Indeed, this approach has been proposed as the most useful to increase the yield of a COPD screening program (91).

In conclusion, although forced spirometry remains as gold standard for airway limitation detection and diagnosis, other easier and faster tools could be incorporated to case finding programs in order to select patients to whom spirometry should be done later to confirm the diagnosis (92).

Where?

Primary care has been pointed out as the main place to develop COPD case finding initiatives (50, 69, 93). Primary care physicians are the leaders of preventive programs, including respiratory diseases. Primary care physicians are most often the

first point of contact, and therefore they are in the best position to identify patients at risk of COPD in early stages (37). They have regular access to "healthy" subjects in whom modifying their daily-life habits (like smoking) could have an impact in their long-term survival. But, as we highlighted previously, COPD underdiagnosis in primary care setting continues to be inordinately common (94). As *Jones et al.* indicates, there are several opportunities to diagnose COPD in the years leading up to diagnosis (95). Their retrospective analyses of a Primary Care Data Base in the United Kingdom found an increase in consultations for lower respiratory symptoms, antibiotic and oral steroid prescriptions in the years preceding the diagnosis.

Secondary/tertiary care should be also involved in COPD case finding. Many patients attending a hospital with possible COPD are not investigated. For example, a Chinese study showed that many smokers with lung cancer are not investigated for COPD (96, 97). COPD exacerbations frequently end with the patient attending an emergency room. Therefore this could be an ideal place to start COPD case finding but sometimes these patients are not correctly diagnosed after their consultation or even after a COPD exacerbation hospitalization (98, 99). Besides, patients with COPD have several comorbidities like heart failure or diabetes (100, 101). Then we should encourage our colleagues from other specialties to seek for a COPD diagnosis in subjects in high risk.

In summary, both, primary and secondary care are appropriates settings to develop effective COPD case programs.

However other options are needed in order to improve early detection, as subjects are often underestimating their symptoms and subsequently not attending

their primary care center looking for advice (102). Patients with mild chronic symptoms or exacerbations will otherwise seek for advice in community-pharmacy or store-front clinics, where they could be investigated for COPD. Spirometry tents or even municipal health departments have been proposed also as suitable places (73, 103-105). But there are anecdotic data published about these options.

However, considering the high amount of community-pharmacies available in our country and their experience in preventive programs, it seems that this option deserves further research.

Community-pharmacy

Introduction

The services provided by community-pharmacy are regulated in Spain under the law 16/1997 that define community-pharmacy as "*private health facilities in the public interest, subject to health planning established by the regional authorities, in which the holder Pharmacist-owner thereof shall provide basic services to the population*" (106).

These services include:

- Collaborative programs promoted by the health authorities on quality assurance of pharmaceutical care and health care in general.
- Promotion and protection of health through disease prevention and health education.

Therefore drug counselling is not the only task of community-pharmacists but the main. Indeed, several statement documents stablish that the future of community-pharmacy is aimed at the implementation of professional services that assume a more active involvement in the health living of each patient (107, 108). That could be the case with COPD.

Healthy Living Pharmacy

"Healthy Living Pharmacy" (HLP) is an emerging concept referred to the potential of community-pharmacy to promote healthy living (109). Community-pharmacy can play an important role in a number of health-promoting programs, including smoking cessation, cardiovascular diseases or screening for major disease. So healthy living is a goal of community-pharmacies, and not only drug counselling.

In Spain, the professional associations are backing new services to extend their role in promoting healthy living. The professional association of Barcelona has been leading these novel programs in Spain. The most successful example is the Colorectal cancer screening service that is currently running (110). Using a simple test, fecal hemoglobin test, working in coordination with referral centers, this program has been able to test thousands of subjects in Barcelona. Indeed, the service is currently funded by the Catalan Health Service. A similar approach, but in HIV, has been developed in the Basque Country. Using a new rapid HIV antibody screening test community-pharmacies could supplement the current screening services with success (111).

So if community-pharmacy services are successful in other diseases, why not in respiratory conditions?

Community pharmacies and respiratory diseases

The relation between community-pharmacy and respiratory diseases has been focused mainly in three areas: early diagnosis, smoking cessation and ambulatory management.

The service that has been largely studied is the value of smoking cessation programs in community-pharmacy (112-114). *Saba et al.* meta-analysis of the effectiveness of smoking cessation interventions in community-pharmacy showed an increase in abstinence relative ratio of 2,21 in the intervention group compared to the control (115). His analysis includes patients from two randomized controlled trials. He concluded that smoking cessation programs in community-pharmacy can significantly impact abstinence rates.

There are also several studies on roll of community-pharmacy in the ambulatory management of respiratory diseases, mainly COPD and asthma. The first and larger randomized controlled trial was focused in pharmacist care for both (116). The results were somehow frustrating. Patients included in the pharmaceutical care program had small benefits compared with peak flow monitoring alone. Besides, pharmaceutical care increased patient satisfaction but also increased the amount of breathing-related medical care sought.

Later studies had more positive results. *Armour CL et al.* investigated, in a randomized trial, the effectiveness of an asthma service in Australian community-pharmacy (117). Asthma control, including asthma control questionnaire (ACQ), and others parameters like quality of life, adherence, perceived control and asthma

knowledge significantly improved in the intervention group. *Ottenbros S et al.* measured the impact of pharmacist intervention to improve drug therapy in asthma and COPD patients (118). The intervention group showed a decreased in number of prescriptions (antibiotics and steroids) as a result of less exacerbations. In Belgium, *Tommelein et al.* pharmacy care intervention in COPD patients had similar results (119). These findings are consistent with previous data from *Vestbo et al.* that found an association in COPD between adherence to inhaled medication and a reduced risk of death and admission to hospital due to exacerbations (120). Finally, *Wright et al.* estimated that a COPD support service in community-pharmacy was cost-effective due to reductions in the use of primary care services (121).

Recently, *Beck et al.* proposed a "pharmacy-level asthma medication ratio" as a useful tool to detect asthma patients with higher morbidity (122). Using this ratio, community-pharmacists would be able to detect subjects with poor control and referred them to primary care.

Case finding in community-pharmacy

Less is known about the role of community-pharmacy in the early diagnosis of chronic respiratory diseases. *Ayorinde et al.* reviewed in 2013 the available evidence about screening for some major diseases in community-pharmacy. His conclusion was that this is a feasible option (123). In fact community-pharmacists, as we mention earlier, are helping with the early diagnosis of various diseases, like colon cancer or HIV (110, 111). It is important to highlight that the authors pointed out that more studies

are needed to compare pharmacy-based screening programs with screening by others providers.

Regarding respiratory diseases, there were scare studies when this thesis was designed. *Mapel et al.* proposed an algorithm based on pharmacy data utilization to identify people at risk of COPD (124). *Burton et al.* explored the use of spirometry in community-pharmacies in Australia (125). But, to our knowledge, there were no other significant experiences published. Even less focus in COPD case finding.

In this context, we decided to investigate if community-pharmacies could potentially help in early diagnosis of COPD. As a first-step, we planned a pilot-study to secure the feasibility of this idea.

Pilot-study

Introduction

The study was approved by the ethics committee of Hospital Clinic i Provincial, Barcelona.

To recruit pharmacist participants, we contacted community-pharmacy in a smoking prevention group formed through the professional association for this sector (Col·legi Oficial de Farmacèutics de Barcelona (COFB)) in Barcelona, Spain. Thirteen of the 19 members of the smoking prevention group accepted, agreeing that a staff pharmacist would attend a four-day spirometry training course in February and March 2007.

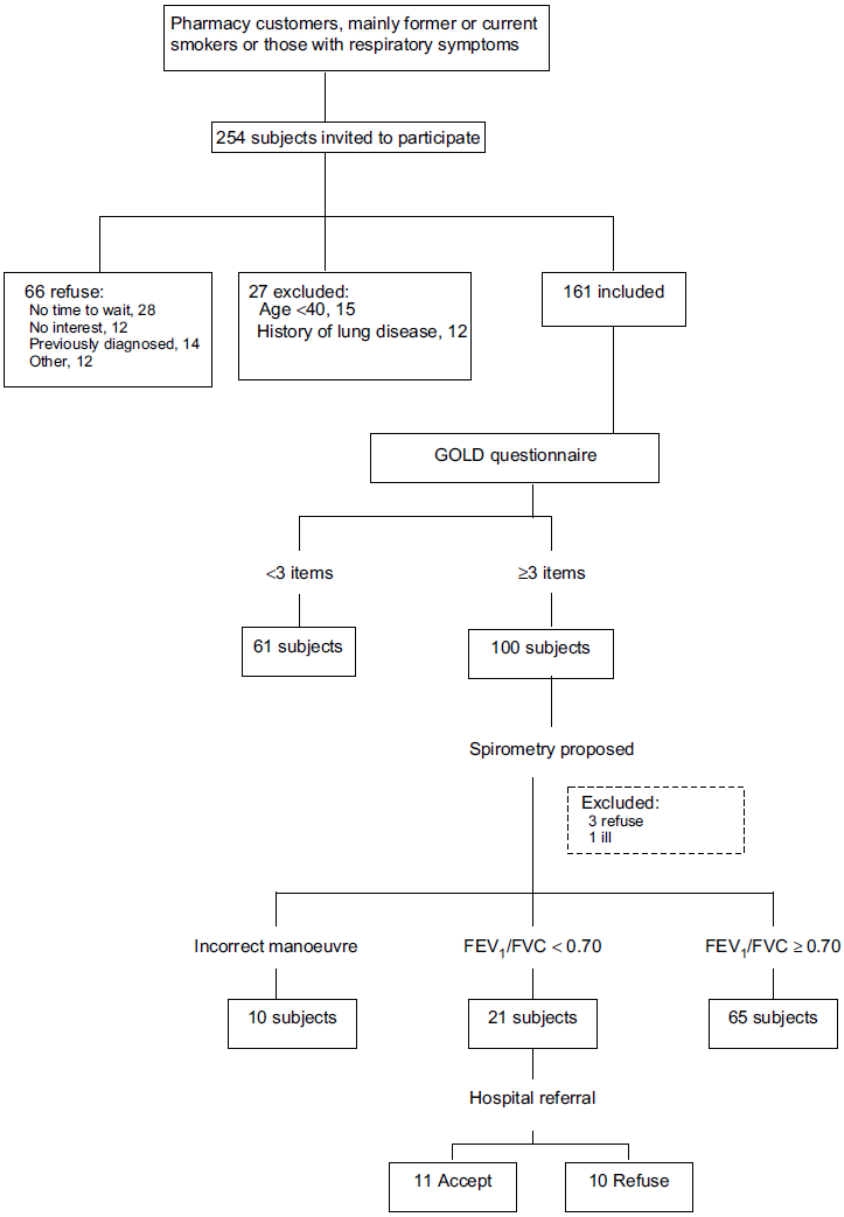
During April and May 2007, customers who entered the participating community-pharmacy and who seemed to be in the targeted age range (older than 40 years) were approached and selected using a 2-step approach (questionnaires plus spirometry) . To assess the risk of COPD, we used the GOLD screening questionnaire, as recommended in the 2006 guidelines (126). Those with a pre-bronchodilator FEV_1/FVC less than 0,7 were referred to a lung function unit in a university hospital (Hospital de la Santa Creu i Sant Pau or Hospital Clinic i Provincial, both in Barcelona).

Within 24-48 hours spirometry was repeated by an expert nurse using the same brand of spirometer. Those with confirmed airflow obstruction were referred to their primary care center. The referral letter is enclosed in **Annex 4.**

Results

A total of 254 customers approached by the pharmacists expressed interest in the study; 188 (74%) agreed to participate by signing the consent form after the nature of the study was explained. Reasons given by the 66 subjects who declined to participate included no time to wait (n=28, 42%), no interest (n=12, 18%), already diagnosed with a respiratory condition (n=14, 21%) and others (n=12, 18%). Twenty-seven of these 188 initial participants were excluded by the pharmacists when criteria were reviewed; reasons for exclusion at this time were age <40 years or previous lung disease (**Figure 4**).

Figure 4. Pilot-Study flow chart.



The 161 remaining volunteers agreed to fill in the GOLD screening questionnaire for COPD. The average age of these participants was 55 ± 11 years, 94 (58%) were women, and 124 (77%) were smokers or ex-smokers. The mean GOLD screening score was 3.0 ± 1.2. Sixty-one of the 161 respondents (38%) had a score <3 and 100 (62%) a score of ≥3, indicating they were at high risk for COPD (**Table 3**).

Table 3. Pilot-study demographics.

	All customers (n = 161)	Low risk (n = 61)	High risk (n = 100)
Age, mean ± SD	55 ± 11	56 ± 11	55 ± 11
Women, n (%)	94 (58)	38 (62)	56 (56)
Smoking history, n (%)	124 (77)	36 (59)	88 (88)[a]
GOLD score, mean ± SD	3.0 ± 1.2	1.7 ± 0.4	3.8 ± 0.8[a]

[a] Significant differences were found between low-risk and high-risk groups for smoking history (smokers or ex-smokers) (P = 0.01) and GOLD score (P = 0.01). GOLD = Global Initiative for Chronic Obstructive Lung Disease.

The age and proportion of women in the two groups were similar. More high risk customers were smokers or ex-smokers, and they also had a higher mean GOLD screening score than those at low risk. Those in the high risk group were offered spirometry; only three refused and one was excluded because she was ill with a respiratory infection at that time. Customers who attended spirometry had at least one symptom. Chronic cough was the most common (66%) but each symptom was present in about half the subjects (chronic sputum 54%, breathlessness 63%). Low risk subjects were more frequently asymptomatic (chronic cough 6%, chronic sputum 5%, and breathlessness 3%)

Thus, 96 high-risk subjects performed forced spirometry in the pharmacy. Sixty-five (68%) had an FEV_1/FVC% ratio ≥0.70 and 21 (22%) had an FEV_1/FVC% ratio <0.70, indicating airflow limitation (**figure 5**). Ten were unable to perform the manoeuvres correctly (**table 4**).

Figure 5. Distribution of airflow limitation by age (Subjects with airflow limitation are represented by filled circles).

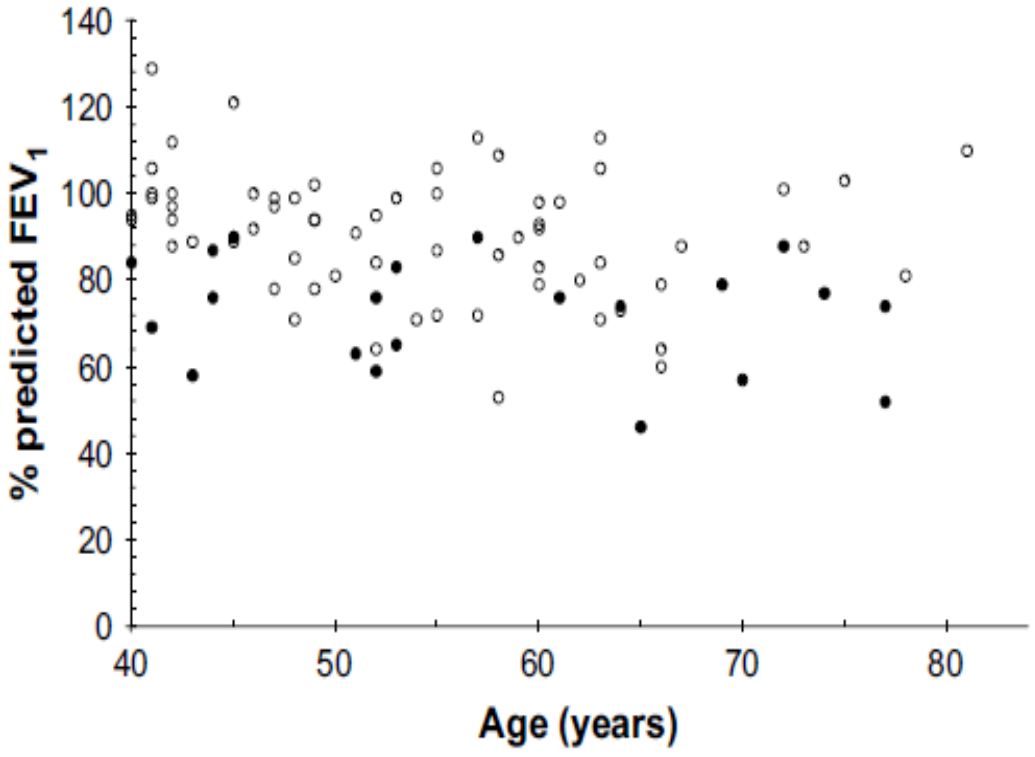


Table 4. Personal characteristics and spirometry results for those who performed a correct spirometry.

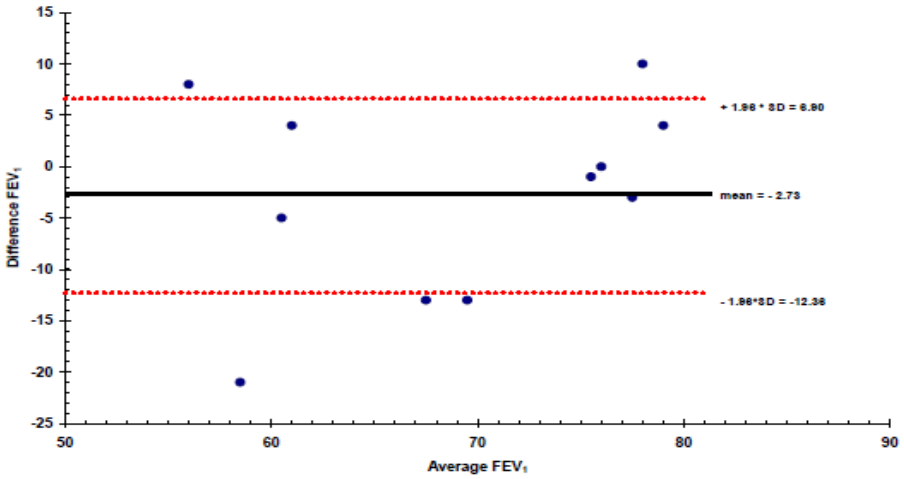
	All spirometries ($n = 86$)	Normal spirometry ($n = 65$)	Airflow limitation ($n = 21$)
Women, *n* (%)	49 (57)	37 (57)	12 (57)
Age (y)	55 ± 11	54 ± 10	57 ± 12
Smoking history, *n* (%)	74 (86)	56 (86)	18 (86)
GOLD score	3.8 ± 0.8	3.8 ± 0.8	3.7 ± 0.8
BMI	27.1 ± 5.1	27.8 ± 4.7	25 ± 5.7[a]
FEV_1 (l)	2.5 ± 0.7	2.7 ± 0.6	2.1 ± 0.7[a]
FEV_1 (% ref. val.)	86 ± 0.2	91 ± 0.1	72 ± 0.1[a]
FVC (l)	3.4 ± 0.9	3.4 ± 0.9	3.24 ± 1.0
FVC (% ref. val.)	89 (0.2)	90 (0.2)	85 (0.1)
FEV_1/FVC ratio	0.76 (0.1)	0.79 (0.1)	0.64 (0.1)[a]

Data are expressed as mean ± SD unless otherwise noted.
[a] Significant differences in BMI ($P = 0.03$), FEV_1 ($P = 0.01$), FEV_1% ($P = 0.01$) and FEV_1/FVC ratio ($P = 0.01$) were found between the normal and abnormal spirometry groups.
FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; and GOLD = Global Initiative for Chronic Obstructive Lung Disease.

According to our pre-bronchodilator data, airflow limitation was mild in 13 (62%) of the subjects in whom it was detected, moderate in 7 (33%) and severe in 1 (5%).

Out of the 86 patients that conducted spirometry, airflow limitation (FEV_1/FVC ratio < 0.70) was detected in 21 (24%), and they were invited for referral to a hospital pulmonary function laboratory for further assessment. Only 11 (52%) subjects both accepted referral and actually went to the laboratory. In all cases, the airway obstruction was confirmed. Moreover, the lung function values recorded in the community pharmacy and in the hospital pulmonary function laboratory were similar in both settings (FEV_1, P = 0.5; FVC, P = 0.89; and FEV_1/FVC ratio, P = 0.14). Of note, among those referred to the hospital, two presented a pre-bronchodilator FEV_1 <60%.

Figure 6. Blant-Altman graph for comparision of the pharmacy-versus hospital obtained percent predicted FEV_1



Finally, spirometric curves in the pharmacy were of acceptable quality overall, with 70% rated as good quality by the spirometer software and 73% were considered of acceptable quality by the lung function expert. The quality rating tended to be even better in subjects with airflow limitation, 76% of whom were considered to have good quality curves, but the difference was not significant (P = 0,71).

Summary

This was the first ever study published evaluating COPD case finding in community-pharmacy using spirometry. The results of this pilot-study showed that this option was feasible. Our data indicated that pharmacists were able to identify customers with respiratory symptoms and/or smokers in a population in which the majority were middle-aged subjects who had never been tested for COPD. Besides community-pharmacist were able to supervise quality spirometries.

This data supported a larger study aimed to confirm feasibility and to investigate the utility of the COPD case finding program in pharmacies.

HYPOTHESIS AND OBJECTIVES

As noted, current evidence concerning COPD screening in community-pharmacy is still preliminary. The overall aim of this thesis was to provide new insights into COPD case finding, in this case via exploring a novel setting. Furthermore, we hope that our findings might contribute to enhance knowledge about community-pharmacy in relation with respiratory conditions. More broadly, research in case finding and spirometry in community-pharmacy provides a powerful source for exploring the relationship between different health providers and could be used to improve chronic diseases' care.

Based on the above, three principal hypotheses were established:

1. Community-pharmacy will show efficiency to detect subjects in high risk of suffering for COPD, not previously tested.

2. Community-pharmacist will show ability to supervise adequate spirometries based on current guidelines.

3. Community-pharmacy will show that they are well placed to develop case finding programs in collaboration with primary care.

Objectives

The specific objectives of this work were:

1. To evaluate the yield of a COPD case finding program in high risk customers of community-pharmacy.

2. To examine the quality of forced spirometry in community-pharmacy using a telemedicine web plataform.

3. To investigate the link between community-pharmacists and primary care physicians in patients with possible COPD.

METHODS

Ethics

The study (hereafter called FARMAEPOC) was approved by the research ethics board at Hospital del Mar, Barcelona, Spain (2008/3128/I). The protocol was consistent with the principles of the Declaration of Helsinki.

Pharmacist selection and training

The COFB offered to all its members the possibility to participate, and 100 community-pharmacy located in the province of Barcelona (both rural and urban settings) volunteered, most of which had previously participated in other community-pharmacy health-care programs.

Community-pharmacists that participated in FARMAEPOC are listed in **Annex 5**.

Community-pharmacies were divided in 5 groups (20 pharmacists each) that participated in the study in five sequential "Study Rounds", from September 2010 to February 2012 (approximately 12 weeks each round). No sites were revisited.

As in the pilot study, every pharmacist participating in the study attended a four-day hands-on training course. Training was based on the guidelines of the National Institute for Occupational Safety and Health (NIOSH), ERS, American Thoracic Society (ATS) and SEPAR (25, 127, 128) (**figure 7**).

Figure 7. FARMAEPOC spirometry training course

Proyecto FARMAEPOC

Curso de Espirometría Forzada

Antecedentes

Mediante la combinación de sesiones teóricas y prácticas, este curso pretende enseñar a los alumnos la técnica correcta para la obtención de valores espirométricos válidos, según las definición del National Institute for Occupational Safety and Health (NIOSH) así como la European Respiratory Society (ERS), la American Thoracic Society (ATS) y Sociedad Española de Neumología y Cirugía Torácica (SEPAR).

Objetivo

- Usar métodos estandarizados para obtener espirometrías válidas y repetibles.
- Calcular correctamente los parámetros de la espirometría.
- Identificar las aplicaciones, ventajas y desventajas de la espirometría en la práctica clínica y fundamentalmente como instrumento para la detección precoz de enfermedades respiratorias y en especial la enfermedad pulmonar obstructiva crónica (EPOC)

Organiza:
Col.legi Oficial de Farmaceutics de Barcelona.
Dirección: F. Burgos, P. Casán, J. Giner.

Duración: 8 horas. Divididas en cuatro jornadas de 2 horas.
Localización: Col.legi oficial de Farmaceutics de Barcelona.

Profesorado:

- Felip Burgos. DE. Laboratorio de función pulmonar (Instituto Clínic del Tórax).
- Pere Casan. Neumologo. Unidad de Función Pulmonar. Hospital de la Santa Creu i Sant Pau.
- Diego Castillo. Residente de Neumología. Departamento de Neumología. Hospital de la Santa Creu i Sant Pau.
- Jordi Giner. DE. Unidad de función pulmonar. Hospital de la Santa Creu i Sant Pau.
- Montserrat Torrejón. DE. Clínica del Asma. Hospital de la Santa Creu i Sant Pau.
- José Luis Romero. DE. Laboratorio de función pulmonar (Instituto Clínic del Tórax).

JORNADA I

- Entrega documentación y presentación del curso
- Aspectos anatómicos y fisiológicos del pulmón
- Qué es la espirometría
- Tipos de espirómetros y concepto flujo volumen
- Parámetros espirométricos

JORNADA II

- Condiciones para la realización de la espirometría
- Valoración de las maniobras, estandarización ERS/ATS: aceptabilidad, repetibilidad y reproducibilidad.
- Valores de referencia

JORNADA III

- Prácticas de espirometría.

JORNADA IV

- Interpretación de los resultados
- Manejo del espirómetro Easy-one. Introducción de datos. Envio de datos.
- Dudas y preguntas. Clausura del curso.

Los alumnos realizaran prácticas de espirometría en grupos reducidos de 5 –10 alumnos por tutor

Documentación:

Se entregará a todos los alumnos un resumen de los temas del curso.

Se entregará un certificado de asistencia.

El curso se incluye dentro del programa de formación continuada del Col.legi Oficial de Farmaceutics de Barcelona.

The course was also officially accredited by the Catalonian Government (129). They were assessed at the end of the course using a questionnaire to certify competence. The length of course was increased because the pharmacists were also instructed in the management of the web-database used during the study to collect all data (Linkcare®) (64).

Spirometer and assessment procedures

The portable spirometer (Easy-One Spirometer, ndd Medical Technologies, Zürich, Switzerland) was chosen because it is easy to handle and has been used in other population screening studies (130-132). The spirometers were calibrated and checked before and after every round to control the quality of the measurements. The device has built-in software that ranks spirometry quality (grades A to F) in accordance with international standard classifications (**Figure 8**) (133).

Figure 8. Spirometry quality score

Quality score	Description
A	3 acceptable maneuvers, and best 2 matched with differences in FVC and/or FEV_1 <0.15 L
B	3 acceptable maneuvers, and best 2 matched with differences in FVC and/or FEV_1<0.20 L
C	2 acceptable maneuvers, and best 2 matched with differences in FVC and/or FEV_1<0.25 ml
D	1 acceptable maneuver
F	None acceptable maneuvers

An A or B rating indicated acceptable quality, because both levels suppose three good manoeuvres with at least two readings of FVC and FEV_1 differing by less than 150-200 millilitres. In addition, an expert in spiromety (Felip Burgos) reviewed and rated manually all measurements loaded into the system and reported back weekly to each community-pharmacists on the quality of their tests, including their repeatability, characteristics and onset (back extrapolation) and end (expiratory time) maneuvers. Pharmacists were then able to ask specific queries and feedback to the expert. The Linkcare® platform provided traceability of all actions and dialogs that occurred during the study.

Lung function measurements included FEV_1, FVC and the FEV_1/FVC ratio. FEV_1 and FVC were expressed in litters and as the percentage of reference values for the Spanish population (134). As proposed elsewhere for mass screening programs, we used pre-bronchodilator lung function to classify airflow limitation, defined by an FEV_1/FVC ratio less than 0,70 (135, 136). As the patients with airflow limitation were referred to primary care, we decided to follow their guidelines regarding COPD diagnosis. Therefore, airflow obstruction was defined by an FEV_1/FVC ratio lower than 0,70(137).

Each community-pharmacy was provided with all the study material, including the spirometer. As recommended by guidelines, each community-pharmacy allocated an adequate space for spirometry testing (separate room). Every community-pharmacy has available a personal computer with internet access so spirometric results were uploaded automatically into a specific web database (Linkcare®).

Finally pharmacists were provided with a list of indications in which to avoid performing spirometry:

Figure 10. Spirometry contraindications

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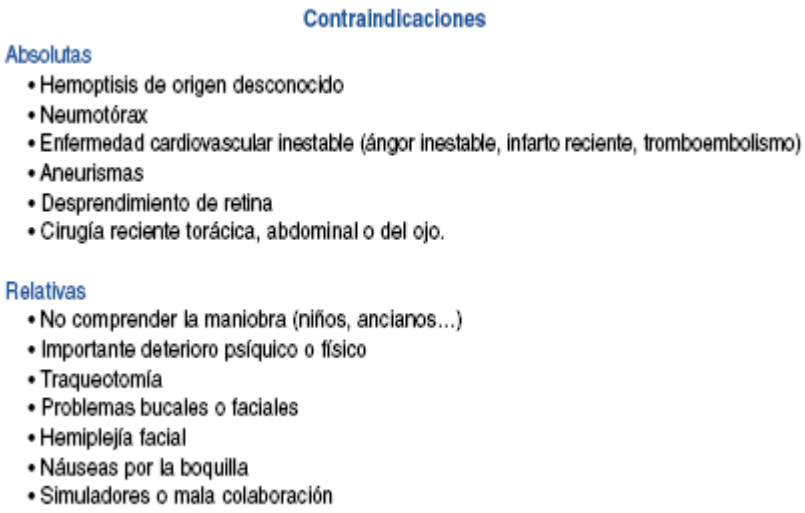

Study design

This was a prospective, cross-sectional, descriptive, multicenter, uncontrolled, remotely supported study. Neither the pharmacist nor primary care physician received any incentives to undertake the study.

The volunteer pharmacists recruited subjects from among customers arriving during their regular work shifts of about 8 hours per day and they conducted interviews and tests between attending customers. The daily routine of the pharmacy was not modified so that our results would not overestimate the number of new cases

of COPD that can be found by this route in real conditions. In all cases, the specific reason(s) for refusal to participate in the study at any stage were recorded (**figure 11**).

Figure 11. FARMAEPOC INCLUSION/EXCLUSION SHEET

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SOCIEDAD ESPAÑOLA DE NEUMOLOGÍA Y CIRUGÍA TORÁCICA
SEPAR

camfic
societat catalana de medicina familiar i comunitària

COL·LEGI DE FARMACÈUTICS DE BARCELONA
FARMAEPOC

PLANTILLA DE RECOGIDA DATOS

Farmacia ☐☐☐☐

Listado de individuos invitados a participar en el Cuestionario de Cribaje

- **Si "Sí"decide participar, pasar a la página del Cuestionario de Cribaje**
- **Si "No"decide participar, recoger mínimo conjunto de datos abajo para realizar el estudio de no-respuesta**

Fecha	**Edad (años)**	**Sexo (H/M)**	**¿Diagnósticos respiratorios?**	**¿Fumador o exfumador?**	**Motivo de no participar** 1-No tiene tiempo 2-No le interesa 3-No quiere de dejar de fumar 4-Otras razones: (especificar en texto)

Customers who entered the participating community-pharmacy and who seemed to be in the targeted age range (older than 40 years) were approached with opening questions about respiratory symptoms or smoking. If a candidate expressed interest in the topic, the pharmacist explained the objectives of the research and the voluntary nature of participation. Participants signed a consent form if interested, and the pharmacist then asked about previous diagnoses of lung disease or use of inhaled medication and sociodemographic data as stipulated by a written questionnaire. Individuals aged <40 years or who had a history of lung disease or use of inhalers were excluded at this time.

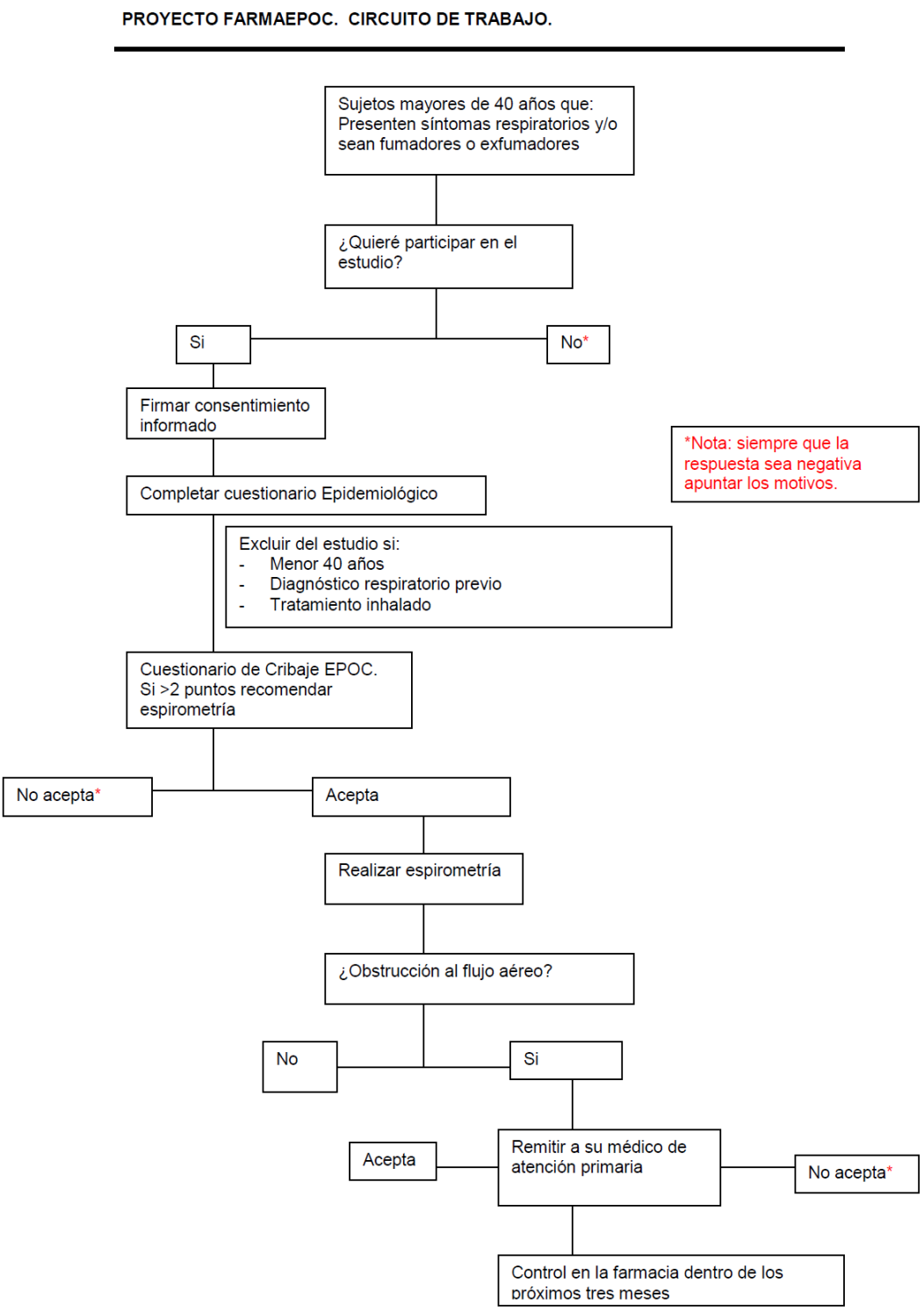
To assess the risk of COPD, we used the GOLD screening questionnaire, as recommended in the 2006 guidelines (126). This questionnaire consisted of questions on five items referring to:

More breathlessness than people of the same age

- Chronic cough
- Chronic sputum
- Age older than 40 years
- Smoking status.

Spirometry was offered to subjects with 3 or more affirmative answers. Those in whom the FEV_1/FVC ratio was less than 0,70 were recommended to contact their primary care physicians for further clinical evaluation, conventional forced spirometry and eventual treatment (**Figure 12**).

Figure 12. FARMAEPOC study flow chart



Besides the primary care physicians were asked to return to the community-pharmacy a questionnaire with the specific diagnostic and/or therapeutic actions taken in that particular individual within the next 3 months (**figure 13**).

Figure 13. FARMAEPOC primary care referral letter

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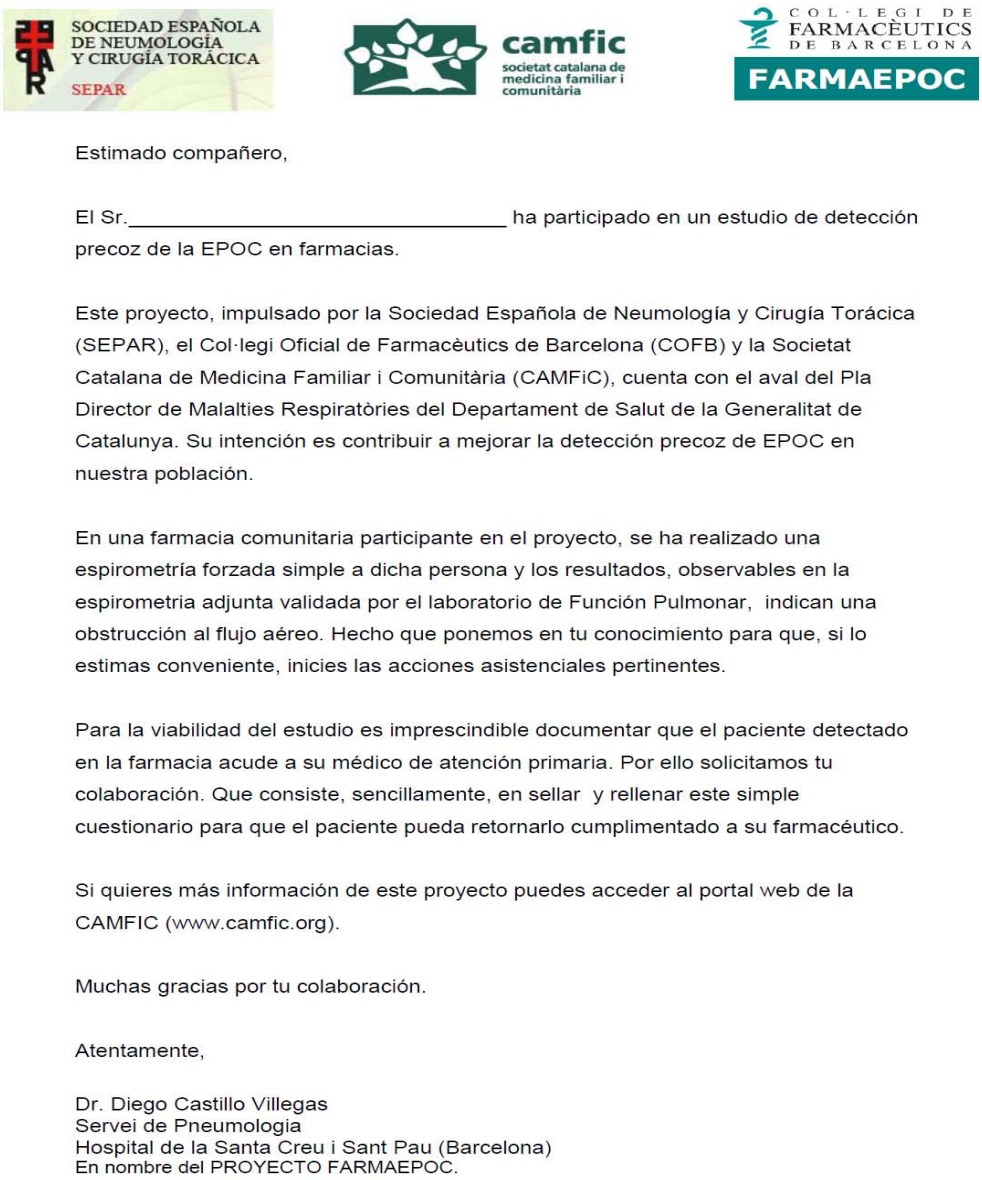

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COL·LEGI DE FARMACÈUTICS DE BARCELONA
FARMAEPOC

Estimado compañero,

El Sr._____ ha participado en un estudio de detección precoz de la EPOC en farmacias.

Este proyecto, impulsado por la Sociedad Española de Neumología y Cirugía Torácica (SEPAR), el Col·legi Oficial de Farmacèutics de Barcelona (COFB) y la Societat Catalana de Medicina Familiar i Comunitària (CAMFiC), cuenta con el aval del Pla Director de Malalties Respiratòries del Departament de Salut de la Generalitat de Catalunya. Su intención es contribuir a mejorar la detección precoz de EPOC en nuestra población.

En una farmacia comunitaria participante en el proyecto, se ha realizado una espirometría forzada simple a dicha persona y los resultados, observables en la espirometria adjunta validada por el laboratorio de Función Pulmonar, indican una obstrucción al flujo aéreo. Hecho que ponemos en tu conocimiento para que, si lo estimas conveniente, inicies las acciones asistenciales pertinentes.

Para la viabilidad del estudio es imprescindible documentar que el paciente detectado en la farmacia acude a su médico de atención primaria. Por ello solicitamos tu colaboración. Que consiste, sencillamente, en sellar y rellenar este simple cuestionario para que el paciente pueda retornarlo cumplimentado a su farmacéutico.

Si quieres más información de este proyecto puedes acceder al portal web de la CAMFIC (www.camfic.org).

Muchas gracias por tu colaboración.

Atentamente,

Dr. Diego Castillo Villegas
Servei de Pneumologia
Hospital de la Santa Creu i Sant Pau (Barcelona)
En nombre del PROYECTO FARMAEPOC.

CUESTIONARIO A CUMPLIMENTAR POR SU MÉDICO DE ATENCIÓN PRIMARIA

GRACIAS POR SU COLABORACIÓN

Fecha de visita: ☐☐/☐☐/☐☐☐☐

¿Confirma que el sujeto acudió a su médico de atención primaria?
☐ Sí ☐ No

¿Qué hará usted respecto al sujeto remitido desde la farmacia?
☐ Conservar la espirometría de farmacia
☐ Repetir la espirometría sin prueba broncodilatadora
☐ Repetir la espirometría con prueba broncodilatadora

¿Se ha incluido el diagnóstico de EPOC en la historia clínica? ☐Sí ☐No

En caso afirmativo ¿se ha clasificado la EPOC? ☐Sí ☐No
¿Cómo? ☐Leve ☐Moderada ☐ Grave ☐ Muy grave

¿Le iniciará tratamiento inhalado? ☐ Sí ☐ No
Si la respuesta es afirmativa ¿Cuál? Marcar varias si precisa:
☐ B2 corta duración
☐ B2 larga duración
☐ Anticolinérgico corta duración
☐ Anticolinérgico larga duración
☐ Corticoide inhalado

Si fumaba ¿Ha sido incluido en un programa de deshabituación tabáquica? ☐Sí ☐No
¿Se ha realizado el consejo antitabáquico? ☐ Sí ☐ No

Sello (o Nombre y Nº col) y Firma del Médico de Atención primaria

Es su médico de cabecera habitual: ☐ Sí ☐ No

NOTA: El sujeto debe retornar este cuestionario a la farmacia en donde le realizaron la espirometría. Gracias por su colaboración.

Smokers were also encouraged to quit smoking through a cessation program, as giving this advice was part of the normal routine for these volunteer community-pharmacists.

To help with recruitment, an advertisement panel was provided in every community-pharmacy (**figure 14**).

Figure 14. FARMAEPOC study advertisement

Figure 15. FARMAEPOC data collection sheet

FARMAEPOC: Estudio de Salud Respiratoria en Farmacias

Farmacia ☐☐☐☐ Farmacéutico ☐☐☐ Número del participante ☐☐☐

¿Acepta participar en el estudio? ☐ Sí ☐ No

Si la respuesta es negativa explicar el motivo:

☐ No tengo tiempo ☐ No tengo interés ☐ Ya estoy diagnosticado/a

☐ Otras razones: _____

Fecha de hoy: ☐☐/☐☐/☐☐☐☐ Hora ☐☐/☐☐

Sexo: ☐ Hombre ☐ Mujer Edad: ☐☐ años Peso: ☐☐ kgs. Talla: ☐☐☐ cms.

Núm. teléfono _____ Fumador: ☐ Sí ☐ No ☐ Ex fumador

☐☐ cigarrillos al día ☐☐ años que fuma/ha fumado

Enfermedades respiratorias diagnosticadas previamente: -

_____

_____

Toma broncodilatadores ☐ Sí ☐ No ¿hace más de 12 horas? ☐ Sí ☐ No

A.- Cuestionario de Cribaje GOLD

1. ¿Tose la mayoría de los días? ☐ Sí ☐ No
2. ¿Arranca flemas con frecuencia? ☐ Sí ☐ No
3. ¿Se fatiga más fácilmente que los demás de su edad? ☐ Sí ☐ No
4. ¿Tiene más de 40 años? ☐ Sí ☐ No
5. ¿Fuma o ha fumado? ☐ Sí ☐ No

**Si responde positivamente a tres preguntas recomendar realizar espirometría.*

¿Se ha podido realizar la espirometría? ☐ Sí ☐ No

Si la respuesta es negativa explicar el motivo:

☐ No tengo tiempo ☐ No tengo interés ☐ Ya estoy diagnosticado/a

☐ Otras razones: _____

☐ **Se intenta la espirometría pero no se realiza satisfactoriamente por dificultad de la persona**

B.- Resultados Espirométricos:

Valores basales (mejor de las tres maniobras)
FVC: ☐ . ☐☐ litros ☐☐☐ % del predicho

FEV_1: ☐ . ☐☐ litros ☐☐☐ % del predicho

cociente FEV_1/FVC: ☐ . ☐☐

NOTA: Si el cociente FEV_1/FVC es igual o inferior a 0.70 referir al Laboratorio de Función Pulmonar

C. Derivación atención primaria

¿Se ha podido derivar a su médico de atención primaria? ☐ Sí ☐ No

Si la respuesta es negativa explicar el motivo:

☐ No tengo tiempo ☐ No tengo interés ☐ Ya estoy diagnosticado/a

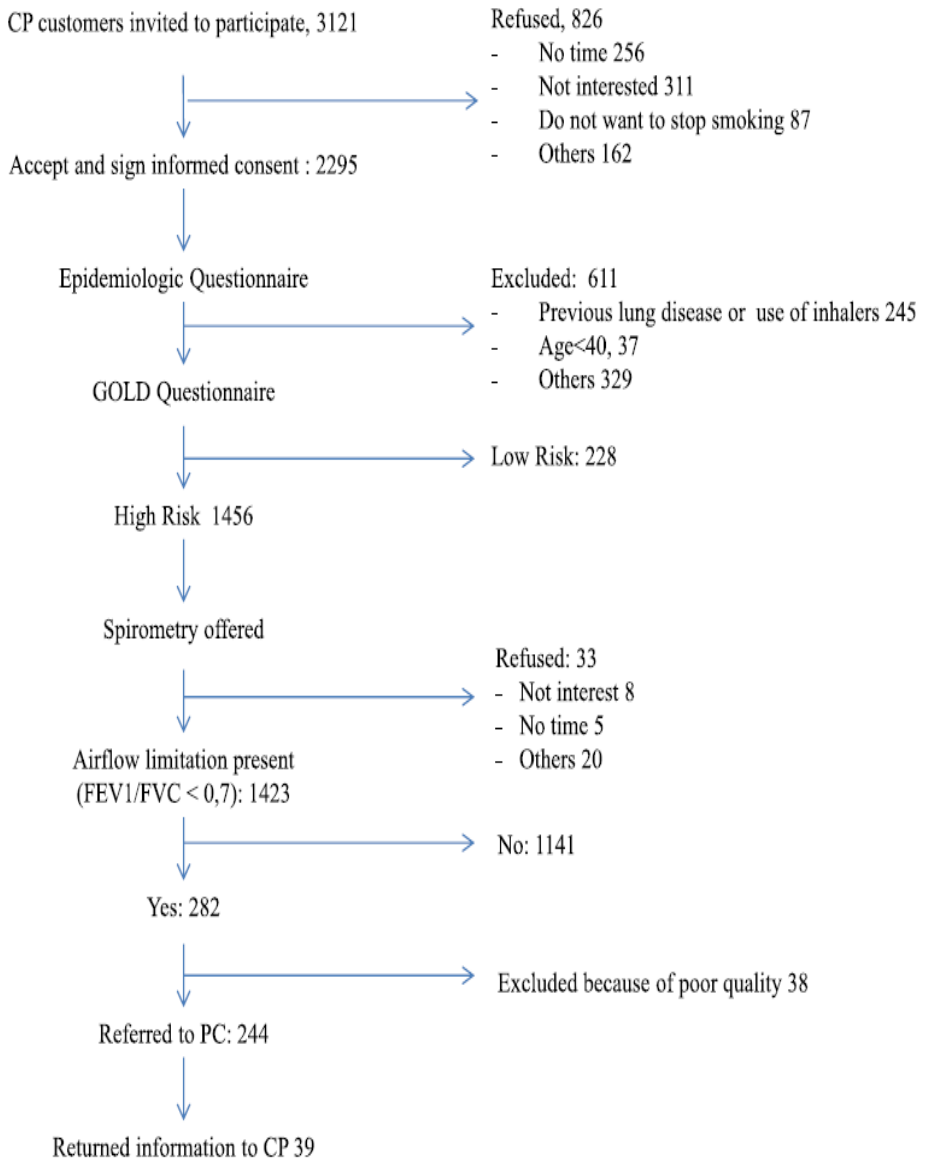
☐ Otras razones: _____

Statistical analysis

Data were quality controlled centrally and a homogeneous template to translate all coding was applied. Variables were double-checked by each pharmacist and the principal investigator, and values that were considered as potential errors or outliers were individually discussed and confirmed, or removed. Comprehensive tabulations with ranges, mean and standard deviation of all quantitative variables, and percentages of all qualitative variables, were available for each community-pharmacy. Results are presented as mean (+/- standard deviation) or n (and percentage) as needed. The Student T-test and Chi^2 test were used to compare differences between groups as appropriate. A $p < 0,05$ was considered statistically significant.

RESULTS

Figure 16. FARMAEPOC participation overview



Of 3.121 community-pharmacy customers (age 55,3±11; 45,8% women) invited to participate in the program, 2.295 (73,5%) accepted (age 55,0±11; 46,4% women). It appears there was no non-response bias, as the age and gender distribution of participants were not significantly different from those not participating. Participants were distributed in each round as following: 18,1%, 21,17%, 16,7%, 23,6% and 19,9%. Of the 2.295 participants, 1.456 (63,4%) were identified as “high risk” for COPD using the GOLD screener questionnaire (**figure 17**).

Figure 17. Distribution of GOLD score among high-risk subjects

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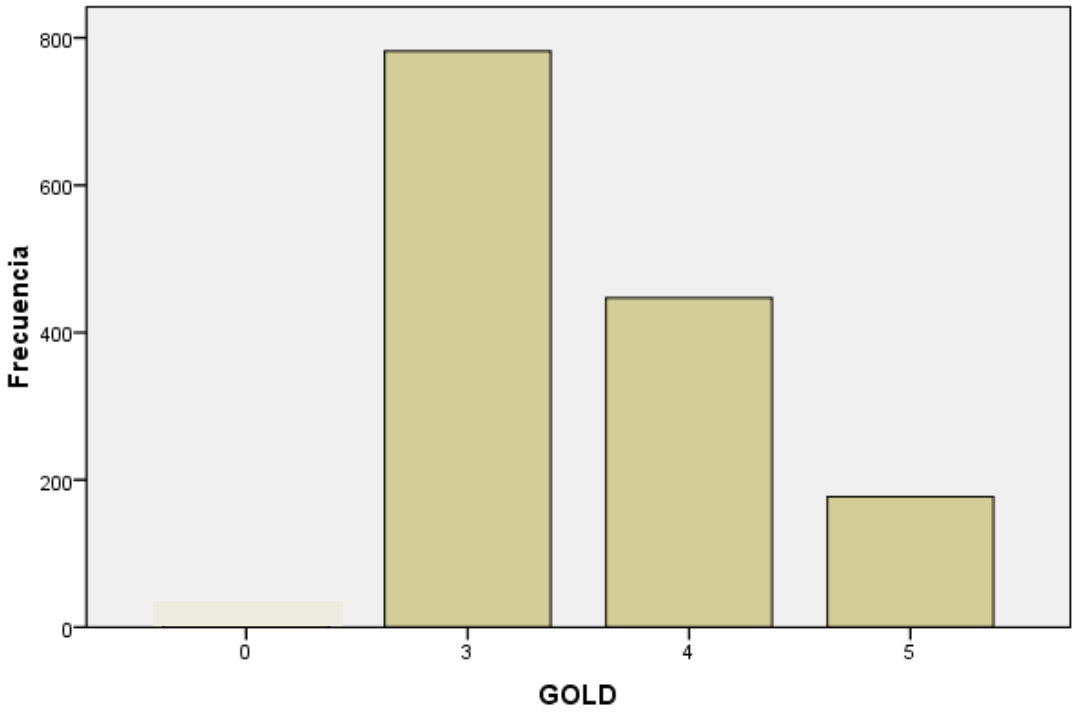

As age was an inclusion criterion in our case finding strategy, every subject scored one point at the least in the GOLD screener questionnaire. Demographic and clinical characteristics of participants at low or high risk groups for COPD are presented, where it can be seen that age was similar in both groups (55,4±10,4 years versus 54,2±10,2 years in the low vs. high risk group, respectively, p n.s.), but participants at high risk were most often male (p<0,05), and with higher smoking exposure and experienced more respiratory symptoms (all these items were included in the screener questionnaire) (**Table 5**).

Table 5. FARMAEPOC demographics

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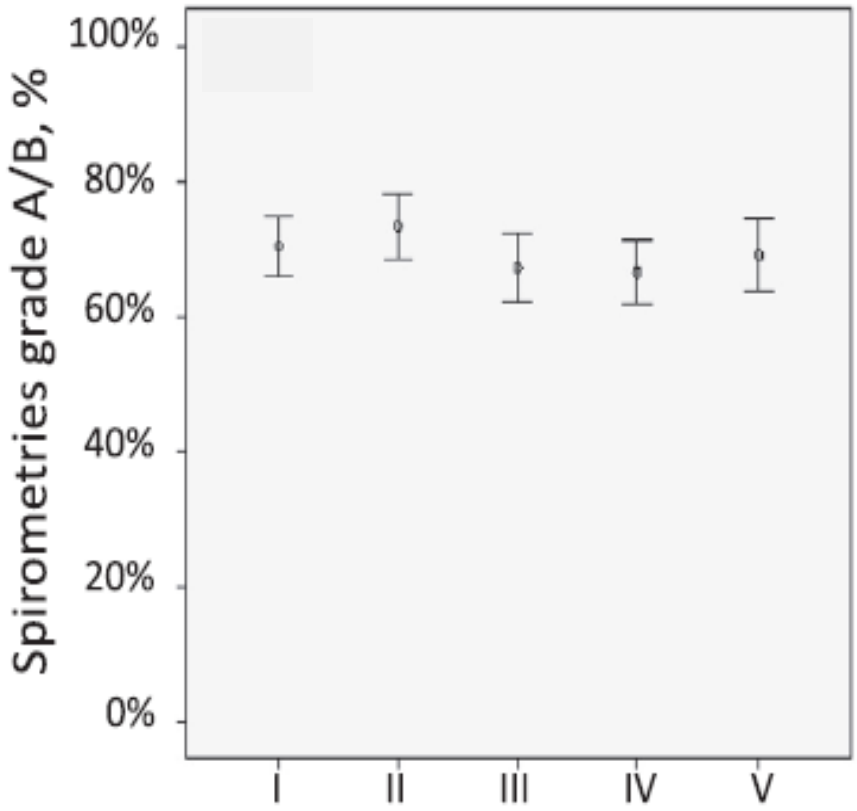
	Low risk (n = 228)	High risk (n = 1456)
Age, mean ± SD	55.4 ± 10.4	54.2 ± 10.2
Women, n (%)	53.7%	45.1%*
Smoking history, (%)		
Never	14.1	0.7*
Current	38.3	64.0*
Former	47.6	35.3*
GOLD risk score, mean ± SD	1.7 ± 0.7	3.6 ± 0.7*
With chronic cough, (%)	1.3	49.2*
With. chronic sputum production, (%)	3.1	48.5*
More breathlessness than people of the same age, (%)	3.1	64.6*
Current or former smoker, (%)	85.9	99.3*

* indicates p<0,05 between both groups

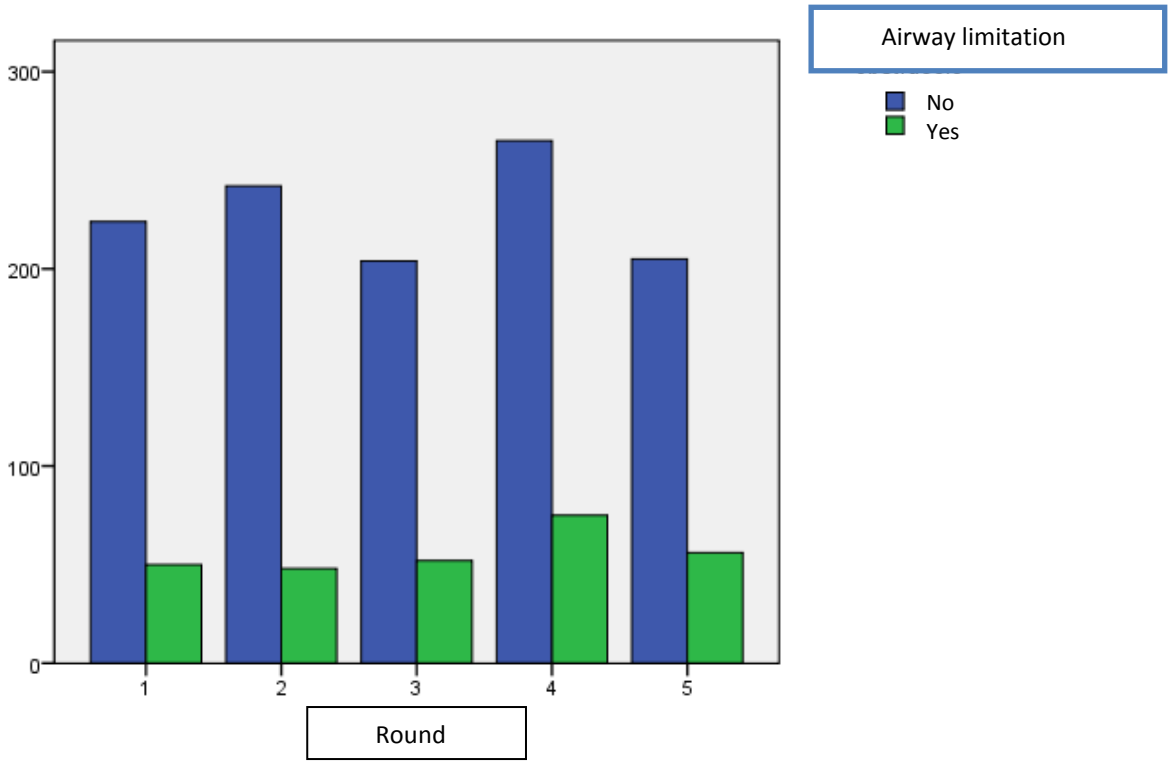
The majority (69,4 %) of spirometries performed were grade A and B, and they were considered of acceptable clinical quality by the expert . This percentage remained stable in the five sequential study rounds (**Figure 18**). As a sensitivity analysis following previous reports, should we had considered grade C also as clinically acceptable, this figure would have risen to 75,1 % (18). Only 8,9% were ranked as quality grade F, the worst possible.

Figure 18. Percentage of A+B spirometries in each round



Of 1.423 individuals completing quality-controlled pre-BD spirometry, 282 (19,8%) had airflow limitation with an FEV1/FVC% ratio <0,70 compatible with COPD.

Figure 19. Cases with airway limitation detected in each round



We did additional analyses to estimate the proportion of misdiagnosis due by using the airflow criteria of fixed ratio instead of LLN. Overall, 586 subjects (41,18%) presented airflow limitation using the LLN. The misdiagnosis was mainly in young adults. While in patients above 60 years old there were no significant differences in prevalence of airflow limitation depending on the criteria used (405 subjects: LLN 136

(33,58%), Fixed Ratio 142 (35,06%)) that was not the case in those under 60 years old (1018 subjects: LLN 450 (44,20%) ; fixed ratio 140 (13,75%)).

The clinical characteristics and spirometric results of participating subjects at high risk for COPD were the following (**table 6**).

Table 6. FARMAEPOC spirometric results

	Normal spirometry (n = 1141)	Airflow limitation (n = 282)
Age, mean ± SD	52.8 ± 9.6	59.7 ± 10.7*
Women, n (%)	47.5	35.5*
Smoking history, (%)		
Never	0.5	0.7
Current	63.5	65.7
Former	36.0	33.6
GOLD screener score, mean ± SD	3.5 ± 0.7	3.7 ± 0.7*
BMI in kg/m^2, mean ± SD	26.9 ± 6.0	26.5 ± 4.4
FEV_1 in L., mean ± SD	2.9 ± 0.69	2.21 ± 0.75*
% predicted FEV_1, mean ± SD	102 ± 2	82 ± 2*
FVC in L., mean ± SD	3.7 ± 0.87	3.5 ± 1.06
% predicted FVC, mean ± SD	101 ± 2	99 ± 2
FEV_1/FVC, mean ± SD	0.78 ± 0.05	0.63 ± 0.07*

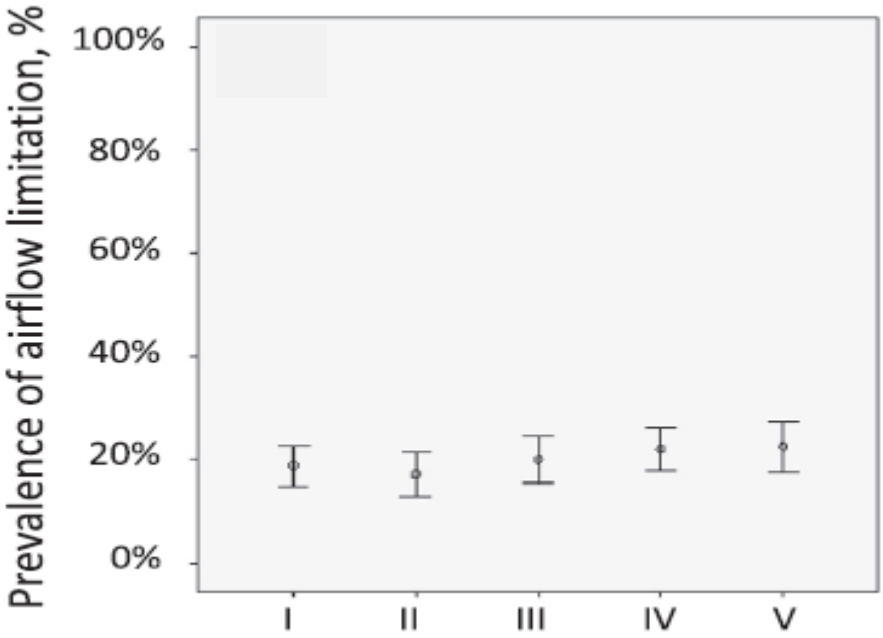
BMI: Body mass index; FEV_1: Forced expiratory volume in the 1st second; FVC: forced vital capacity.

* indicates p<0,05 between both groups

Patients with airflow limitation were significantly older, mostly males and (by definition) had worse lung function than those with normal spirometry but interestingly, cumulative smoking exposure and body-mass index (BMI) were similar in both groups.

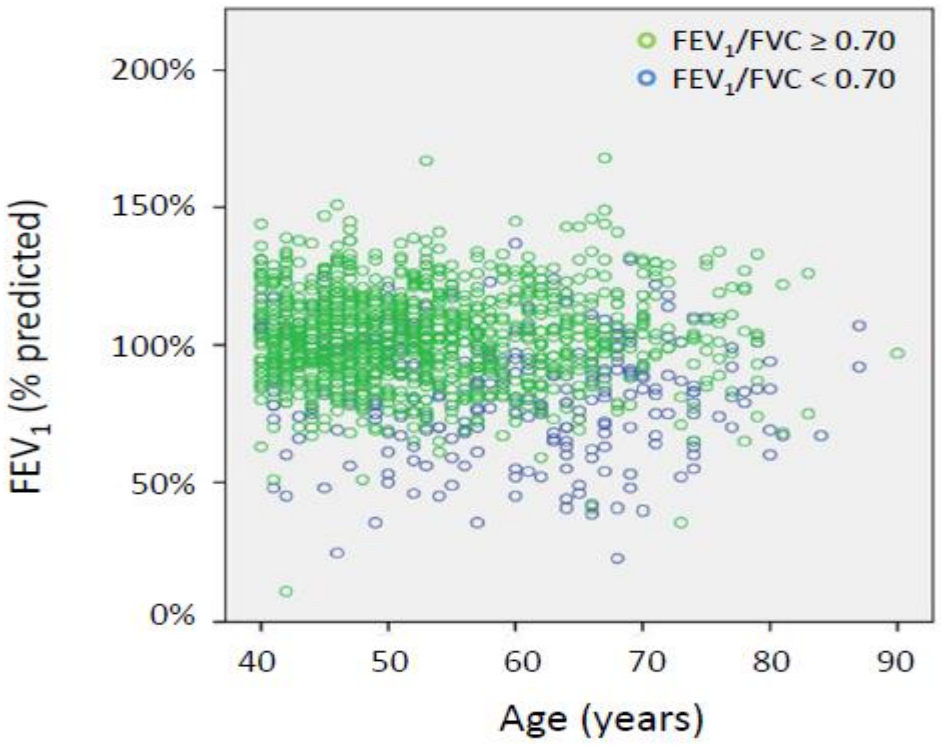
The percentage of airway limitation detected was remarkably reproducible in all temporal study rounds (Chi2 20 p for trend n.s.) with a slight trend to increase overtime (**Figure 20**).

Figure 20. Airway limitation trend among rounds



The distribution of 1 FEV1 (% predicted) by age in participants with and without airflow limitation was the following (**Figure 21**).

Figure 21. FEV1 distribution by age and FEV1/FVC ratio



All subjects (244) with pre-BD airflow limitation unless those 38 (13.5%) with poor quality spirometry were referred to their primary care offices for further evaluations. Community-pharmacy were unsuccessful to retrieve follow-up data from primary care physicians as only 39 (15%) of them provided feed-back to their community-pharmacists and returned the filled up questionnaire requested. In eleven of them (28%) COPD was confirmed by the primary care physicians, and in 6 (15%) inhaled treatment was started.

DISCUSSION

Summary of findings

FARMAEPOC project is the first published program evaluating the roll of community-pharmacy in COPD case finding using spirometry. The results of this thesis shows that individuals at high risk for COPD can be detected in community-pharmacy. Using a 2-step approach, community-pharmacists were able to identify customers in high risk of suffering COPD. The majority were middle-aged subjects who had never been tested for.

Moreover, community-pharmacists were able to supervise high quality forced spirometry manoeuvres in around 70% of subjects, finding one case of airflow limitation for every five individuals tested, a rate that is similar to that reported in primary care. However, the link between primary care and community-pharmacy shall be improved to achieve a complete successful program.

Overall, the findings support community-pharmacy as a novel place for COPD case finding.

Subject Selection

As we mention in the introduction, widespread use of spirometry in screening for COPD has been questioned (69). The current recommendations are to study subjects at high risk (1, 29, 138). But there is no consensus in the method to select these high risk subjects (PEF, microspirometry, questionnaires, etc.). Different approaches have been used in primary care. We followed a 2-step approach (questionnaire plus spirometry) because it had been suggested as the most useful strategy to improve the yield in case finding programs (91).

Moreover all subjects offered spirometry in our study were symptomatic as detected by the questionnaire, suggesting that inappropriate resource consumption can also be kept under control by applying a GOLD-criteria–based screening questionnaire.

However, other strategies could be useful in community-pharmacies. For example, *Solidoro et al.* studied the roll of FEV6 assessment using a PiKo-6© electronic spirometer. Customers of 500 pharmacies were evaluated. Male smokers have a percentage of airway limitation similar to one predicted in obstructive lung disease in international literature (7%). The results suggest that this is a valid screening tool for the detection of possible airway limitation in this setting. (139).

From our perspective, a prospective study comparing different methods is needed to clarify the appropriated method to select high-risk subjects in screening programs, either in primary care or community-pharmacy.

Gender predominance

Given that the prevalence of COPD in Spain has been found to be 14.3% in men and 3.9% in women in a population-based study, we expected males to predominate among the tested subjects (7). Indeed, there were no differences in gender in the tested subjects, but this was not the case in the subjects with airflow obstruction, who were predominantly men.

Interestingly, in the pilot study women accounted for 57% of the spirometries with airflow limitation. Probably this was a bias due to a small sample.

Spirometry quality

As noted, widespread use of spirometry in screening for COPD has been questioned due to significant concerns about quality. By contrast, the current recommendations are to study subjects at high risk in primary care.

However, guided by our experience in many years of spirometry training, we thought that community-pharmacies, learning through an appropriate course, will be able to supervise high quality spirometries. Besides we had the results of a small experience in rural community-pharmacies of Australia. There were able to obtain adequate spirometry in 63%% subjects (125). Then, although we could try other easier tools we decided to detect airflow limitation using the standard test: spirometry.

As first step, we design the pilot-study with a comparison between community-pharmacy and a referral lung function laboratory. The quality of spirometry was reflected in the lack of differences between both measurements for the same subjects. Overall 70% of the spirometry curves were judged to be of A- or B-level quality after review by an expert in lung function testing; that success rate was higher than reported in community-pharmacy. Only 10% of the subjects who were invited to perform spirometry in the community were unable to produce correct maneuvers under the pharmacists' supervision, a situation quite similar to that reported in primary care (49, 80). This positive result supported the use of spirometry in the following studies.

In our case finding program we found that the majority of the spirometries were of clinically acceptable quality grade (69,4%). Our study required the evaluation of a huge numbers of spirometries in community-pharmacy and clearly indicates that well-trained and supervised pharmacists can obtain high quality spirometries in community-pharmacy.

Regular education has an enormous impact in long-term quality. If we review the data published by *Llauger et al.* in a similar setting that our study (primary care centers in Catalonia) we observed that although more than 50% of the centers performed formal training there was no information available on the quality. Indeed, in 68% of cases there were a lack of quality control (61).

It is important to highlight that our study used a web-based tool to assess quality. This platform allows continuous improvement thorough feedback from an expert after each test. Technicians require regular update to maintain and improve their skills.

Telemedicine is a useful tool to keep spirometry quality and enhanced technicians training and would help to expand high quality spirometry outside pulmonary function laboratories. Maybe it will became a crucial element for widespread of COPD case finding. Notably, the "PROMETE study" by *Segrelles Calvo et al.* indicates that telemedicine could be also useful in other areas of care, like follow-up of severe COPD patients with significant comorbidities (140). Home telemedicine is safe and help to reduce healthcare resources utilization.

Our study is the largest ever done in community-pharmacy using spirometry. Nearly 1400 spirometries were done by community-pharmacists. A number enough to suggest that quality spirometry can be performed in community-pharmacy under adequate supervision. But, as seen in primary care, regular education is needed to avoid loss of quality.

Case finding in community-pharmacy

The results of this thesis add new facts to the emerging concept of "Healthy Living Pharmacy" (HLP) which explores the potential of community-pharmacy to promote healthy living (109). Community-pharmacy can play an important role in a number of health-promoting programs, including smoking cessation, cardiovascular diseases or screening for major disease. Besides, customers are satisfied by the introduction of pharmaceutical care programs, as *Kassam et al.* showed in a study conducted in 55 community-pharmacies (141).

Less is known about the role of community-pharmacy in screening for COPD. The results of this work showed that one high risk individual in five assessed customers (20%) was identified. This figure is remarkably similar to that published in primary care, indicating that this type of case finding strategies are likely to work similarly in community-pharmacy (142, 143). Moreover, the proportion of individuals with airflow limitation was independent of the study round, supporting the internal validity of this observation.

After the publication of our pilot study, *Fuller et al.* published an article following a similar approach to detect subjects with possible COPD in community-pharmacies in Cincinnati, USA. (144). The percentage of airway limitation found in this population was 9%. Based in the evidence provide by this two studies, *Fathima et al.* suggested in 2013 that community-pharmacy can play an effective role in screening of people with undiagnosed COPD (145). The results of this thesis support this assertion. Furthermore, in 2015 *Wright et al.* evaluated the cost-effective of a COPD case finding by community-pharmacist in England. They estimated that this intervention provided a cost saving of 392.67 pound per patient screened (146).

Moreover, an interesting study by *Mehuys et al.* took place in Belgium aimed to evaluate the management of COPD in primary care (147). Based on questionnaires done to COPD subjects in community-pharmacy they were able to detect four areas of improvement: (1) drug adherence, (2) inhalation technique with pMDIs, (3) influenza vaccination in COPD patients younger than 65 years, and (4) smoking cessation. Another item can be added thanks to our data: COPD underdiagnosis.

Overall, healthy living programs in community-pharmacy shall include COPD case finding because is a feasible, useful and cost-effective intervention.

Community-pharmacy and primary care link

Of course, it is important to clarify that COPD diagnosis is out of pharmacist scope. Identified high-risk COPD patients should be referred to PC, where a GP will investigate and diagnose them. Admittedly, the diagnosis of COPD requires the combination of exposure to risk factors, symptoms, non-fully reversible airflow limitation and the exclusion of other obstructive airway diseases such as asthma and bronchiectasis, among others (137). Given that only a minority of individuals returned the information requested to their primary care physicians, we cannot provide a final figure for a confirmed diagnosis of COPD. This finding does not detract from the validity of the case finding strategy in community-pharmacy investigated here because, as stated above, clinical diagnosis cannot be a goal in community-pharmacy. Exact opposite, this finding illustrates the need to improve the coordination between formal (primary care) and informal (community-pharmacy) stake-holders in our health-care system to develop a useful program.

Where? Revisited

This thesis explores the roll of community-pharmacies in COPD case finding, adding new facts that probably will become the cornerstone for future plans in

community-pharmacy. We understand that "where" could be now extended to community-pharmacies.

Our findings also support, against previous statements, that quality spirometry and case-finding programs could be developed out of the doctor's office. FARMAEPOC has opened an international debate about this matter. Two well-known COPD experts, as Dr. Celli and Dr. Enright, discussed recently in the *Chest Journal* about Storefront Clinics as providers of COPD case finding (104, 105). Storefront clinics are very popular in the United States for health screenings, treatment of acute illness and management of common chronic medical conditions (148). However, the main concern about this proposal was quality. Dr. Celli argued that in our pilot-study only 70% of spirometries were qualified as A or B. One can think over that for screening purposes is enough. Indeed, it doesn't differ too much from primary care data.

From our perspective, we have to leave this debate and learn from cardiovascular diseases. A nice example was provided by *Vera-Remartinez et al.* study about prevalence of chronic diseases and risk factors among the Spanish prision population (149). Although smoking was the main risk factor, only 2,2% have a diagnosis of COPD. The reason was that there is no spirometer in any Spanish prison. But they have tools to measure the blood pressure or cholesterol levels. Spread of spirometry or other simpler (but effective) tolls is urgently needed, especially in high-risk populations.

LIMITATIONS

A limitation of this study was the absence of a bronchodilator test. Although most guidelines recommend the use of post-bronchodilator spirometry to diagnose and stage COPD, other authors call for simplicity, especially for large-scale screening. Recently, Kjeldgaard et al. data support that the use of post-bronchodilator in screening program of high risk subjects could result in underdiagnosis due to exclusion of those with a positive bronchodilator test (150). Yet, pre-bronchodilator spirometry has been widely used in epidemiological studies (1, 26, 27, 36, 50, 136). We ruled out the use of post-bronchodilator tests in pharmacies because of evident concerns about practicality, safety, and efficiency. Should this approach be implemented, we continue to consider that bronchodilator tests should be performed in the hospital laboratory after referral.

Regarding the use of Fixed Ratio (<0,70) versus LLN to define airway limitation in our studies, certainly one can argue that Fixed Ratio increases COPD misdiagnosing. However, given the relatively young distribution of our participants, this misdiagnosis by the fixed ratio was an underestimate of results by LLN. *Viegi et al*. showed that the estimated prevalence of airflow limitation depends much on the criteria used for definition (151). Our results confirm what *Cerveri et al.* have shown previously: this gap is higher in young adults (152). The current GOLD Guidelines, as the Catalonian and Spanish Primary Care COPD guidelines, still recommend the use of Fixed Ratio. Then we decided that participant community-pharmacies should work in keeping with PC to avoid misunderstandings. Nonetheless, these results highlight the value of using LLN in

young subjects and the need of a standardized airflow limitation definition across different guidelines.

Another limitation is that our strategy involved the use of higher trained than average pharmacists, telemedicine support, two questionnaires and quality-controlled forced spirometry. It can be argued it is too cumbersome for many community-pharmacies. As we discussed previously, simpler screening strategies perhaps using questionnaires and peak-expiratory flow measurements deserve investigation (85, 86).

Finally, the main logistical problem of this study is related to referral of subjects with possible COPD from community-pharmacy to the primary care. In the pilot-study, nearly half of those with spirometry results indicating airflow limitation declined a hospital appointment. No time or lack of interest were the reasons most often stated. We suspect that declining referral may reflect either a lack of interest in quitting smoking or milder symptoms. The general population has little knowledge about COPD, in comparison with other conditions such as cardiovascular disease, and they therefore do not consider respiratory disease to be a serious personal threat (45).

In this study low feedback from primary care was documented. When the study was designed, a link between primary care and community-pharmacy could have been developed to obtain follow up from the majority subjects. However, because this would be a special case set up, aside for real life, this idea was discarded as the results would have not presented every day community-pharmacies practice. Besides a negative result, as we have observed, could be more helpful than a positive “artificial” one to strengthen future programs implementing primary care and community-pharmacy coordination.

CONCLUSIONS

This is the largest study in the literature evaluating the yield of a COPD case finding program in high risk customers of community-pharmacy using spirometry.

The conclusions of this thesis are the following:

- Community-pharmacy is a health provider currently not involved in screening for COPD but whose participation may represent a useful complementary strategy for early COPD case finding.
- Adequately trained and supported community-pharmacists can effectively identify individuals at high risk of suffering COPD, with results that are similar to those previously reported at primary care.
- Community-pharmacists are able to perform good quality forced spirometry.
- Although this program could be a useful tool to reduce COPD underdiagnosis, developing useful links between primary care and community-pharmacy is mandatory to achieve a successful program.

FUTURE DIRECTIONS

Our finding that the community pharmacy can provide a complementary setting for COPD case finding in the general population offers hope of improving the health care system's screening potential.

But despite the promising results, the speed of the integration of pharmacy services in the ambulatory care of respiratory diseases will depend on two factors: continuing professional development and comprehensive care.

Most of the pharmacists who participated in this project received appropriate training and supervision, without which the studies would not have been so successful. For example, in the field of respiratory diseases, previous studies have revealed room for improvement in the pharmacist's understanding of and approach to the management of inhaled therapy (153), suggesting that those wishing to participate in these programs must receive appropriate, accredited continuing professional development.

Furthermore, there is little doubt that the great challenge facing community pharmacies is coordinating their services with those of medical professionals, in particular primary care. For example, as shown in this thesis, if a pharmacist detects a possible COPD, there must be a reliable and effective mechanism for informing the primary care physician. The primary care physician must also be informed of the pharmacy care given to a COPD patient who has recently begun treatment. This is clearly the cornerstone of any healthcare program that aims to include the community

pharmacy. Coordination via a shared clinical history and electronic prescription systems are essential if the efforts of several different healthcare services are to be effectively managed (108).

The findings of this thesis suggest that the time has come to emulate other medical specialties, and to take steps to include community pharmacy care in our efforts to achieve our ultimate aim: to improve the prevention, diagnosis and treatment of respiratory diseases. To achieve this, all stakeholders must come together to bring down the barriers and replace them with bridges.

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ANNEXS

Annex 1. Pilot Study.

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COPD case finding by spirometry in high-risk customers of urban community pharmacies: A pilot study

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KEYWORDS
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Summary
Background: COPD case finding is currently recommended at primary and tertiary care levels only.
Aim: To evaluate the feasibility of a community pharmacy program for COPD case finding in high-risk customers by means of spirometry.
Methods: Pilot cross-sectional descriptive study in 13 urban community pharmacies in Barcelona, Spain, from April to May 2007. Customers >40 years old with respiratory symptoms and/or a history of smoking were invited to participate in the study during pharmacists' routine work shifts. High-risk customers were identified by means of a 5-item COPD screening questionnaire based on criteria of the Global Initiative for Chronic Obstructive Lung Disease, and were invited to perform spirometry accordingly. Those with an FEV_1/FVC ratio less than 0.70 were referred to the hospital for a repeat spirometry.
Results: Of the 161 pharmacy customers studied, 100 (62%) scored 3 or more items in the COPD screening questionnaire, and after spirometry, 21 (24%) had an FEV_1/FVC ratio < 0.7. When these subjects with airflow limitation were offered referral to a hospital respiratory function laboratory for further assessments, 11 (52%) attended the appointment. Over 70% of spirometries were rated as being of acceptable quality. No significant differences were observed in lung function parameters between the pharmacy and hospital measurements.

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Conclusions: COPD case finding by spirometry in high-risk customers of urban community pharmacies is feasible. Similarly to primary care practitioners, pharmacists have access to high-risk, middle-aged subjects who have never been tested for COPD. Pharmacists can help with early detection of COPD if they are correctly trained.

Introduction

Early diagnosis of COPD is important because smokers with demonstrated airway obstruction are more likely to quit smoking.[1] Recently, the U.S. Preventive Services Task Force (USPSTF) recommended against screening the general population for chronic obstructive pulmonary disease (COPD) using spirometry (grade D recommendation).[2] However, the same document recognised that individuals presenting respiratory symptoms (chronic cough, increased sputum production, wheezing, or dyspnea) should be tested. This position is consistent with the recommendations of other relevant groups: the American Thoracic Society (ATS) and the European Respiratory Society (ERS) advise performing spirometry on all persons with smoking exposure, a family history of chronic respiratory illness, or respiratory symptoms,[3] and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends that clinicians consider a diagnosis of COPD 'in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease' and that the 'diagnosis should be confirmed by spirometry'.[4]

At present, detection of COPD is limited to case finding at the primary or tertiary care levels, a strategy that has proven largely inadequate. One large population-based survey showed that a high percentage (63%) of subjects with airflow limitation had never received a diagnosis of obstructive lung disease.[5] In Spain, underdiagnosis has been estimated to be around 80%.[6]

Pharmaceutical care, which has been useful in the management of ambulatory patients with chronic diseases such as asthma,[7] might offer a new approach to COPD case finding. Community pharmacists trained to perform spirometry have been successful in improving access to lung function measurement in rural communities,[8] and we hypothesized that they might also be able to help in an urban general population. For such an approach to work, the pharmacist would need to be able to select high-risk individuals in whom spirometry should be performed. The aim of this pilot study was to assess the feasibility of a program of case finding of COPD by spirometry in community pharmacies.

Methods

Pharmacist selection and training

To recruit pharmacist participants, we contacted community pharmacies in a smoking prevention group formed through the professional association for this sector (Official College of Pharmacists, COFB) in Barcelona, Spain. The study had been approved by the ethics committee of Hospital Clinic i Provincial, Barcelona. Thirteen of the 19 members of the smoking prevention group accepted, agreeing that a staff pharmacist would attend a four-day spirometry training course in February and March 2007. Training was based on the guidelines of the National Institute for Occupational Safety and Health (NIOSH),[9] the ERS/ATS,[10] and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[11] The volunteer pharmacists recruited subjects from among customers arriving during their regular work shifts of about 8 h per day and they conducted interviews and tests between attending customers. The daily routine of the pharmacy was not modified so that our results would not overestimate the number of new cases of COPD that can be found by this route in real conditions.

Spirometer and assessment procedures

The portable spirometer (Easy-One Spirometer, ndd Medical Technologies, Zürich, Switzerland) was chosen because it is easy to handle and has been used in other population screening studies.[12] Calibration was checked at the beginning of the study and did not have to be re-checked daily. The device has built-in software that ranks spirometry quality (grades A–F) in accordance with standard European classifications.[10] An A or B rating indicated acceptable quality, because both levels supposed three good manoeuvres with at least two readings of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) differing by $<$150–200 ml. In addition, an expert in lung function (F.B.) reviewed and rated all spirometry curves according to the same criteria.

Lung function measurements included FEV_1, FVC and the FEV_1/FVC ratio. FEV_1 and FVC were expressed in liters and as the percentage of reference values for the Spanish population.[13] According to the Spanish COPD guidelines,[14] and as recently proposed elsewhere for mass screening programs,[15] we used pre-bronchodilator lung function to classify airflow limitation, defined by an FEV_1/FVC ratio < 0.70.

Subject selection and evaluation

During April and May 2007, customers who entered the participating community pharmacies and who seemed to be in the targeted age range ($>$40 years) were approached with opening questions about respiratory symptoms or smoking. If a candidate expressed interest in the topic, the pharmacist explained the objectives of the research and the voluntary nature of participation. Participants signed a consent form if interested, and the pharmacist then asked about previous diagnoses of lung disease or use of inhaled medication and sociodemographic data as stipulated by

a written questionnaire. Individuals aged < 40 years or who had a history of lung disease or use of inhalers were excluded at this time. To assess the risk of COPD, we used the GOLD screening questionnaire, as recommended in the 2006 guidelines.[4] This questionnaire consisted of questions on five items referring to more breathlessness than people of the same age, chronic cough, chronic sputum, age > 40 years, and smoking. Subjects with ≥3 affirmative answers were offered spirometry. Those in whom the FEV_1/FVC ratio was <0.70 were referred to a lung function unit in a university hospital (Hospital de la Santa Creu i Sant Pau or Hospital Clinic I Provincial, both in Barcelona). Within 24–48 h spirometry was repeated by an expert nurse using the same brand of spirometer. Refusal to continue participating in the study was recorded with the specified reason. Smokers were also encouraged to quit smoking through a cessation program, as giving this advice was part of the normal routine for these volunteer community pharmacists.

Statistical methods

Descriptive data of participants and subgroups are presented as mean and standard deviation unless otherwise stated. We compared participants with a low and high COPD risk, and spirometry data in the normal and abnormal groups, using *t*-tests for normally distributed parametric data and the Kolmogorov–Smirnov test for non-parametric data (quality spirometry, gender, tobacco exposure and GOLD screening score). Using the Wilcoxon rank sum test we compared each subject's expiratory flow rates measured at the pharmacy and the hospital. A Bland–Altman graph was also created to show individual differences between pharmacy and hospital FEV_1 values. Statistical significance was set at $P \leq 0.05$ for comparisons between groups. All analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (SPPS Inc., Chicago, Illinois, USA).

Results

A total of 254 customers approached by the pharmacists expressed interest in the study; 188 (74%) agreed to participate by signing the consent form after the nature of the study was explained. Reasons given by the 66 subjects who declined to participate included no time to wait ($n = 28$, 42%), no interest ($n = 12$, 18%), already diagnosed with a respiratory condition ($n = 14$, 21%) and others ($n = 12$, 18%). Twenty-seven of these 188 initial participants were excluded by the pharmacists when criteria were reviewed; reasons for exclusion at this time were age < 40 years or previous lung disease (Fig. 1).

The 161 remaining volunteers agreed to fill in the GOLD screening questionnaire for COPD. The average age of these participants was 55 ± 11 years, 94 (58%) were women, and 124 (77%) were smokers or ex-smokers. The mean GOLD screening score was 3.0 ± 1.2. Sixty-one of the 161 respondents (38%) had a score < 3 and 100 (62%) a score of ≥3, indicating they were at high risk for COPD (Table 1). The age and proportion of women in the two groups were similar. More high-risk customers were smokers or ex-smokers, and they also had a higher mean GOLD screening score than those at low risk. Those in the high-risk group were offered spirometry; only three refused and one was excluded because she was ill with a respiratory infection at that time. Customers who attended spirometry had at least one symptom. Chronic cough was the most common (66%) but each symptom was present in about half the subjects (chronic sputum 54%, breathlessness 63%). Low-risk subjects were more frequently asymptomatic (chronic cough 6%, chronic sputum 5%, breathlessness 3%).

Thus, 96 high-risk subjects performed spirometry in the pharmacy. Sixty-five (68%) had an $FEV_1/FVC\%$ ratio ≥ 0.70 and 21 (22%) had an $FEV_1/FVC\%$ ratio < 0.70, indicating airflow limitation. The distribution of airflow limitation by age is shown in Fig. 2. Ten were unable to perform the manoeuvres correctly. Personal characteristics and spirometry results for those who performed a correct spirometry are shown in Table 2. According to our pre-bronchodilator data, airflow limitation was mild in 13 (62%) of the subjects in whom it was detected, moderate in 7 (33%) and severe in 1 (5%).

Out of the 86 patients who underwent spirometry, airflow limitation (FEV_1/FVC ratio < 0.70) was detected in 21 (24%), and they were invited for referral to a hospital pulmonary function laboratory for further assessment. Only 11 (52%) subjects both accepted referral and actually went to the laboratory. In all cases, the airway obstruction was confirmed. Moreover, the lung function values recorded in the community pharmacy and in the hospital pulmonary function laboratory were similar in both settings (FEV_1, $P = 0.5$; FVC, $P = 0.89$; and FEV_1/FVC ratio, $P = 0.14$) (Fig. 3). Of note, among those referred to the hospital, two presented a pre-bronchodilator $FEV_1 < 60\%$.

Finally, spirometric curves in the pharmacy were of acceptable quality overall, with 70% rated as A or B quality by the spirometer software and 73% were considered of acceptable quality by the lung function expert. The quality rating tended to be even better in subjects with airflow limitation, 76% of whom were considered to have A or B quality curves, but the difference was not significant ($P = 0.71$).

Discussion

Individuals at high risk for COPD can be detected by spirometry screening undertaken by adequately trained pharmacists in urban community pharmacies. Our data show that pharmacists were able to identify customers with respiratory symptoms and/or smokers in a population in which the majority were middle-aged subjects who had never been tested for COPD. Furthermore, the pharmacists were able to supervise high quality spirometry manoeuvres in 70% of subjects, finding one case of airflow limitation for every five individuals tested, a rate that was similar to that reported for the UK primary care setting.[16]

Spirometry in the primary care setting has been shown to be useful in screening for COPD and it continues to be promoted as the means for diminishing the population underdiagnosis of this disease.[17] Additionally, the usefulness of reporting individual lung age to smokers has been elegantly confirmed recently.[19] However, lack of technical or human resources in primary care is a limiting

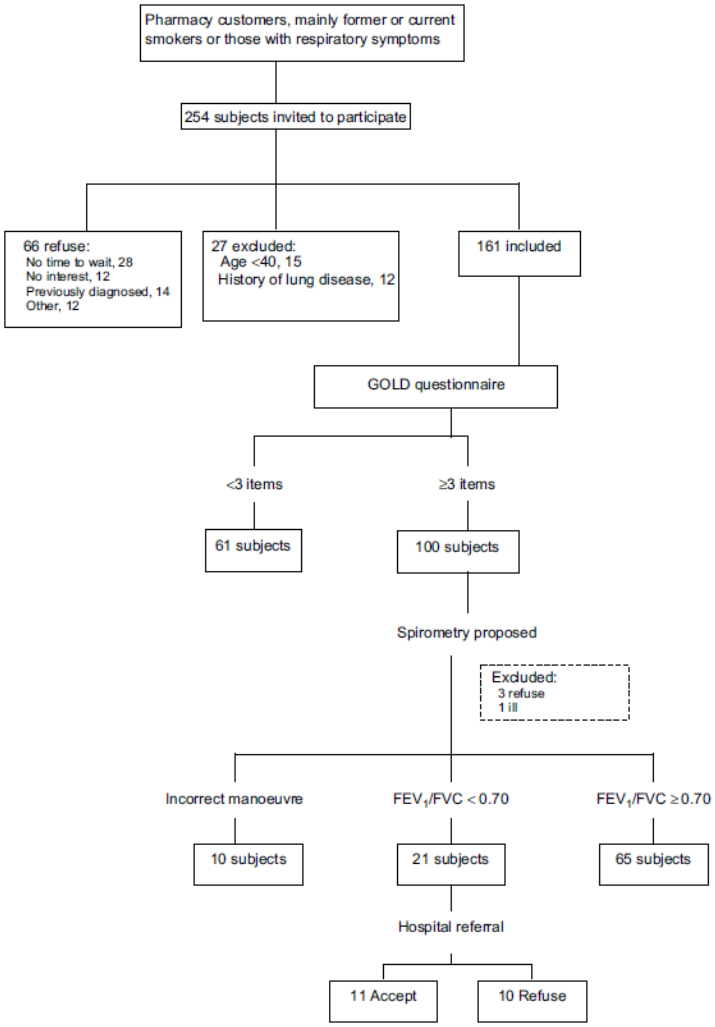

Figure 1 Flow chart showing subject processing from pharmacy to hospital referral.

factor,[18] compounded by primary care physicians' low rate of request for spirometry.[20] Therefore, underdiagnosis in the primary care setting continues to be inordinately common.[21] In this pilot study, our finding that the community pharmacy can provide a complementary setting for COPD case finding in the general population offers hope of improving the health care system's screening potential.

Table 1 Characteristics of the participating pharmacy customers.

	All customers ($n = 161$)	Low risk ($n = 61$)	High risk ($n = 100$)
Age, mean ± SD	55 ± 11	56 ± 11	55 ± 11
Women, *n* (%)	94 (58)	38 (62)	56 (56)
Smoking history, *n* (%)	124 (77)	36 (59)	88 (88)[a]
GOLD score, mean ± SD	3.0 ± 1.2	1.7 ± 0.4	3.8 ± 0.8[a]

[a] Significant differences were found between low-risk and high-risk groups for smoking history (smokers or ex-smokers) ($P = 0.01$) and GOLD score ($P = 0.01$). GOLD = Global Initiative for Chronic Obstructive Lung Disease.

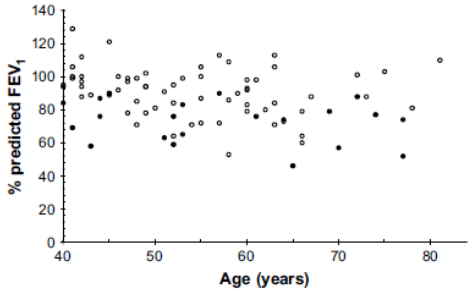

Figure 2 Distribution of percent predicted FEV_1 by age for all participants (subjects with airflow limitation are represented by filled circles).

Widespread use of spirometry in screening for COPD has been questioned.[2] The current recommendations are to study subjects at high risk.[2–4] All subjects offered spirometry in our study were in fact symptomatic as detected by the questionnaire, suggesting that inappropriate resource consumption can be kept under control by applying a GOLD-criteria-based screening questionnaire. Our use of the GOLD screening questionnaire to assess the risk of COPD followed recommendations in the 2006 guidelines,[4] although recently validated questionnaires with the same goal are available elsewhere.[22]

Our study also shows that pharmacists can obtain valid spirometries if they are well-trained and highly motivated. Seventy percent of the spirometry curves were judged to be of A- or B-level quality after review by an expert in lung function testing; that success rate was higher than the reported 63% in a previous pharmacy study.[8] Only 10% of the subjects who were invited to perform spirometry in the community were unable to produce correct manoeuvres under the pharmacists' supervision, a situation quite similar to that reported for the primary care level.[23] The quality of spirometry was also reflected in the lack of differences in results in pharmacy and hospital measurements for the same subjects.

An interesting finding was the predominance of women among the pharmacy customers. Given that the prevalence of COPD in Spain has been found to be 14.3% in men and 3.9% in women in a population-based study,[6] we expected males to predominate among the tested subjects. However, women accounted for 58% of the subjects and 57% of the positive spirometries. The pharmacy seems to be a particularly good setting, therefore, to find cases in women, among whom the prevalence of COPD seems to be rising.[24]

A limitation of this study was the absence of a bronchodilator test. Although most guidelines recommend the use of post-bronchodilator spirometry to diagnose and stage COPD, other authors call for simplicity, especially for large-scale screening.[15,25,26] We ruled out the use of post-bronchodilator tests in pharmacies because of evident concerns about practicality, safety, and efficiency. Should this approach be implemented, we continue to consider that bronchodilator tests should be performed in the hospital laboratory after referral. Another limitation and the main logistical problem of this study is related to referral of subjects with possible COPD from the community pharmacy to the hospital. In our study, nearly half of those with spirometry results indicating airflow limitation declined a hospital appointment. No time or lack of interest were the reasons most often stated. We suspect that declining referral may reflect either a lack of interest in quitting smoking or milder disease. The general population has little knowledge about COPD,[27] in comparison with other conditions such as cardiovascular disease, and they, therefore, do not consider respiratory disease to be a serious personal threat.

To conclude, in this pilot study, we have shown that COPD case finding by spirometry in urban community pharmacies is feasible. Pharmacists have access to high-risk, middle-aged subjects who have never been tested for COPD, and if the pharmacists are correctly trained, they can detect airflow limitation by spirometry with results that are similar to those previously reported at primary care level. Pharmacists are health service professionals who are not presently involved in screening for COPD but whose

Table 2 Characteristics and respiratory function data for subjects who performed spirometry correctly and were classified by FEV_1/FVC ratio as having normal (ratio ≥ 0.70) or reduced airflow.

	All spirometries ($n = 86$)	Normal spirometry ($n = 65$)	Airflow limitation ($n = 21$)
Women, *n* (%)	49 (57)	37 (57)	12 (57)
Age (y)	55 ± 11	54 ± 10	57 ± 12
Smoking history, *n* (%)	74 (86)	56 (86)	18 (86)
GOLD score	3.8 ± 0.8	3.8 ± 0.8	3.7 ± 0.8
BMI	27.1 ± 5.1	27.8 ± 4.7	25 ± 5.7[a]
FEV_1 (l)	2.5 ± 0.7	2.7 ± 0.6	2.1 ± 0.7[a]
FEV_1 (% ref. val.)	86 ± 0.2	91 ± 0.1	72 ± 0.1[a]
FVC (l)	3.4 ± 0.9	3.4 ± 0.9	3.24 ± 1.0
FVC (% ref. val.)	89 (0.2)	90 (0.2)	85 (0.1)
FEV_1/FVC ratio	0.76 (0.1)	0.79 (0.1)	0.64 (0.1)[a]

Data are expressed as mean ± SD unless otherwise noted.

[a] Significant differences in BMI ($P = 0.03$), FEV_1 ($P = 0.01$), FEV_1% ($P = 0.01$) and FEV_1/FVC ratio ($P = 0.01$) were found between the normal and abnormal spirometry groups.

FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; and GOLD = Global Initiative for Chronic Obstructive Lung Disease.

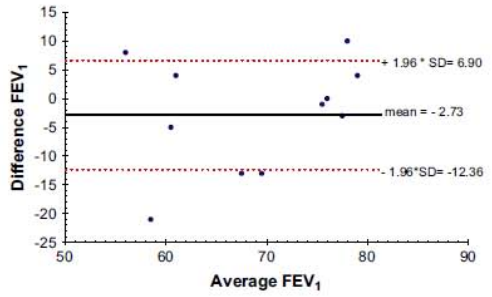

Figure 3 Bland–Altman graph for comparison of the pharmacy- versus hospital-obtained percent predicted FEV_1.

participation may represent a useful complementary strategy for early case finding.

Conflict of interest statement

Dr. Diego Castillo: Research grant: Boehringer–Ingelheim. Dr. Rafael Guayta, Jordi Giner, Felip Burgos, Carme Capdevila, Dr. J.B. Soriano, Merce Barau and Dr. Pere Casan: none of these authors have a conflict of interest to declare in relation to this work.

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Annex 2. Study 2.

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Airflow obstruction case finding in community-pharmacies: A novel strategy to reduce COPD underdiagnosis

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KEYWORDS
COPD;
Comunity-pharmacies;
Forced spirometry;
Case finding

Summary
Background: Community pharmacies (CP) have access to subjects at high-risk of suffering Chronic Obstructive Pulmonary Disease (COPD). We investigated if a COPD case finding program in CP could be a new strategy to reduce COPD underdiagnosis.
Methods: Prospective, cross-sectional, descriptive, uncontrolled, remotely supported study in 100 CP in Barcelona, Spain. Pharmacists were trained in a four-day workshop on spirometry and COPD, and each was provided with a spirometer for 12 weeks. The program included questionnaires and forced spirometry measurements, whose quality was controlled and monitored by web-assistance.
Findings: Overall 2295 (73.5%), of 3121 CP customers invited to participate in the program accepted, and 1.456 (63.4%) were identified as "high risk" for COPD using the GOLD questionnaire.

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Only 33 could not conduct spirometry, and a pre-bronchodilator airflow limitation (FEV_1/FVC ratio <0.7) was confirmed in 282 (19.8%); 244 of these were referred to their primary care (PC) physician for further diagnostic and therapeutic work-up, but only 39 of them (16%) fed-back this information to the pharmacist. Clinically acceptable quality spirometries (grade A or B) were obtained in 69.4% of the cases.

Conclusion: This study shows that adequately trained and supported community pharmacists can effectively identify individuals at high risk of having COPD and can thus contribute to ameliorate underdiagnosis in this disease. Links between PC and CP should be improved to achieve a useful program.

Introduction

It is now estimated there are at least 328 million people with chronic obstructive pulmonary disease (COPD) in the world, yet 80% or more of them are not diagnosed and, hence, not treated [1,2]. Several position papers have recently emphasized the importance of strategies to reducing under-diagnosis in COPD [3,4].

COPD case finding using spirometry in high risk subjects is the primary strategy based in the results of previous European studies. But these experiences have been mainly investigated in primary or secondary care and therefore these results have not been validated outside this setting [5].

In a previous small pilot study, we showed that COPD case finding in community-pharmacies (CP) is feasible [6]. Now, in the current study: 1- we extend this pilot observation to a much large number of CP (n = 100); 2- we use Information and Communication Technologies (ICT) to provide remote spirometric quality control to CP, as recently shown in primary care (PC) [7]; and, 3- we explore the real-life effectiveness of this COPD case finding program by focusing in particular on the inter-relationship between components of the health-care system (PC and CP).

Methods

Design, setting and patients of the study

This was a prospective, cross-sectional, descriptive, multicenter, uncontrolled, remotely supported study. The Official College of Pharmacists of Barcelona (*Col·legi Oficial de Farmacèutics de Barcelona-COFB*) offered to all its members the possibility to participate, and 100 CP located in the province of Barcelona (both rural and urban settings) volunteered, most of whom had previously participated in other CP health-care programs. CP services in Barcelona are no different from the rest of Spain. CP were divided in 5 groups (20 pharmacists each) that participated in the study in five sequential "Study Rounds", from September 2010 to February 2012 (approximately 12 weeks each round). No sites were revisited. All participants signed a consent form.

In brief (Fig. 1), during regular working hours, CP customers within the targeted age range (>40 years) were asked by the attending pharmacists about respiratory symptoms and smoking. If the customer expressed an interest in the topic, the pharmacist explained the volunteer nature, objectives, goals and risks of the study. If interested, customers signed a consent form and answered a standardized questionnaire that included socio-demographic data as well as questions about previous respiratory diseases and use of respiratory medications. Individuals younger than 40 years or with a previous history of lung disease or use of respiratory medication were excluded from the study at this time (Fig. 1). Remaining participants were asked to answer a 5-item questionnaire (older than 40 years of age?, current or previous smoking exposure?, more breathlessness than peers of the same age? and presence of chronic cough or expectoration?) to identify subjects at high-risk of suffering COPD (those with 3 or more "yes" answers), as proposed by the Global Initiative for Chronic Obstructive Disease (GOLD) [8]. High risk subjects were then offered a standardized forced spirometry (FS) (see below), and those with evidence of airflow limitation (as defined by an FEV_1/FVC ratio lower than 0.70), were recommended to contact their PC physician for further clinical evaluation, conventional spirometry and eventual treatment (Fig. 1). Finally, the PC physician was asked to return to the CP a questionnaire with the specific diagnostic and/or therapeutic actions taken in that particular individual within the next 3 months. In all cases, the specific reason(s) for refusal to participate in the study at any stage (Fig. 1) were recorded.

Every pharmacist participating in the study attended a four-day (16 h) hands-on training course on FS according to international guidelines and officially accredited by the Catalonian Government using the spirometer later employed in the study (Easy-One®, ndd Medical Technologies and Sonmedica, Zurich, Swizerland) [9—11]. They were assessed at the end of the course using a questionnaire to certify competence. Pharmacists were also instructed in the management of the web-database used during the study to collect all data (Linkcare®). Following their everyday practice, all smokers were encouraged to quit smoking and those in high risk for COPD (not confirmed by the test) were recommended to contact PC.

Neither the pharmacist or PC physician received any incentives to undertake the study.

Measurements

Like in our pilot study, spirometry was conducted by using an Easy-One® spirometer, because it has been shown to be

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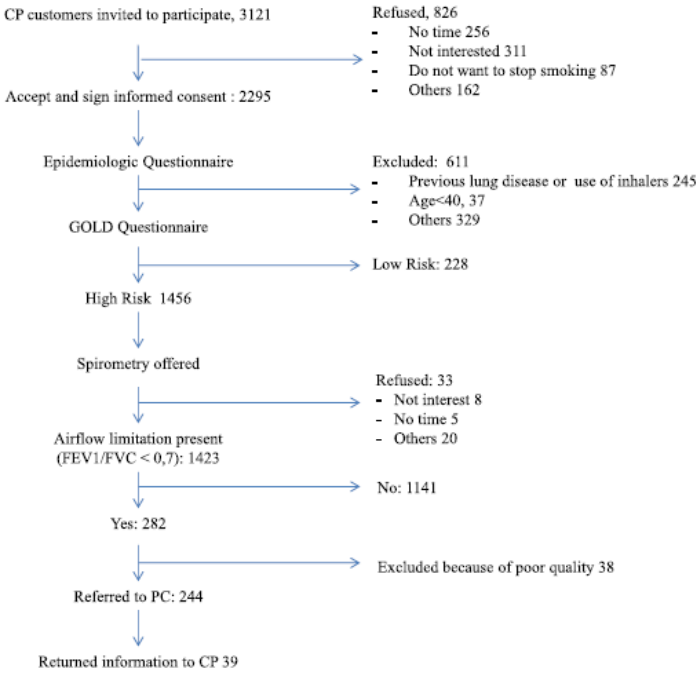

Figure 1 STROBE flowchart of participation in the study.

adequate for population studies, it does not require regular calibration, and it fulfills all ERS/ATS technical recommendations [6,12—14]. However, spirometers were calibrated and checked before and after every round to control the quality of the measurements. As recommended by guidelines, each CP allocated an adequate space for spirometry testing (separated room). Every CP has available a personal computer with internet access so spirometric results were uploaded automatically into a specific web database (Linkcare®) [7].

As the patients were referred to primary care, airway obstruction was defined following their current recommendation that define airflow obstruction as GOLD [15]. Only pre-bronchodilator spirometry was done. Reference values used correspond to the Spanish population [16]. Spirometry quality was classified into grade A to F following international recommendations (Appendix 1) [17]. An expert in spirometry (FB) reviewed and rated manually all measurements loaded into the system and reported back weekly to each CP on the quality of their tests, including their repeatability, characteristics and onset (back extrapolation) and end (expiratory time) maneuvers. Pharmacists were then able to ask specific queries and feedback to the expert. The Linkcare® ICT platform provided traceability of all actions and dialogs that occurred during the study [7].

Statistical analysis

Data were quality controlled centrally and a homogenous template to translate all coding was applied. Variables were double-checked by each pharmacist and the principal investigator, and values that were considered as potential errors or outliers were individually discussed and confirmed, or removed. Comprehensive tabulations with ranges, mean and standard deviation of all quantitative variables, and percentages of all qualitative variables, were available for each CP. Results are presented as mean (±standard deviation) or n (and percentage) as needed. The Student T-test and Chi^2 test were used to compare differences between groups as appropriate. A $p < 0.05$ was considered statistically significant.

Ethical approval

The study was approved by the research ethics board at Hospital del Mar, Barcelona, Spain (2008/3128/I). The protocol is consistent with the principles of the Declaration of Helsinki.

Role of the funding source

None of these funders (SEPAR and Boehringer-Ingelheim) had any part in the collection, management, analysis and interpretation of the data. Also they were not involved in preparation, review or approval of the manuscript.

Results

The flow of participation in the study is presented in Fig. 1. Of 3121 CP customers (age 55.3 ± 11; 45.8% women)

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invited to participate in the program, 2295 (73.5%) accepted (age 55.0 ± 11; 46.4% women). It appears there was no non-response bias, as the age and gender distribution of participants were not significantly different from those not participating. Participants were distributed in each round as following: 18.1%, 21.17%, 16.7%, 23.6%, 19.9%. Of the 2295 participants, 1456 (63.4%) were identified as "high risk" for COPD using the GOLD screener questionnaire. As age was an inclusion criterion in our case finding strategy, every subject scored one point at the least in the GOLD screener questionnaire. Demographic and clinical characteristics of participants at low or high risk groups for COPD are presented in Table 1, where it can be seen that age was similar in both groups (55.4 ± 10.4 years versus 54.2 ± 10.2 years in the low vs. high risk group, respectively, p n.s.), but participants at high risk were most often male ($p < 0.05$), and with higher smoking exposure and, experiencing more respiratory symptoms, all these being items within the screener questionnaire (Table 1).

The majority (69.4%) of spirometries performed were grade A and B, and they were considered of acceptable clinical quality by the expert (FB). This percentage remained stable in the five sequential study rounds (Fig. 2, panel A). As a sensitivity analysis following previous reports, should we had considered grade C also as clinically acceptable, this figure would have risen to 75.1% [18]. Only 8.9% were ranked as quality grade F, the worst possible.

We did additional analyses to estimate the proportion of misdiagnosis due by using the airflow criterion of fixed ratio instead of Lower Limit of Normal (LLN). Overall, 586 subjects (41.18%) presented airflow limitation using the LLN. The misdiagnosis was mainly in young adults. While in patients above 60 years old there were no significant differences in prevalence of airflow limitation depending on the criteria used (405 subjects: LLN 136 (33.58%), Fixed Ratio 142 (35.06%)) that was not the case in those under 60 years old (1018 subjects: LLN 450 (44,20%); fixed ratio 140 (13.75%))".

Table 1 Demographic and clinical characteristics of participants at low and high risk of COPD. Asterisk indicate $p < 0.05$ between the two groups.

	Low risk (n = 228)	High risk (n = 1456)
Age, mean ± SD	55.4 ± 10.4	54.2 ± 10.2
Women, n (%)	53.7%	45.1%*
Smoking history, (%)		
Never	14.1	0.7*
Current	38.3	64.0*
Former	47.6	35.3*
GOLD risk score, mean ± SD	1.7 ± 0.7	3.6 ± 0.7*
With chronic cough, (%)	1.3	49.2*
With. chronic sputum production, (%)	3.1	48.5*
More breathlessness than people of the same age, (%)	3.1	64.6*
Current or former smoker, (%)	85.9	99.3*

Table 2 shows the clinical characteristics and spirometric results of participating subjects at high risk for COPD. Of 1423 individuals completing quality-controlled pre-BD spirometry, 282 (19.8%) had airflow limitation with an $FEV_1/FVC\%$ ratio <0.70 compatible with COPD. This was remarkably reproducible in all temporal study rounds (Chi^2 p for trend n.s.) (Fig. 2, **panel B**), with a slight trend to increase overtime. Patients with airflow limitation were significantly older, mostly males and (by definition) had worse lung function than those with normal spirometry but interestingly, cumulative smoking exposure and body-mass index (BMI) were similar in both groups (Table 2). Fig. 3 presents the distribution of FEV_1 (% predicted) by age in participants with and without airflow limitation.

All subjects (244) with pre-BD airflow limitation but those 38 (13.5%) with poor quality spirometry were referred to their PC physician for further evaluations. But CP were unsuccessful to retrieve follow-up data from PC physicians as only 39 (15%) of them provided feed-back to the CP and returned the filled up questionnaire requested. In eleven of them (28%) COPD was confirmed by the PC physician, and in 6 (15%) inhaled treatment was started.

Discussion

Our findings extends our previous pilot experience to a larger population of community pharmacies (n = 100) and confirms that a COPD case finding program in high-risk customers is feasible. Besides, this program can effectively identify probable underdiagnosis COPD patients. Also confirms that the use of an ICT platform to control the quality of spirometries is both feasible and effective in CP. But an improved coordination between PC and CP is needed to develop an useful program.

Underdiagnosis, hence undertreatment, is one of the main unmet medical needs in COPD. Decreased quality of life and daily life activities have been reported in undiagnosed COPD subjects [19,20]. Unfortunately, epidemiological studies in Spain showed that from 1997 to 2007 COPD underdiagnosis was reduced by only 5 percentage points, from 78% to 73% [21]. Therefore, reducing COPD underdiagnosis is a public-health priority. COPD case finding has been defined as a useful strategy to help reducing underdiagnosis. Zielinski et al. explored in Poland the option of screening high-risk COPD population through mass media advertisement using spirometry. High-risk subjects were encouraged to contact one of the 12 participating centers to attend for a spirometry. The prevalence of airflow obstruction was 24.3% [22,23]. Moreover, Van Schayck et al. investigated the effectiveness of case finding program in general practise [24]. Their results showed that by testing one smoker a day, an average practice could identify one patient at risk a week with little cost to the practice. Maio et al. explored an opportunistic approach with the European Respiratory Society tent. The results highlighted the usefulness of detecting airway obstruction in large numbers of city residents during large awareness initiatives [25]. Nonetheless, Jordan et al. showed the systematic case-finding strategy can potentially identify 70% more new cases than opportunistic identification alone in PC [26]. In the finding program assessed in our study, one high risk

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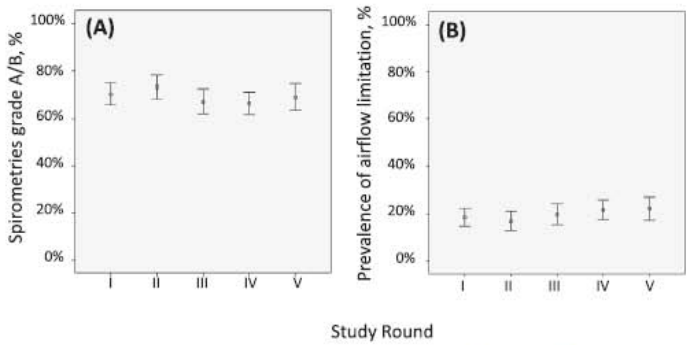

Figure 2 **Panel A.** Proportion of A and B grade spirometries by study rounds. Footnote: There were no statistically significant differences between them. **Panel B.** Proportion of high-risk subjects for COPD with airflow limitation ($FEV_1/FVC < 0.70$) by study rounds. There were no statistically significant differences between them.

individual was identified in five assessed customers (20%). Further, the proportion of individuals with airflow limitation in our study was independent of the study round (Fig. 2, panel B), supporting the internal validity of this observation. This figure is remarkably similar to that published in primary care, indicating that this type of case finding strategies are likely to work similarly in CP [5,24,27].

Ours is amongst the first studies to explore spirometric screening in pharmacies [28]. Our study required the evaluation of a huge numbers of spirometries in CP and clearly indicates that well-trained and supervised (using web-based tools) pharmacists can obtain high quality spirometries in CP. This result is similar to those published recently in a primary care setting using similar tools [7,29]. We found that most spirometries were of clinically acceptable quality grade (Fig. 2, panel A).] High quality FS is essential for the diagnosis and management of several lung diseases, including COPD [2,30–33]. Adequate training following international/national guidelines is basic to perform high quality spirometries. Besides technicians requires regular update to maintain and improve their skills. Telemedicine is a useful tool to keep spirometry quality and enhanced technicians training and would help to expand high quality spirometry outside pulmonary function laboratories. Therefore, these results support that in the future, if it is necessary and under adequate quality supervision, spirometry could be perfomed in CP.

Table 2 Clinical characteristics and respiratory function for COPD high risk subjects who performed spirometry correctly and were classified by FEV_1/FVC ratio as normal or with airflow limitation (FEV_1/FVC <0.70). Asterisk indicate $p < 0.05$ between the two groups.

	Normal spirometry (n = 1141)	Airflow limitation (n = 282)
Age, mean ± SD	52.8 ± 9.6	59.7 ± 10.7*
Women, n (%)	47.5	35.5*
Smoking history, (%)		
Never	0.5	0.7
Current	63.5	65.7
Former	36.0	33.6
GOLD screener score, mean ± SD	3.5 ± 0.7	3.7 ± 0.7*
BMI in kg/m^2, mean ± SD	26.9 ± 6.0	26.5 ± 4.4
FEV_1 in L., mean ± SD	2.9 ± 0.69	2.21 ± 0.75*
% predicted FEV_1, mean ± SD	102 ± 2	82 ± 2*
FVC in L., mean ± SD	3.7 ± 0.87	3.5 ± 1.06
% predicted FVC, mean ± SD	101 ± 2	99 ± 2
FEV_1/FVC, mean ± SD	0.78 ± 0.05	0.63 ± 0.07*

BMI: Body mass index; FEV_1: Forced expiratory volume in the 1st second; FVC: forced vital capacity.

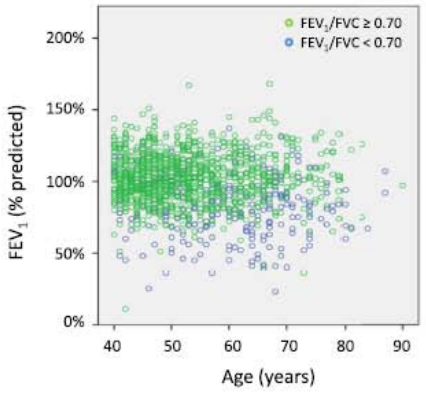

Figure 3 Relationship between age and FEV_1 (% predicted) in participants with (blue circles) and without (green circles) airflow limitation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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In fact, these observations add to the emerging concept of "Healthy Living Pharmacy" (HLP) that explores the potential of CP to promote healthy living [34]. CP can play an important role in a number of health-promoting programs, including smoking cessation, cardiovascular diseases or screening for HIV [35,36]. Within respiratory diseases, previous studies have shown that CP can help in the management of asthma, but to our knowledge, their role in COPD case finding had not been well addressed before (other than in previous small pilot studies) [7,37,38]. Of course, COPD diagnosis is out of pharmacist scope. Identified high-risk COPD patients should be referred to PC, where a GP will investigate and diagnose them. Admittedly, the diagnosis of COPD requires the combination of exposure to risk factors, symptoms, non-fully reversible airflow limitation and the exclusion of other obstructive airway diseases such as asthma and bronchiectasis, among others [30]. Given that only a minority of individuals returned the information requested to their PC physician (Fig. 1), we cannot provide a final figure for a confirmed diagnosis of COPD. This finding does not detract from the validity of the case finding strategy in CP investigated here because, as stated above, clinical diagnosis cannot be a goal in CP. Exact opposite, this finding illustrates the need to improve the coordination between formal (PC) and informal (CP) stake-holders in our health-care system to develop a useful program.

Our study has some limitations. First, it could be a possible cohort effect due to the use of an old reference equation. Because of logistic issues, we did not measure post-bronchodilator spirometry despite that this is recommended for COPD diagnosis [2,30]. Yet, pre-bronchodilator spirometry has been widely used in epidemiological studies [39]. Regarding the use of Fixed Ratio (<0.70) versus LLN to define airway obstruction in CP, certainly one can argue that Fixed Ratio increases COPD misdiagnosing. However, given the relatively young distribution of our participants, this misdiagnosis by the fixed ratio was an underestimate of results by LLN. Viegi et al. showed that the estimated prevalence of airflow limitation depends much on the criteria used for definition [40]. Our results confirm what Cerveri et al. have shown previously: this gap is higher in young adults [41]. The current GOLD Guidelines, as the Catalonian and Spanish Primary Care COPD guidelines, still recommend the use of Fixed Ratio. Then we decided that the CP should work in keeping with PC to avoid misunderstandings. Nonetheless, these results highlight the value of using LLN in young subjects and the need of a standardized airflow limitation definition across different guidelines Finally, our strategy involved the use of higher trained than average pharmacists, ICT support, two questionnaires and quality-controlled forced spirometry. It can be argued it is too cumbersome for many CP, so simpler screening strategies, perhaps using questionnaires and peak-expiratory flow measurements, deserve investigation [42,43]. Finally, as discussed previously, low feed-back from PC is another limitation. When the study was designed, a link between PC and CP could have been developed to obtain follow up from the majority subjects. However, because this would be a special case set up, aside for real life, this idea was discarded as the results would have not presented every day CP practice. Besides a negative result, as we have observed, could be more helpful than a positive "artificial" one to strength future programs implementing PC and PC coordination.

Conclusion

In summary, this study shows that adequately trained and supported community pharmacists can effectively identify individuals at high risk of suffering COPD. CP could be a useful tool to help reducing COPD underdiagnosis. However, developing useful links between PC and CP is mandatory to achieve a successful program.

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Contributors

All authors participated in the study conception, designed and data analysis. JBS was responsible for supervision statistical analyses. PL for handling of data and study database. All authors wrote and revised the manuscript. All authors have given final approval of the version to be published.

Declaration of interest

All authors report that the study was funded by Boehringer-Ingelheim and Spanish Respiratory Society; but authors have nothing else to disclose except that FB has stocks from Linkcare Health Solutions.

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Appendix 1. Quality scores of spirometry maneuvers according to ATS/ERS standardization. (17) A and B scores are considered high quality measurements

Quality score	Description
A	3 acceptable maneuvers, and best 2 matched with differences in FVC and/or FEV_1 <0.15 L
B	3 acceptable maneuvers, and best 2 matched with differences in FVC and/or FEV_1<0.20 L
C	2 acceptable maneuvers, and best 2 matched with differences in FVC and/or FEV_1<0.25 ml
D	1 acceptable maneuver
F	None acceptable maneuvers

Appendix 2. Pharmacists collaborators

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Annex 3. FarmaEpoc Editorial.

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Editorial

El papel de las farmacias comunitarias en el control de las enfermedades respiratorias

The role of community pharmacies in respiratory disease control

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La farmacia comunitaria (oficina de farmacia) es una pieza fundamental del entramado de los sistemas de salud. Aunque su actividad principal consiste en la dispensación de fármacos, esta no es exclusiva, puesto que la farmacia realiza una enorme labor en el campo de la prevención de enfermedades y en el seguimiento de pacientes crónicos. Es un hecho muy consolidado la evolución constante hacia una farmacia asistencial más orientada al paciente. En consecuencia, el futuro del farmacéutico comunitario se dirige a la implantación de servicios profesionales que suponga una implicación más activa en los procesos de salud de cada paciente.

A pesar de que hay un amplio consenso sobre la importancia de implantar servicios de atención farmacéutica en la farmacia comunitaria, el proceso de cambio está siendo lento y la implantación generalizada es aún minoritaria. Sin embargo, la actualidad ha imprimido velocidad a este cambio puesto que el sistema prima optimizar los recursos. Por lo tanto, urge definir el papel de los farmacéuticos comunitarios en el control de las enfermedades crónicas más prevalentes. Y lo más importante, redefinir los programas de salud incorporando las herramientas que esta pueda proporcionar[1].

En este escenario, es importante que las enfermedades respiratorias no queden rezagadas frente a otras especialidades. En consecuencia será importante diseñar conjuntamente con sociedades científicas y colegios profesionales programas de atención farmacéutica en el campo de la medicina respiratoria.

Desde nuestra perspectiva debería contemplarse de forma prioritaria las siguientes acciones:

1. *Diagnóstico precoz:* actualmente la farmacia comunitaria ya participa en programas de detección precoz de enfermedades como, por ejemplo, el cáncer colorrectal y el HIV de forma exitosa[2,3]. Es bien conocido que el infradiagnóstico es un problema de gigantesca repercusión en enfermedades respiratorias crónicas como la enfermedad pulmonar obstructiva crónica (EPOC). Por lo tanto, ¿podrían las farmacias participar en el estudio de casos de EPOC? Los estudios científicos nos dicen que sí. Un estudio pionero auspiciado por la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) demostró que los farmacéuticos están en contacto con sujetos de riesgo de padecer EPOC, en general adultos de mediana edad, previamente no estudiados, a los que son capaces de seleccionar y estudiar utilizando un cuestionario y realizando una espirometría[4]. Experiencias similares se han realizado en asma y, probablemente esta estrategia sea extrapolable a otras enfermedades como el síndrome apnea-hipoapneas del sueño (SAHS). Un detalle interesante de estos estudios es la confirmación de la capacidad de los farmacéuticos para realizar espirometrías de calidad bajo un entrenamiento y control de calidad adecuado. No obstante, hay otros instrumentos de cribado más sencillos que potencialmente pueden tener más utilidad en medios extrahospitalarios como la farmacia comunitaria. En definitiva, es obvio que los farmacéuticos pueden contribuir a la lucha contra el infradiagnóstico de la EPOC aunque aún queda por definir la herramienta más adecuada.
2. *Deshabituación tabáquica:* no podemos olvidar que el primer paso en la prevención de enfermedades respiratorias es el asesoramiento sobre hábitos saludables entre los que se encuentra la abstinencia tabáquica. Por otro lado, una vez diagnosticada la enfermedad, el abandono del tabaquismo es fundamental para evitar la progresión de la enfermedad. Por todo ello, el asedio contra el tabaquismo no debe decaer. Existen en la literatura científica numerosas experiencias que evalúan el valor de las farmacias en la labor de deshabituación tabáquica en la población general. De entre ellas, destacan los alentadores resultados de 2 ensayos clínicos aleatorizados, que demostraban el positivo impacto de un programa de atención farmacéutica en los índices de abstinencia tabáquica entre sus participantes[5]. Por lo tanto, la incorporación e integración de las farmacias comunitarias en los programas de deshabituación tabáquica en cooperación con

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los centros de atención primaria y la atención especializada podría ayudar en la lucha contra el tabaquismo.

3. *Seguimiento de pacientes crónicos:* este es sin duda el servicio más estudiado y sobre el que encontramos más experiencia en diferentes países. Principalmente en las 2 enfermedades crónicas más prevalentes: asma y EPOC. En esta última, los estudios han demostrado que la farmacia puede incidir sobre 4 aspectos fundamentales: adherencia al tratamiento, técnica inhalatoria, vacunación antigripal y, como se mencionó previamente, deshabituación tabáquica[6]. Esto repercute positivamente en parámetros como calidad de vida, visitas al médico de atención primaria o gasto sanitario[7]. En el campo del asma, es importante destacar la labor desarrollada en Australia. Con programas innovadores han demostrado que la farmacia comunitaria puede contribuir al manejo del asma incidiendo en pacientes con mal control de la enfermedad. La implementación de un programa de atención farmacéutica permite mejorar aspectos como la técnica inhalatoria, calidad de vida o conocimiento de la enfermedad, con un impacto positivo que se refleja en cuestionarios de control de asma[8]. En resumen, la farmacia comunitaria puede desarrollar un papel positivo en el control de los pacientes con enfermedades respiratorias crónicas.
4. *Formación continuada:* a pesar de los alentadores resultados expuestos previamente, 2 requerimientos son necesarios para acelerar el proceso de integración de los servicios de farmacia: formación continuada y asistencia integrada. Los farmacéuticos que han participado en los proyectos antes mencionados han recibido, en su gran mayoría, una formación y supervisión adecuada. Sin ella, muchos de estos programas no hubieran sido tan exitosos. Por ejemplo, diferentes estudios han observado que existe un margen de mejora en los conocimientos y actitudes de los farmacéuticos sobre el manejo de la terapia inhalada[9]. Esto pone de manifiesto que aquellos que deseen participar en estos programas deben recibir la correspondiente formación continuada acreditada.
5. *Asistencia integrada:* pero sin duda, el gran reto que afronta la farmacia comunitaria es la integración de sus servicios con la asistencia médica y en especial, con la atención primaria[4]. Por ejemplo, si un farmacéutico detecta a un posible EPOC, debe de haber una manera segura y eficaz de que su médico de atención primaria tenga conocimiento de ello. O de la labor de atención farmacéutica realizada en un paciente asmático que recientemente ha iniciado tratamiento. Es sin duda la pieza angular de cualquier programa de salud que pretenda incorporar a la farmacia comunitaria. La coordinación a través de la historia clínica compartida y los sistemas de prescripción electrónica son un elemento estratégico imprescindible para la coordinación de los diferentes servicios sanitarios[10].

Sin duda, como han hecho otras especialidades médicas, es tiempo de iniciar los pasos para sumar al farmacéutico y la farmacia comunitaria al objetivo último de nuestra labor diaria: mejorar la prevención, diagnóstico y tratamiento de las enfermedades respiratorias. Para ello, es necesario que todos los colectivos implicados contribuyan a derribar las barreras y en su lugar, construyan puentes. Aquellos pacientes que los transiten serán sin duda unos peatones más saludables.

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Annex 4. Pilot Study. Referral letter to primary care.

FULL DE DERIVACIÓ

Benvolgut company,

El Sr/Sra.....ha participat en un estudi poblacional que té per objectiu la validació del procés de cribratge ambulatori de la MPOC mitjançant la realització d'una espirometria a les oficines de farmàcia de la província de Barcelona.

Aquest estudi es fruit d'una col·laboració subscrita entre la Sociedad Española de Neumología y Cirugía Toràcica i el Col·legi de Farmacèutics de Barcelona i compta amb el suport del Servei Català de la Salut.

En el context de l'estudi, aquest pacient ha presentat uns valors espiromètrics alterats, susceptibles de MPOC, que haurien de requerir una avaluació diagnòstica per part del metge del seu equip d'atenció primària.

Agraint la teva col·laboració,
Atentament,

Equip de l'estudi FarmaEpoc.

Annex 5. Pharmacists collaborators

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