

Long term follow-up of a tobacco prevention and cessation program in cystic fibrosis patients

Seguimiento a largo plazo de un programa de prevención y cesación tabáquica en pacientes con fibrosis quística

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Abstract

This study evaluates the impact over time of a telephone-based intervention in tobacco cessation and prevention targeting patients with cystic fibrosis (CF) in the Mediterranean region of Murcia, Spain. We conducted an experimental prospective study with a cohort of CF patients using an integrative smoking cessation programme, between 2008 and 2013. The target population included family members and patients from the Regional CF unit. The study included an initial tobacco exposure questionnaire, measurement of lung function, urinary cotinine levels, anthropomorphic measures and the administered intervention at specific time intervals. Of the 88 patients tracked through follow-up, active smoking rates were reduced from 10.23% to 4.55% ($p = 0.06$). Environmental tobacco exposure was reduced in non-smoker patients from 62.03% to 36.90% ($p < 0.01$) during the five year follow-up. Significant reductions in the gradient of household tobacco smoke exposure were also observed with a decrease of 12.60%, from 31.65% ($n = 25/79$) to 19.05% ($n = 16/84$) in 2013 ($p = <0.01$). Cotinine was significantly correlated with both active and passive exposure ($p < 0.01$) with a significant reduction of cotinine levels from 63.13 (28.58-97.69) to 20.56 (0.86-40.27) ng/ml ($p < 0.01$). The intervention to significantly increase the likelihood of family quitting (smoke-free home) was 1.26 (1.05-1.54). Telephone based interventions for tobacco cessation and prevention is a useful tool when applied over time. Trained intervention professionals in this area are needed in the environmental health approach for the treatment of CF.

Key words: Environmental tobacco smoke, cystic fibrosis, smoking prevention and cessation.

Resumen

Este estudio evalúa el impacto en el tiempo de una intervención telefónica de prevención y cesación tabáquica dirigida a pacientes con fibrosis quística (FQ) en la Región de Murcia, España. Estudio prospectivo experimental en una cohorte de pacientes con FQ utilizando un programa integrativo de cesación tabáquica, entre 2008 y 2013. La población diana incluye a pacientes y familiares de la unidad regional de FQ. El estudio incluyó un cuestionario inicial de exposición al tabaco, medición de la función pulmonar, niveles de cotinina en orina, medidas antropomórficas y la intervención realizada en intervalos de tiempo. De los 88 pacientes seguidos, la tasa de fumadores activos se redujo de 10,23% a 4,55% ($p = 0,06$). La exposición al humo ambiental de tabaco se redujo en los pacientes no fumadores de 62,03% a 36,90% ($p < 0,01$) durante los cinco años de seguimiento. Se observaron reducciones significativas en la exposición al humo ambiental de tabaco en los hogares, de 31,65% ($n = 25/79$) a 19,05% ($n = 16/84$) en 2013 ($p = <0,01$). La cotinina se correlacionó significativamente con la exposición al tabaco activa y pasiva ($p < 0,01$) con una reducción significativa de los niveles de cotinina de 63,13 (28,58-97,69) a 20,56 (0,86-40,27) ng/ml ($p < 0,01$). La intervención para aumentar significativamente la probabilidad de abandono familiar (hogar libre de humo) fue de 1,26 (1,05-1,54). La intervención telefónica mantenida en el tiempo es una herramienta útil para la prevención y cesación tabáquica. Profesionales entrenados en este modelo de intervención con enfoque en salud medioambiental son necesarios para mejorar el tratamiento de FQ.

Palabras clave: Humo ambiental de tabaco, fibrosis quística, prevención y cesación tabáquica.

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Cystic fibrosis (CF) is an autosomal recessive disease detected in 0.73 per 10,000 people in the Europe Union (Farrell, 2008), whose major manifestations are: pancreatic insufficiency, malabsorption, progressive deterioration of lung function and growth retardation (Beers & Berkow, 1999; Tyc & Throckmorton-Belzer, 2006). Patients with CF possess an increased risk for harm from exposure to tobacco smoke (Kopp et al., 2015; Ortega-García et al., 2012a; Raju et al., 2013). Several studies report that prenatal and/or postnatal exposure to tobacco smoke adversely affects children's lung function. The published CF studies report a prevalence of exposure to tobacco smoke from 6% to 21% lower than in general population (Mc Ewan, Hodson & Simmonds, 2012; Ortega-García et al., 2012a; Stern, Byard, Tomaszewski & Doershuk, 1987; Verma, Clough, McKenna, Dodd & Webb, 2001). Smoking is known to irritate mucosal linings and increase coughing and phlegm production in the respiratory tract, resulting in increased likelihood of bacterial infections, worsening of symptoms, and increased hospitalizations in patients with CF. Several studies have even found a dose-dependent relationship between the number of cigarettes smoked and the severity of respiratory disease in these patients. (Cook, Strachan & Carey, 1998; Ortega-García et al., 2012a; Smyth, O'Hea, Williams, Smyth & Heaf, 1994; Verma et al., 2001). Despite evidence of the deleterious effects of CF more studies are needed that evaluate interventions among CF patients and smoking cessation (Cook et al., 1998).

Telephone-based assistance programs are a useful methodology in tobacco cessation but more exploration is needed to measure its efficacy in CF patient populations (Lancaster & Stead, 2005). Additionally, the benefits of telephone assisted interventions plus counseling have yielded success (Lancaster et al., 2005; Ramon et al., 2013; Stead, Hartmann-Boyce, Perera & Lancaster, 2013). This intervention modality for smoking prevention and cessation in CF patients and their families has shown adequate adherence during one year follow-up (Ortega-García et al., 2012a). The objective of the present study is to evaluate the longitudinal impact of an integrated telephone based tobacco prevention and cessation intervention program amongst a cohort of CF patients during five-year follow-up in Murcia, Spain.

Patients and Methods

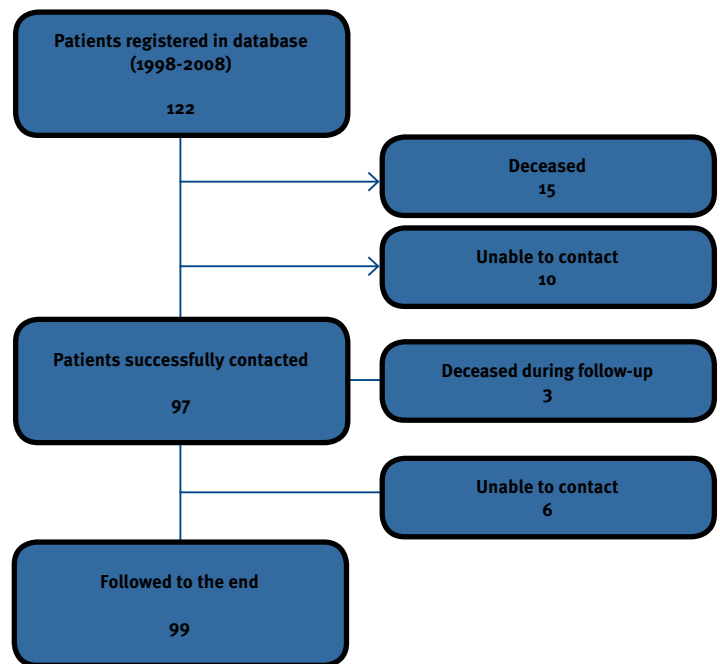
We conducted an experimental prospective study with one cohort of patients in the Region of Murcia, Spain. The study follows CF patients before and after an integrative smoking cessation program with proactive telephonic brief counselling, between 2008 and 2013. The study included all CF patients registered at the Regional CF Unit of the University Hospital, Virgen of the Arrixaca from 1998 to 2008. More than 95% of the study sample was obtained from the regional hospital unit's patient registry. The study was approved by the hospital network ethics committees and the institutional review boards.

Patients were verified for positive CF diagnosis through medical record review and assignment into the regional hospital unit; from 2007, patients were also diagnosed through neonatal screening. The study followed 88 of the 122 patient participants enrolled from the Pneumology and Environmental Health units. Figure 1 shows the algorithm for enrollment and follow-up in the intervention.

Initial contact with families was made via the mailing of an introduction letter from the Regional CF unit announcing the study's inception. The letter introduced the program and provided health education on the importance of maintaining a tobacco-free home for patients with CF and instructed participants that a trained tobacco cessation counsellor would be in contact in the incoming weeks.

Those families that consented to participate in the intervention were contacted by a nurse or physician from the Paediatric Environmental Health Specialty Unit (PEHSU) trained in tobacco cessation. Intervention staff completed a tobacco cessation training that consisted of 40 hours of theoretical and 100 hours of practical training. The intervention was made up of telephone based brief counseling and follow-up, carried out 2 or 3 times per year for five years.

Once contacted, the participants were screened with an introductory questionnaire that assessed active and passive environmental tobacco exposures during critical periods of the patient's development. Socio-demographic variables of interest included: tobacco exposure and consumption, family composition, income, structural aspects of patient



Note. 34 participants were lost to follow-up and were not included in the analysis as they did not complete the five year follow-up. The requisite five attempts were made to each participant in order to contact them, as per protocol. Eighteen participants exited the study as a result of death; of the known causes of death, two were from cardiac arrest related to complications from CF.

Figure 1. Enrollment and follow-up algorithm

household, education level of the patients and their parents. Results regarding these data collected at baseline were previously published by the authors (Ortega-García et al., 2012a).

We have used the following classification of smoking (Ferris, 1978). 1. Non-smoker: a) no tobacco smoke exposure, and b) passive smoker, exposure to smoke from individuals in their social and family environment. 2. Occasional smoker: does not smoke daily. 3. Smoker: smokes at least 1 or more cigarettes/day. 4. Ex-smoker: does not smoke at the time of the study, and has not smoked for at least 6 months.

With all this data, we created an “exposure at home” variable, which collects any type of tobacco exposure of special interest, especially in non-smoking patients: 1. Non-smoker without exposure at home. 2. Non-smoker living with smokers at home. To assess the effect of genetic mutations associated with CF, participants were divided into three groups: F508del homozygotes, F508del heterozygotes, and those without the F508del mutation. *Pseudomonas aeruginosa* (Pa) colonization (yes/no) was also considered.

Participant height and weight were obtained via self-reported by patients or their families in order to calculate body mass index (BMI). The BMI was constructed utilizing standard deviations by age and gender as defined by the World Health Organization. BMI was then categorized into three areas within two standard deviations: underweight, <2SD (<10th percentile), normal (between 10th – 85th percentile), and overweight >2SD (>85th percentile).

Cotinine urine levels were solicited from the CF cohort participants. Cotinine levels reveal concentrations with a cut-off of <10 ng/ml in patients not exposed to tobacco smoke, with corresponding concentrations increasing with a higher grade of exposure. Cotinine has been analyzed as a dichotomous, valuable variable in intervals (intervals < 10 ng/ml; 10 – 50 ng/ml; 51 – 200 ng/ml; 201 – 400 ng/ml; > 400 ng/ml), and as a continuous variable; we imputed a value of “9” for those patients with <10ng/ml.

Clinical variables such as spirometric values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC relation (all expressed as a percentage of the predicted value) were obtained through medical records. Data obtained before 5 years of age or after lung transplantation were excluded.

Intervention phases

The intervention logarithm below is adapted from the Tyc & Throckmorton-Belzer (2006) model for clinician delivered tobacco-use counselling strategies for adolescents with chronic illness as well as the 5 steps, called the 5 A's: ask for advice/ or advise, assess, assist, and arrange follow-up mentioned in our previous work (Ortega-García et al., 2012a). The intervention with proactive telephone counselling included:

1. Educate through brief counseling in short and long-term physical/medical effects of smoking in patients with CF and health benefits of quitting.

2. Assess participant's exposure to environmental passive tobacco in and outside of the home.
3. If any tobacco exposure was assessed, participants were given psycho-health education about the importance of reducing their exposure.
4. Assess participant desire to quit smoking; desire to quit is based on phase determination according to Prochaska and DiClemente (pre-contemplation, contemplation, preparation, action and relapse).
5. Classification of level of dependence and motivation according to Fagerström and Richmond's tests.
6. Provide brief counseling on how to select a quit date and strategies on how to choose that date.
7. Reinforce the benefits of quitting.
8. Selection of the next appointment, telephonic or face to face.

Calls were placed to participants to recruit them into the intervention and schedule interviews. During the follow-up, sequenced calls from a trained cessation counsellor were made every 6 months (in homes with no smoker present) and every 4 months (in homes where a smoker was present). Interviews were conducted between 2008 and 2013 with each interview lasting between 5 to 20 minutes depending on the details of their smoking exposure. All patients received tobacco prevention and cessation counseling at each appointment as per usual in the pediatric pulmonology unit. As a compliment to the intervention, trained tobacco cessation counsellors collected and assessed CF patient's passive environmental tobacco exposure. These variables are defined as passive tobacco exposure at home (yes or no), and gradient of global environmental tobacco exposure measured as, active, passive or no exposure.

SPSS version 15.0 was utilised for data analysis, established quality control measures and protocols for fidelity to the study model were preserved throughout the investigation. Distribution, frequency measures and contingency tables were constructed for univariate analysis and parametric tests were conducted for paired measurements. Spearman correlation was utilized for continuous and interval variables. To assess measurements of association and impact of the intervention, we calculated risk relative, absolute risk reduction and NNT (number needed to treat).

Results

88 patients completed the 5 year follow-up; 49 (56.32%) were male and 38 (43.68%) were female. The mean age of participants was 23.61 (95% CI 20.93 – 26.29). Table 1 shows the socio-demographic characteristics of sample.

Tobacco smoke exposure

The number of active smokers was reduced by half at the end of follow-up, from 10.23% (n=9) to 4.55% (n=4), p=0.06. In 2008, these patients smoked a mean of 45.25

(95% CI 13.07 - 77.43) cigarettes per week and started smoking at a mean age of 15.3 (95% CI 13.6 - 17.2).

Any passive exposure to environmental tobacco in non-smokers (n=49 vs 29) was reduced by 25.1 % during the five year intervention (62.0 % vs 36.9%, p<0.01). Figure 2 demonstrates significant reductions annually in the active and passive tobacco exposures at the end of follow-up. Figure 3 shows the time trend of the variable "exposure at home" during the five year follow-up.

Urinary Cotinine Levels

Urinary cotinine levels were consistent with tobacco exposure reduction. Levels compared between baseline samples in 2008-2009 and samples in 2012-2013 showed a reduction of 27.38% (p=0.006) from 63.13 (28.58- 97.69) to 20.56 (0.86 - 40.27) ng/ml (p<0.01). Differences in the categorical and continuous variable are presented in table 2. Cotinine was significantly correlated with active (31%) and exposure at home (32%), p=0.02.

We found a negative correlation with family's monthly net income and education level in 2008 (0.38, p<.001) and no correlation with any in 2013.

Smoking cessation and intervention effect

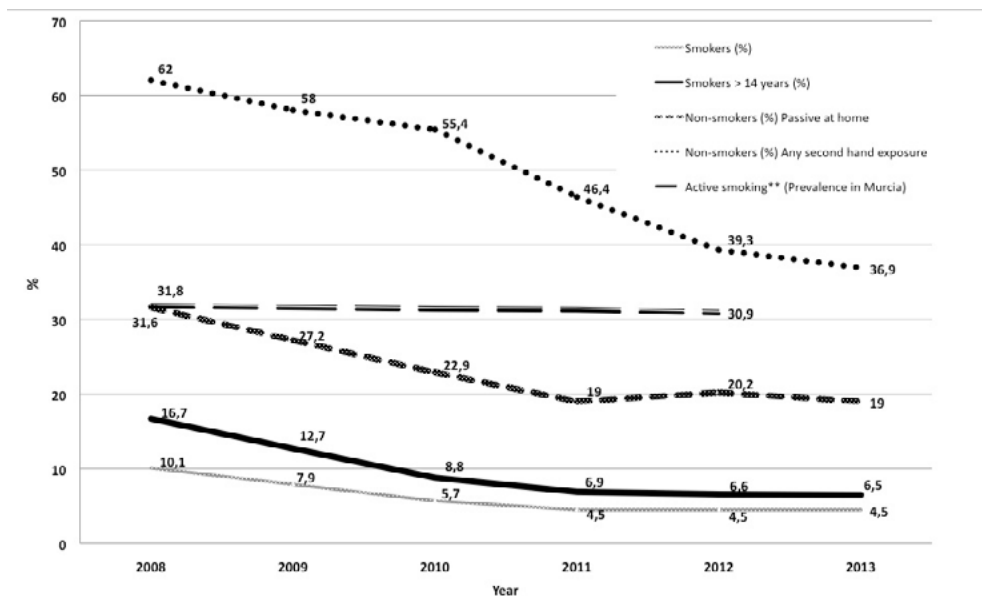
A total of 47 smokers were found (9 patients, 2 wives, 2 siblings, 16 fathers, 17 mothers and 1 grandfather). At the five year follow-up, serious efforts were made to achieve smoking cessation and ultimately leaving 18 (38.29%) of them as non-smokers (5 patients, 6 fathers, 5 mothers, 2 siblings and 1 wife) during the last 6 months (cooximetry of 0 in patients).

Two patients, 1 mother and 1 father stopped smoking after going through a personalized consultation. Of these, only two were treated with nicotine replacement therapy.

Upon comparing the active tobacco smoke exposure at baseline (n=9) and after follow-up (n=4) our findings suggest that the risk of smoking is 56% lower with a relative risk

Table 1. Socio-demographic characteristics at baseline

Baseline Characteristics	
	n %
Sex	
Male	49 (56.32)
Female	38 (43.68)
Age (mean)	23.61 (20.93-26.29. CI 95%)*
Education	
None	29 (36.25)
Primary	18 (22.5)
Secondary	22 (27.5)
University	11 (13.75)
Income (€/month)	
< €800	11 (17.19)
€800-1500	22 (34.38)
€1500-2000	14 (21.88)
€2000-2500	9 (14.06)
> €2500	8 (12.50)



Note. **Smoking prevalence is adapted from the Spanish National Health Survey 2006, 2008 and 2011-2012. Prevalence measures are reflective of 2006, 2009 and 2011-2012 data and respectively reflect consumers of tobacco in Spain in populations over 16 (2006, 2009) and 15 years of age (2011-2012).

Figure 2. Time trend comparison of active smoking and passive exposure to environmental tobacco in the homes without any smoker present with prevalence of active smokers in Region of Murcia**

Time trend of patients smokers and exposure in the homes without any patients smokers

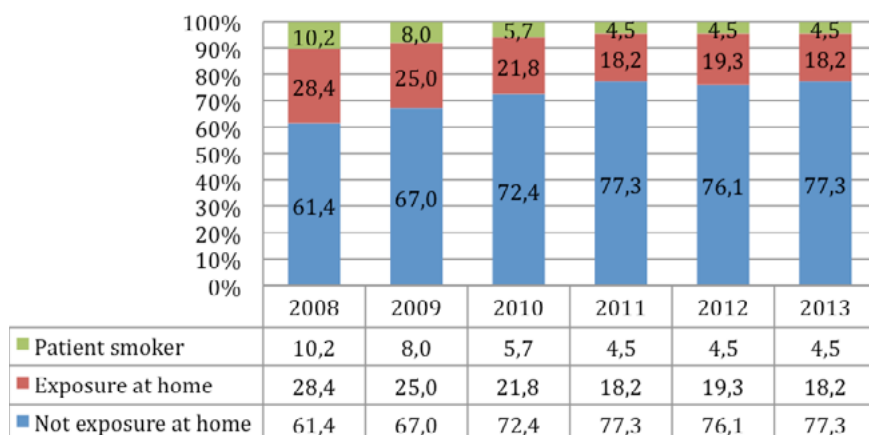


Figure 3. Time trend of exposure at home in cystic fibrosis cohort

Table 2. Summary of analysis

Variable	2008	2013	p value for paired samples
Tobacco Exposure			
Active Smokers	10.23 (9/88)	4.55 (4/88)	0.062
Environmental exposure in the home	31.65 (25/79)	19.05 (16/84)	<0.01
Cotinine Levels			
>10	52.38 (33/63)	25.00 (12/48)	0.230
Cotinine Intervals *			
<10 ng/mL	34.1 (30/88)	39.8 (35/88)	
10-50 ng/mL	28.4 (25/88)	12.5 (11/88)	
51-200 ng/mL	2.3 (2/88)	-----	
201-400 ng/mL	1.1 (1/88)	-----	
>400 ng/mL	5.7 (5/88)	1.1 (1/88)	
Dat Imputed	28.4 (25/88)	46.6 (41/88)	
Continuos Cotinine (ng/mL)	63.13 (28.58- 97.69)	20.56 (0.86 - 40.27)	0.0001
Spirometric Parameters**			
FVC (%)	86.534 (TE 3.1643)	93.06 (TE 3.040)	0.017
FEV ₁ (%)	78.884 (TE 3.4891)	80.147 (TE 3.6364)	0.637
FEV ₁ /FVC (%)	83.11 (TE 2.176)	74.864 (TE 2.4152)	<0.001
FEF ₂₅₋₇₅ (%)	52.637 (TE 4.5619)	52.431 (TE 5.2767)	0.952
Other Covariates			
Pseudomonas colonization	45.45 (35/77)	41.27 (26/63)	0.238
Genetics			
F508 del Homozygous		12.05 (10/83)	
F508del Heterozygous		45.78 (38/83)	
Other Mutations		42.17 (35/83)	
BMI			
Normal (p10-85)		61.19 (41/67)	
Underweight (<p10)		19.4 (13/67)	
Overweight (>p85)		19.4 (13/67)	

Note. *Cotinine Levels are reported for 2008/2009 baseline and 2011/201 follow-up and include values imputed.

**Values are indicative of Spirometric value comparisons 2009 and combined 2012-2013, reported with median values and values for typical error (TE).

Table 3. Multivariate analysis of spirometric parameters as outcomes adjusted by age and gender

Outcomes	Predictor Variable	Regression Coefficient	95% CI	p Value
FEV ₁	Pseudomonas	-13.844	-28.300 – 0.644	0.002
	BMI <i>underweight</i>	20.862	1.813 – 39.911	0.033
FEF ₂₅₋₇₅	Pseudomonas	-24.537	-44.599 – -4.475	0.088
	BMI <i>underweight</i>	27.599	1.255 – 53.942	0.041
FVC	Pseudomonas	-12.034	84.294 – 122.599	<0.001
FEV ₁ /FVC	Pseudomonas	-0.411	-0.715 – -0.106	0.009

(RR) not significant of 0.44 (CI 95% 0.14-1.39). A significant reduction was observed in environmental tobacco exposure 'smoke-free homes' with a RR 0.59 (CI 95% 0.37-0.94) and RAR 0.16 (CI 95% 0.02-0.29) with a NNT=7 (CI 95% 4-41). The intervention to significantly increase the likelihood of family quitting (smoke-free home) was 1.26 (1.05-1.54). In 2008 54 from 88 homes had at least one smoker and in 2013 only 20 households still had tobacco smoke exposure.

Lung function

We observed an increase in the global spirometric parameters at the end of follow-up in regards to baseline measures with significant differences in FVC and FEV₁/FVC.

No significant differences were seen in the student T-test for spirometric parameters among patients exposed to active or passive tobacco exposures between baseline and end of follow-up outcomes. In the multivariate analysis, see table 3, we found that Pa colonization was a predictive factor for all spirometric parameters. Underweight BMI was also associated with FEV₁ and FEF₂₅₋₇₅, after adjusting for age and gender. Other clinical variables assessed yielded no significance in the multivariate analysis.

Discussion

In this study we observed that longitudinally active and passive environmental smoking exposures reduced consistently among the CF patients that participated in the integrated telephone prevention and cessation program. Our results suggest that interventions which actively involve patients and relatives could promote an adequate perception of tobacco risk so as it promote behaviour change. The available scientific evidence evaluating tobacco consumption among CF populations is limited. Nonetheless, studies in the United States have reported that tobacco consumption amongst CF patients is 11%, and smoking amongst youth with a CF diagnosis is 20% (Stern et al., 1987). Another study in the United Kingdom that investigated "risky behaviours" in adults with CF revealed that 6% were smokers (Mc Ewan et al., 2012).

Previous studies have demonstrated an inverse relationship between the number of cigarettes smoked and the re-

sult of spirometric variability in CF patients (Ortega-García et al., 2012a). Nevertheless, in this study, the relationship was statistically insignificant most likely attributed to the small sample size of the representative group of smokers.

Kopp et al. (2015) recently demonstrated that exposure to tobacco smoke is associated with higher rates of colonization by methicillin-resistant *Staphylococcus aureus* and other anaerobic bacteria. Tobacco smoke is also associated with increased bronchodilator responsiveness, air trapping, and decreased growth during the first year of life (Kopp et al., 2015). The screening of tobacco smoke exposure and treatment for smoking cessation in all family members should be an important part in the care of CF patients.

Interventions developed with the goal of preventing and eliminating tobacco consumption have evolved through different applications. The implementation strategies included face-to-face and telephone interviewing. Telephone-based tobacco cessation programs have reported 12% reductions in cessation with high satisfaction in the intervention population (Redmond, Adsit, Kobinsky, Theobald & Fiore, 2010). Telephone interventions have demonstrated effective when used with pharmacological tobacco cessation therapies resulting in improvements of 10 to 25% (Stead & Lancaster, 2012). This suggests that outcomes improve with increased follow-up and contact. Tobacco cessation interventions have shown better results in programs that incorporate elements sensitive to stage of change, motivational enhancement and cognitive behavioural therapy, rather than pharmacological interventions (Stanton & Grimshaw, 2013).

Our brief interventions have proven to be effective although most are not on-site or in person. Other programs such as computerized interventions have resulted in tobacco abstinence of 32% (Chen et al., 2012). Here, the telephone interview has demonstrated the effectiveness in utilizing family members of patients in implementing smoking cessation programs (Carreras Castellet et al., 2012; Winickoff, Hillis, Palfrey, Perrin & Rigotti, 2003). Our results reinforce the utility and sustainability of tobacco cessation in the context of the phone intervention. The value of telephone-based interventions must be recognized and it's vital to make them an available option to individuals interested in quitting smoking. Currently, telephone counselling and

nursing interventions are useful modalities in approaching tobacco cessation; RR 1.37, CI: 1.26 – 1.50 and RR 1.29, CI: 1.20 – 1.39, respectively (Rice, Hartmann-Boyce & Stead, 2013; Stead et al., 2013).

Limitations include potential biases related to participant memory re-call. Standardized interventions were employed by personnel with specialized training in the conceptual and procedural aspects of tobacco cessation to manage these types of patients and biases. Moreover, the impetus to maintain a rigorous follow-up methodology mediates this impact on our results.

Another limitation of this study is the lack control group for the basis of scientific comparison. This aspect was considered in the experimental design but was quickly outweighed by the ethical medical responsibility to provide treatment to vulnerable CF populations in need of care. Results that reflect passive environmental tobacco exposure may be skewed partially due to the recent anti-tobacco legislation that regulates the use of tobacco in closed establishments in the country (Anti-Tobacco Law of 2010). But, our results reflect an observed reduction that occurred prior to the legislation passing and persisted after its implementation, see figure 2. Another potential factor associated with the decrease in tobacco consumption is the legislation's impact on social tobacco use and access due to increases in cost. Ng et al. (2014) recently discussed the significant reduction in prevalence of exposure to tobacco smoke in 187 countries between 1980 to 2012. The Region of Murcia is of particular interest in developing integrated smoking interventions when considering the 30.9% statewide tobacco consumption was higher in 2012 relative to Spain's 27.0% national tobacco consumption (Ministry of Health, 2007). Unlike the natural tendency in many countries and regions, Murcia has increased slightly the prevalence of tobacco compared to previous years (MurciaSalud, 2006). Additionally, recent studies investigating the level of tobacco exposure indicate up to 62% of healthy children in Murcia are exposed to environmental tobacco smoke (Ortega-García et al., 2012b). Our findings are geographically significant, given that the smoking prevalence has increased in the Region of Murcia over the last 5 years (Ministry of Health, 2007; MurciaSalud, 2006). Economic system variability, instability in employment and inconsistencies in participant incomes were not evaluated and could potentially influence outcomes. In analyzing the socioeconomic variables previously noted we observed the protective effect of increased income in relation to passive environmental tobacco exposure, and an associated reduction of passive exposure as age increases, OR = 0.12 (1.09 – 1.17), $p=0.02$.

Our study has strived to remain below the threshold of acceptable missing data (15%), however, as some patients exited the study due to death or were lost to follow-up it was necessary to utilize multiple imputation methods for certain values, including imputed cotinine levels <9.

These data are reinforced by the objective measure of urinary cotinine levels, which directly reflect tobacco exposure. The subjective bias present in the patient self-report is mitigated by the solid evidence provided by cotinine levels. Further strengths of our study include our systematic method of data collection, delivery of our screening tool by trained tobacco cessation counsellors.

The preceding indicates that this intervention can assist in the cessation of tobacco use amongst CF patients. The findings are significant from multiple perspectives. For instance, the associated annual pharmacological treatment costs associated with CF in adults (>17) is an estimated € 21,603 per patient/year (Eidt-Koch, Wagner, Mittenford & Graf von der Schulenburg, 2010). Our findings bolster the need to expand tobacco cessation programs available to CF patients. Further implementation of these interventions could alleviate the cost burden associated with treating the long-term impacts of tobacco related diseases.

A future aspect to consider is the role that smokers in the house of minors play in CF disease burden; as a significant percentage of the patients in the cohort were minors. Broadening the availability of tobacco cessation programs is relevant as children are most vulnerable to passive tobacco exposure. Children and minors rely on their caretakers to ensure the environmental safety of their homes and lack the ability to advocate for environmental justice in their communities. This responsibility lies with us, the adults, medical staff and public health workforce sanitarians entrusted to ensure their environmental safety. Nonetheless, more than a third (36.5%) of minors under the age of 19 live with a smoker, and in the Region of Murcia half of all children live in homes with at least one smoker (Ortega García, Ferrís Tortajada & Sánchez Solís, 2008). The literature reports reductions of up to 80% in tobacco consumption in youth's family members with chronic pathologies (Butz & Rosenstein, 1999).

Telephone based interventions in CF populations are an integrative and sustainable modality that is relevant to the family environment where tobacco is consumed around patients with CF. A paramount implication of our research is that the reduction of passive tobacco exposure is more noteworthy after two years of follow-up due to the intervention. This data contributes to the lacking research in intervention methods with vulnerable CF populations. Previous evidence and natural history of the disease allow for us to consider the use and amplification of telephone based interventions and its training with a global perspective in Europe and the world alike.

What is known on this subject

Patients with CF possess an increased risk for harm from exposure to tobacco smoke. Telephone assisted interventions is a useful tool in tobacco cessation and prevention. More research is needed in evaluating tobacco intervention programs over time

What this study adds

Telephone based interventions for tobacco cessation and prevention targeting patients with cystic fibrosis (CF) is a feasible and effective tool when applied over long periods of time.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

References

Beers, M. H. & Berkow, R. (1999). Cystic Fibrosis. In: R. S. Porter (Ed.), *Merck Manual: Diagnosis & Therapy*. 17th ed. (pp. 2366-2371). Whitehouse Station, NJ: Merck & Co Inc.

Butz, A.M. & Rosenstein, B. J. (1999). Passive smoking among children with chronic respiratory disease. *Journal of Asthma*, 29, 265-272.

Carreras Castellet, J. M., Maldonado Aróstegui, B., Quesada Laborda, M., Sánchez Sánchez, B., Nerín de la Puerta, I. & Sánchez Agudo, L. (2012). Tratamiento por teléfono del tabaquismo. Factores predictivos de éxito. *Medicina Clínica (Barcelona)*, 138, 242-5.

Chen, Y. F., Madan, J., Welton, N., Yahaya, I., Aveyard, P., Bauld, L.,... Munafò, M. R. (2012). Effectiveness and cost-effectiveness of computer and other electronic aids for smoking cessation: a systematic review and network meta-analysis. *Health Technology Assessment*, 16, 1-205.

Cook, D. G., Strachan, D. P. & Carey, I. M. (1998). Parental smoking and spirometric indices in children. *Thorax*, 53, 884-893.

Eidt-Koch, D., Wagner, T. O., Mittendorf, T. & Graf von der Schulenburg, J. M. (2010). Outpatient medication costs of patients with cystic fibrosis in Germany. *Applied Health Economics and Health Policy*, 8, 111-118.

Farrell, P. M. (2008). The prevalence of cystic fibrosis in the European Union. *Journal of Cystic Fibrosis*, 7, 450-453.

Ferris, B. G. (1978). Epidemiology standardization project (American Thoracic Society). *American Review of Respiratory Diseases*, 118, 1-120.

Kopp, B. T., Sarzynski, L., Khalfoun, S., Hayes, D. Jr., Thompson, R., Nicholson, L.,... Groner, J. (2015). Detrimental effects of secondhand smoke exposure on infants with cystic fibrosis. *Pediatric Pulmonology*, 50, 25-34. doi: 10.1002/ppul.23016.

Lancaster, T. & Stead, L. F. (2005). Individual behavioural counselling for smoking cessation. *Cochrane Database of Systematic Reviews*, 18, CD001292.

Ley 42/2010. Medidas sanitarias frente al tabaquismo y reguladora de la venta, el suministro, el consumo y la publicidad de los productos del tabaco. Boletín Oficial del Estado, Madrid, 30th of December of 2010. Available at: <http://www.boe.es/boe/dias/2010/12/31/pdfs/BOE-A-2010-20138.pdf>. Accessed [14 June 2014].

Mc Ewan, F. A., Hodson, M. E. & Simmonds, N. J. (2012). The prevalence of "risky behaviour" in adults with cystic fibrosis. *Journal of Cystic Fibrosis*, 11, 56-58.

Ministerio de Sanidad y Consumo. (2007). *Encuesta Nacional de Salud de España 2006: estilos de vida (lifestyles)*. Madrid: Ministerio de Sanidad y Consumo. Available at: <http://www.msc.es/estadEstudios/estadisticas/encuestaNacional/encuesta2006.htm>. Accessed [14 June 2014].

Murcia Salud. (2006). *Consumo de tabaco en Murcia y España* [on line]. Available at: <http://www.murciasalud.es/pagina.php?id=87967> Accessed [19 June 2014].

Ng, M., Freeman, M. K., Fleming, T. D., Robinson, M., Dwyer-Lindgren, L., Thomson, B.,... Gakidou, E. (2014). Smoking Prevalence and Cigarette Consumption in 187 Countries, 1980-2012. *JAMA*, 311, 183-192.

Ortega García, J. A., Ferrís Tortajada, J. & Sánchez-Solís, M. (2008). Ambientes saludables para la infancia y adolescencia [Healthy environments for children and adolescents]. In: M. T. Muñoz-Calvo, M. I. Hidalgo-Vicario, J. Clemente-Pollán (Eds.), *Pediatría Extrahospitalaria*. 4th ed. (pp. 235-244). Madrid: Ergón.

Ortega-García, J. A., Gutierrez-Churango, J. E., Sánchez-Saucó, M. F., Martínez-Aroca, M., Delgado-Marín, J. L., Sánchez-Solis, M.,... Martínez-Lage, J. F. (2012b). Head circumference at birth and exposure to tobacco, alcohol and illegal drugs during early pregnancy. *Child's Nervous System*, 28, 433-439.

Ortega-García, J. A., López-Fernández, M. T., Llano, R., Pastor-Vivero, M. D., Mondéjar-López, P., Sánchez-Saucó, M. F. & Sánchez-Solís, M. (2012a). Smoking prevention and cessation programme in cystic fibrosis: integrating an environmental health approach. *Journal of Cystic Fibrosis*, 11, 34-39.

Raju, S. V., Jackson, P. L., Courville, C. A., McNicholas, C. M., Sloane, P.A., Sabbatini, G.,... Rowe, S. M. (2013).

- Cigarette smoke induces systemic defects in cystic fibrosis transmembrane conductance regulator function. *American Journal of Respiratory and Critical Care Medicine*, 188, 1321-1330.
- Ramon, J. M., Nerin, I., Comino, A., Pinet, C., Abella, F., Carreras, J. M.,... Aumatell, C. (2013). A multicentre randomized trial of combined individual and telephone counselling for smoking cessation. *Preventive Medicine*, 57, 183-8.
- Redmond, L. A., Adsit, R., Kobinsky, K. H., Theobald, W. & Fiore, M. C. (2010). A decade of experience promoting the clinical treatment of tobacco dependence in Wisconsin. *Wisconsin Medical Journal*, 109, 71-78.
- Rice, V. H., Hartmann-Boyce, J. & Stead, L. F. (2013). Nursing interventions for smoking cessation. *Cochrane Database Systematic Reviews*, 8, CD001188.
- Smyth, A., O'Hea, U., Williams, G., Smyth, R. & Heaf, D. (1994). Passive smoking and impaired lung function in cystic fibrosis. *Archives of Disease in Childhood*, 71, 353-354.
- Stanton, A. & Grimshaw, G. (2013). Tobacco cessation interventions for young people. *Cochrane Database of Systematic Reviews*, 8, CD003289.
- Stead, L. F. & Lancaster, T. (2012). Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. *Cochrane Database of Systematic Reviews*, 12, CD009670.
- Stead, L. F., Hartmann-Boyce, J., Perera, R. & Lancaster T. (2013). Telephone counselling for smoking cessation. *Cochrane Database of Systematic Reviews*, 8, CD002850.
- Stern, R. C., Byard, P. J., Tomashefski, J. F. Jr. & Doershuk, C. F. (1987). Recreational use of psychoactive drugs by patients with cystic fibrosis. *Journal of Pediatrics*, 111, 293-299.
- Tyc, V.L. & Throckmorton-Belzer, L. (2006). Smoking rates and the state of smoking interventions for children and adolescents with chronic illness. *Pediatrics*, 118, 471-487.
- Verma, A., Clough, D., McKenna, D., Dodd, M. & Webb, A. K. (2001). Smoking and Cystic Fibrosis. *Journal of the Royal Society of Medicine*, 94, 29-34.
- Winickoff, J. P., Hillis, V. J., Palfrey, J. S., Perrin, J. M. & Rigotti, N. A. (2003). A smoking cessation intervention for parents of children who are hospitalized for respiratory illness: The Stop Tobacco Outreach Program. *Pediatrics*, 111, 140-145.