PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of the comprehensive smoke-free law on time trends in smoking behaviour in Primary Health Care patients in Spain: a longitudinal observational study
AUTHORS	Pons-Vigués, Mariona; Rando-Matos, Yolanda; Rodriguez-Blanco, Teresa; Ballvé-Moreno, Josep Lluís; Ripoll, Joana; Llobera, Joan; Morán, Julio; López-Jiménez, Tomàs; Violan-Fors, Concepción; Bolibar, Bonaventura

VERSION 1 – REVIEW

REVIEWER	Cristina Lidon Moyano Universitat Internacional de Catalunya
REVIEW RETURNED	06-Nov-2017

GENERAL COMMENTS	This is a well written manuscript on an interesting topic regarding smoke-free law in Spain. I only have some suggestions with the aim of improving the author's work, 1. Introduction, page 5, line48: I would recommend to include reference 29 as it also analyze the compound impact of both laws. 2. Introduction, page 5, paragraph 4: I would also mention those studies that show a decrease in smoking prevalence. As is written now it seem there only studies showing no difference in the trend or an increase in smoking prevalence. 3. Some figures and tables need to be checked in order to improve their quality (Figure 1, Table 2). 4. Variables, page 7, line 12: I would say We obtained/created instead of we calculated. 5. Variables, page 7, line 24: Patient 'who/that' was.. who/that is missing. 6. Data analyses, page 7, line 45: Change they for Balearic Islands. 7. Results, page 8, line 22: Cite again Figure 1. 8. Although the authors include a lot of relevant information I am missing some graphic regarding the studied trends as this would make this work more informative and easy to interpret.

REVIEWER	Anton Kunst
	AMC University of Amsterdam Netherlands
REVIEW RETURNED	11-Nov-2017

GENERAL COMMENTS	The paper addresses an issue that has been the topic of many previous analyses, including in Spain. A new feature of this paper is the use of data from GP registries instead of population-based interview surveys. Yet, I think that the added value of this paper is limited, for a number of reasons.
	1. The "objective" measurement of smoking at GPs is mentioned as a main strength, but the reporting on smoking by patients to their GPs is not necessarily more reliable that the reporting by participants in an anonymous health surveys.
	2. The study period is relatively short, especially in Balearic Islands, thereby making it hard to discern trends before the new policy from trends after the introduction of the new policy.
	3. It is not documented how frequently the patients have visited their GP, and therefore it is uncertain with what frequency the individual-level changes in smoking habits were measured.
	4. According to Figure 1, a large proportion of the potential study participants had to be excluded because of data problems. It is uncertain whether inclusion into the study was selective on relevant variables, and whether this may have affected the generalisability of the results.
	5. The data are analysed with joint-point regression. This type of analyses may be useful as an exploratory tool. However, to assess the impact of a policy, it would have been more informative to employ methods that are designed to test a priori hypotheses of policy impact, such as regression discontinuity analysis.
	6. Related to this previous point: the number of figures is excessively large, which make it hard to identify the results that are key to testing hypotheses regarding the impact of policies. Why not combine the results of the three regions? Why not focus on the few smoking outcomes that are most likely to be related to the new policy?
	7. Also related to this point: the Discussion is not focussed on assessing the strength of evidence regarding an impact of the policy. Instead, much of the discussion deals with male-female comparisons (not relevant to this paper) or makes descriptive summaries of previous Spanish studies.

REVIEWER	Kate Frazer
	University College Dublin
	Author of Cochrane Review on Impact of Legislative Smoking bans. No other competing interests
REVIEW RETURNED	08-Jan-2018

GENERAL COMMENTS	This is a very important public health paper. There is a need for more evidence and longitudinal data on the impact of legislative smoking bans on active smoking rates - this study adds to this body of evidence.

	The limitations of the data are described. Legislative bans are one component of the WHO FCTC and MPOWER and you could include this within your discussion.

REVIEWER	Iñaki Galan Labaca Centro Nacional de Epidemiología. Instituto de Salud Carlos III, Spain
REVIEW RETURNED	11-Jan-2018

GENERAL COMMENTS	In the introduction, is important to conceptualize why the authors think that the Law 42/2010, which is a reform of the Law 28/2005, where smoking was banned in hospitality venues, can produce changes in tobacco consumption in the general population. The study participants and mainly the way of collecting information are not clear. The inclusion criteria in the Balearic Islands are different from those of the other two regions, with patients allocated in PHCT in 2013 and evaluated retrospectively because there was not annual comprehensive register of patients. Taking into account no updated electronic information during the period of study and the scarce number of date (three quarters) before the law came into force, it would be better to exclude this region from the analysis. The design, based in a closed cohort where nobody is excluded after the study begins, is controversial. It is supposed that some patients will change of General Practitioner and PHCT due to social or work conditions. From initial database, after excluding those patients <16 and >100 years old, patients with no PHC visit during 2007-2013 or 2010-2013, patients with no allocated PHCT for all years of the study, there is recorder information about smoking in the last quarter of 2007 or the 1st quarter of 2010 (Balearic Islands), in 40,1% of Catalonia, 39,2% of Navarre and 56,7% of Balearic Islands. The higher rate in recorded information on tobacco in the Balearic Islands suggests that it is related to an improvement in date collecting over time, a situation that could cause an artifact in the analysis of trends. Another aspect that suggests being conditioned by the data collection rather than self-selection bias, is the very low prevalence of ex-smokers, especially in Navarre and the Balearic Islands. The information on smoking habit is a mix of clinical variables, codes from ICD 10, ICD 9 and ICP-2. This is confusing because some indicators (i.e. new ex-smokers, relapse) must be collected with ad-hoc questions. The update of information about smoking to estimate the prevalence each quarter is not clear. Few patients visit their GP every quarter, so authors say that if the EHR did not register smoking status at some point in time, the last observation was carried forward. This point should be clarified because it is probably that information about smoking is imputed in most quarters. The longitudinal data analysis is performed like a cross-sectional study. Regarding that the outcomes are repeated measurements, this should be taking into account in the analysis, i.e. using Generalized Estimating Equations or mixed models (multilevel regression models). The authors should discuss about advantages and disadvantages of Jointpoint analysis because most studies that have evaluated the impact of smoke-free policies have not chosen this method, using mostly Interrupted Time Series Analysis. Joinpoint is a useful method to describe changes in time series but generally

	requires changes in trend of a certain magnitude to detect a segment change. Furthermore, the position of joinpoints is not fixed by the researcher, but it is established on the basis of a statistical criterion. In addition, if the effect of regulations is immediate but not maintained over time, Jointpoint may not be the best technique for analysis. Interrupted Time Series Analysis is a quasi-experimental design that can be applied to healthcare data to evaluate the effect of interventions, which involves the analyst pre-specifying the time point of interest in the data series. Authors conclude that the introduction of the Spanish comprehensive Law 42/2010 does not significantly modify incidence and prevalence trends of smoking behavior. However, when we see with detail tables S2 and S3 (results of Catalonia and Navarre) there is a strong change in no smoking prevalence just when the law came into force: the non-smokers prevalence decreases around 10% in the first quarter of 2011. Surprisingly, this important result (in case it was real) is not described in the text.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1. Cristina Lidon Moyano
This is a well written manuscript on an interesting topic regarding smoke-free law in Spain.
ANSWER: Thank you very much for the comment.

I only have some suggestions with the aim of improving the author's work,
1. Introduction, page 5, line48: I would recommend to include reference 29 as it also analyze the compound impact of both laws.
ANSWER: We have included reference 29 (*Lidón-moyano C, Fu M, Ballbè M, et al. Impact of the Spanish smoking laws on tobacco consumption and secondhand smoke exposure: A longitudinal population study. Addict Behav 2017;75:30–5*)(1) in the introduction section (reference number: 24):
"Moreover, some studies evaluate only the partial law, whereas others analyse the compound impact of both laws.[19,20,23,24]".

2. Introduction, page 5, paragraph 4: I would also mention those studies that show a decrease in smoking prevalence. As is written now it seem there only studies showing no difference in the trend or an increase in smoking prevalence.
ANSWER: As suggested by the reviewer, we have modified the following sentence in the introduction section:
"The results of these studies are often conflicting; while some conclude that the partial SFL does not have any effect on the downward trend in the prevalence of smokers,[13,19,23] other studies show a reduction in smoking prevalence[24], an increase of the smoking quit-ratio in the short term[18] and minor increases in the prevalence of active smoking[20]".

3. Some figures and tables need to be checked in order to improve their quality (Figure 1, Table 2).
ANSWER: Figure 1 and all tables in the manuscript have been revised in this new version.

4. Variables, page 7, line 12: I would say We obtained/created instead of we calculated.
ANSWER: We have modified the sentence as follows:
"We created the following variables at the end of each quarter of the study period:"

5. Variables, page 7, line 24: Patient 'who/that' was who/that is missing.
ANSWER: We have revised the sentence as follows:
"New ex-smoker: the patient was a smoker two years before the considered quarter and has continuously abstained from tobacco for at least 12 months".

6. Data analyses, page 7, line 45: Change they for Balearic Islands.
ANSWER: The pronoun 'they' refers to the three regions studied: Catalonia, Navarre and the Balearic Islands. These three regions used different standards and software, different complementary measures

to the smoke-free legislation (SFL) and in the particular case of the Balearic Islands, a shorter study period (four vs six years).

We have clarified the sentence as follows:
"Because the three regions used different electronic health records (EHR) systems (different standards and software), different complementary measures to the SFL and also due to the shorter study period in the Balearic Islands, we performed a stratified analysis per region, overall and by sex".

7. Results, page 8, line 22: Cite again Figure 1.
ANSWER: We have added 'Figure 1' to the following sentence:
"The study population was 392,966 patients: 141,071 in Catalonia, 73,644 in Navarre and 178,251 in the Balearic Islands (Figure 1)".

8. Although the authors include a lot of relevant information I am missing some graphic regarding the studied trends as this would make this work more informative and easy to interpret.
ANSWER: Following the reviewer's recommendation, we have added two Supplementary Figures:
- Figure S1: Overall trends in prevalence of smoking status in Catalonia, Navarre and the Balearic Islands
- Figure S2: Overall trends in incidence trends of new smokers, ex-smokers and ex-smoker relapse in Catalonia, Navarre and the Balearic Islands

Reviewer: 2. Anton Kunst

The paper addresses an issue that has been the topic of many previous analyses, including in Spain. A new feature of this paper is the use of data from GP registries instead of population-based interview surveys. Yet, I think that the added value of this paper is limited, for a number of reasons.

1. The "objective" measurement of smoking at GPs is mentioned as a main strength, but the reporting on smoking by patients to their GPs is not necessarily more reliable that the reporting by participants in an anonymous health surveys.
ANSWER: In Spain, 70% of the population attend Primary Health Care (PHC) services at least once a year and smokers attend more frequently than non-smokers. PHC is the first port of call to the health services, is highly accessible and offers continuity of care. It therefore offers opportunities for primary prevention in non-smokers and provides effective options for smoking cessation (2). PHC professionals approach smoking in the consultation room in agreement with the recommendations of the Programme of Prevention Activities and Health Promotion (PAPPS) (2), the Consensus Document for the Clinical Care of Smoking in Spain (3) and current clinical guidelines. For instance, the PAPPS of the Spanish Society of Family and Community Medicine advises PHC practitioners to ask all people over 10 years of age about smoking at each consultation and to register cigarette consumption in the electronic medical records. Smoking screening should take place at least every 2 years. Most PHC centres have yearly incentives for screening and following up smoking habits. PHC electronic records have proven reliable as a source of data in English studies based on the General Practice Research Database, (4,5) and also in Spanish studies (6,7).
In summary, we believe that PHC provides a unique setting for intervention and prevention for a large section of the population and that the registered information on smoking is a reliable and up- to-date source of population habits.

We have added the following sentence in the discussion section:
"Used as a research tool, electronic health records (EHR) portray real-life conditions and provide comprehensive, long-term health histories from a large population sample, ensure high representativeness and external validity and minimize potential recall bias".

In addition, we have changed the following sentence in the box "strengths and limitations of this study":
"Used as a research tool, electronic health records portray real-life conditions and provide comprehensive, long-term health histories from a large population sample"

2.The study period is relatively short, especially in Balearic Islands, thereby making it hard to discern trends before the new policy from trends after the introduction of the new policy.
ANSWER: We agree with the reviewer and have added a limitation in the discussion:

"In view of the limited length of the study period, particularly in the Balearic Islands, we consider these results a first approximation to be succeeded by follow-up research. We should underscore that rather than just comparing two different periods, joinpoint analysis evaluates longitudinal trends, thus producing a more accurate assessment".

3. It is not documented how frequently the patients have visited their GP, and therefore it is uncertain with what frequency the individual-level changes in smoking habits were measured.
ANSWER: Table 1 describes the mean, median and interquartile range (IQR) PHC number of visits per patient and by region at the onset of the study. The visits consisted of consultations with the nurse or GP. As explained in the first paragraph of results, Catalonia presented the highest median number of visits (9, IQR: 3 -16), the Balearic Islands the second highest (7, IQR: 3-15) and Navarre the lowest (7, IQR: 3-12). In summary, the study population attend PHC services frequently, thus facilitating continuity of smoking interventions.

We have previously explained that PHC professionals approach smoking in the consultation room in agreement with the recommendations of the Programme of Prevention Activities and Health Promotion (PAPPS) (2), the Consensus Document for the Clinical Care of Smoking in Spain (3) and current clinical guidelines. For instance, the PAPPS of the Spanish Society of Family and Community Medicine advises PHC practitioners to ask all people over 10 years of age about smoking at each consultation and to register cigarette consumption in the electronic medical records. Smoking screening should take place at least every 2 years. All smokers should be personally and clearly advised to quit smoking, should receive help to that end and follow up must be scheduled during the first weeks after quitting smoking. Moreover, since some PHC professionals received annual incentives to register smoking habits, we should assume that the EHR were up to date and that they reflected real life.

Despite these recommendations, there will always be a small percentage of patients with no reliable record of smoking status. Moreover, it is widely recognized that missing data are one of the major limitations of electronic PHC records. Consequently, stringent inclusion criteria were included (as seen in the next comment of the reviewer) in order to maximize the internal validity of the study.

In this study, we constructed the smoking status variable for each trimester. The use of joinpoint for quarterly data analysis achieves results with greater precision than the analysis before-after the implementation of the law. The last recorded information closest to the end of each quarter was used to create the variable. This information could be recorded in the quarter under analysis or previously. We should emphasize that the lack of a quarterly entry in the EHR does not mean that the information is not up to date, but that no changes have taken place and thus the last entry is considered valid.

We have modified the following sentence in the methods section:
"Smoking status (three categories): 1) non-smoker: patient that has never been a tobacco consumer, 2) smoker: tobacco consumer or patient that has quit smoking for less than 12 months; and 3) ex-smoker: patient who used to smoke but has quit smoking for at least 12 continuous months. If the EHR did not contain a new entry related to smoking status, we assumed that no changes had taken place and thus the last observation was carried forward".

4. According to Figure 1, a large proportion of the potential study participants had to be excluded because of data problems. It is uncertain whether inclusion into the study was selective on relevant variables, and whether this may have affected the generalisability of the results.
ANSWER: The inclusion criteria aimed to monitor the smoking status in an unfluctuating population. Most selection criteria were unrelated to data issues.
Exclusion criteria were as follows:

- Patients <16 and >100 years of age: In Spain, people under 16 are not under the care of GPs but of paediatricians (in Spain paediatricians take care of children up to 14 or 15 years old, depending on the region); people over 100 were excluded to avoid outliers and inaccurate data.

- Patients assigned to a professional with a reduced patient-list: Few patients were excluded under this criterion (27 in Catalonia and 17 in the Balearic Islands). Professionals with a reduced patient-list (for instance, the primary care director) provide health care on a part-time basis and their clinical practice might differ from other professionals of the same PHC centre.

- Patients with no PHC visit during the study period: In the case of patients that did not attend consultations during the study period, the professionals could not register recent information on smoking habits in the EHR.

- Patients with no allocated PHC team (PHCT) for all years of the study (for Catalonia and Navarre): When the patient was not assigned to the same PHC during the whole study period, the information could not be considered comprehensive. We believe that the follow up of the same population during the study period facilitated data monitoring and maximized the internal validity of the study. In the Balearic Islands, the participants were patients allocated to participant PHCT in 2013 and evaluated retrospectively, since no historical annual comprehensive register of allocation of patients was available.

- Patients without baseline data on smoking status: Many patients were excluded from the study because of lack of baseline data on smoking. Missing data is a common problem in studies based on EHR. In order to prevent bias caused by the improvement in recording smoking habits and to make certain that the data responded to changes in behaviour, we excluded the cases with no information at the beginning of the study, thus maximizing the internal validity of the study.

Of all the selection criteria, the generalisation of results can be affected by the "information on smoking habit recorded in the EHR for the quarter prior to the onset of the study". Although 70% of the population attend PHC services at least once a year and smokers attend more frequently than non-smokers, a section of the population does not contact the PCHT and thus lack baseline information of their smoking status. For instance, the younger population and patients that consult private health services. Consequently, the study population represents solely the population attending primary care services.

We have modified different sentences in the discussion section:
"In addition, many patients were excluded from the study because of lack of baseline data on smoking (missing data is a common problem in studies based on EHR). In order to prevent bias caused by improved smoking records, we excluded the cases with no information at the beginning of the study. The selection criteria and the longitudinal design aimed to maximize the internal validity of the study."

"The results are only generalizable to PHC users".

5.The data are analysed with joint-point regression. This type of analyses may be useful as an exploratory tool. However, to assess the impact of a policy, it would have been more informative to employ methods that are designed to test a priori hypotheses of policy impact, such as regression discontinuity analysis.
ANSWER: Joinpoint regression analysis is used to identify when a significant change occurred in the rates and crucially, to determine if changes are statistically significant. Joinpoint has two major advantages: it identifies the point in time when significant changes in the trend occur and it estimates the magnitude of the increase or decrease observed in each interval through the calculation of the annual percentage change (APC) (8,9). With joinpoint we can answer the main questions of our research. On the other hand, an essential requirement of regression discontinuity analysis is the control group, which we did not have in our study. Also, regression discontinuity analyses focus on generating estimates of the causal effects of an exposure with a continuously measured variable used to assign the exposure to individuals based on a threshold rule (usually, when patients receive a treatment based on scoring above or below a cut-off point).

While other statistical analyses are also valid, joinpoint has been widely used and is adequate to attain our goals. We have found similar articles that have used joinpoint analysis to evaluate the impact of smoke-free legislation (SFL) (10–13).

In the methods section of the new version of the manuscript, we have modified the following paragraph:
"Joinpoint analysis was used to analyse the trends of age-standardized prevalence (smokers and ex-smokers) and incidence rates (new smokers, new ex-smokers and ex-smoker relapse) and to identify the best-fitting points (the 'joinpoints', in calendar quarters) where the rate changes significantly in the linear slope of the temporal trend. Significant changes include changes in direction or in the rate of increase or decrease[29]. Joinpoint analysis estimates the magnitude of the increase or decrease observed in each specified time interval by calculating the annual percentage change (APC). In addition, temporal trends were also expressed as the average annual percent change (AAPC), computed to

summarize and compare these trends over the entire time period. Ninety-five percent confidence intervals (95% CI) of APC and AAPC were calculated".

We have also added the following in the discussion section:
"We should underscore that rather than just comparing two different periods, joinpoint analysis evaluates longitudinal trends, thus producing a more accurate assessment. While other statistical models could have been used, we believe that joinpoint is a suitable method to achieve the study objectives with the available data, as shown in previous studies.[43-45]" (10,12,14)

6. Related to this previous point: the number of figures is excessively large, which make it hard to identify the results that are key to testing hypotheses regarding the impact of policies. Why not combine the results of the three regions?
ANSWER: We are aware of the large number of tables in the manuscript and have accordingly only included the tables with trends in the main text, since we consider that these contain the most relevant results. The remaining tables can be found as supplementary materials. In our view, the results required stratified analysis per region since the three regions used different EHR systems (different standards and software) and implemented different complementary measures to the SFL, and also due to the shorter study period in the Balearic Islands.

Why not focus on the few smoking outcomes that are most likely to be related to the new policy?
ANSWER: We realise that the manuscript presents 6 different outcomes stratified per region, overall and by sex, which results in a large amount of data. The tables show all the figures, whereas the written results section of the manuscript highlights the most relevant results. While the results do not show changes with respect to previous trends in any variable, we believe that the information presented is relevant for PHC professionals. The prevalences of smoking status are the most commonly presented outcome in the literature, but the analysis of lesser studied variables such as incidence of new smokers, new ex-smokers or relapse of ex-smokers are of great relevance for everyday PHC practice, where smoking cessation is more intensely promoted and where help to quit is readily available to patients. Most smokers are aware that they need to quit smoking, the complexity lies in how to achieve this end. Quitting smoking involves overcoming nicotine addiction, unlearning behaviour and modifying the influence of the environment. These goals are not achieved in a single step, but cyclically through various phases (according to the Transtheoretical Model of Change of Prochaska and DiClemente (15)), where PHC professionals provide support, tools and follow up. The 5 As strategy is recommended: ask about smoking, advise, assess willingness, assist and arrange (16–18). It can be useful for PHC practitioners to understand the impact on smoking relapse of Law 42/2010, which effectively denormalises smoking in society.

We have modified the following sentence in the discussion section:
"We should also highlight that this study includes the evaluation of novel variables such as incidence of new smokers, new ex-smokers and ex-smoker relapse, which we consider of great relevance in relation to PHC interventions for smoking cessation".

7. Also related to this point: the Discussion is not focussed on assessing the strength of evidence regarding an impact of the policy. Instead, much of the discussion deals with male-female comparisons (not relevant to this paper) or makes descriptive summaries of previous Spanish studies.
ANSWER: Following the recommendations of the reviewer, we have modified the discussion in the new version of the manuscript. Please, see the new text in the manuscript file.

Reviewer: 3. Kate Frazer

This is a very important public health paper. There is a need for more evidence and longitudinal data on the impact of legislative smoking bans on active smoking rates - this study adds to this body of evidence.
ANSWER: Thank you for your comment.

The limitations of the data are described. Legislative bans are one component of the WHO FCTC and MPOWER and you could include this within your discussion.
ANSWER: We have included this aspect in the discussion section of the manuscript (before limitations):

"The SFL is a keystone of the WHO Framework Convention on Tobacco Control (FCTC) and the MPOWER policy package (M=Monitor; P=Protect; O=Offer; W=Warm; E=Enforce; R= Raise) (19).[40] The enforcement of Laws 28/2005 and 42/2010 have significantly advanced smoking control in Spain, in particular the "Protect people from tobacco" strategy. However, the remaining MPOWER strategies have been patchily implemented and require further development (20).[23] On balance, a combination of specific, feasible, pragmatic, sufficiently funded policies and interventions aimed at populations and individuals is essential to achieve progress regarding smoking behaviour".

Reviewer: 4. Iñaki Galan Labaca.

In the introduction, is important to conceptualize why the authors think that the Law 42/2010, which is a reform of the Law 28/2005, where smoking was banned in hospitality venues, can produce changes in tobacco consumption in the general population.
ANSWER: We have accordingly added the study hypothesis before the objective:
"We hypothesized that Law 42/2010 does not only reduce exposure to environmental cigarette smoke and its harmful effects but crucially, it promotes smoking denormalisation in society, thus encouraging smokers to quit or reduce consumption and discouraging non-smokers from initiating this habit."

The study participants and mainly the way of collecting information are not clear. The inclusion criteria in the Balearic Islands are different from those of the other two regions, with patients allocated in PHCT in 2013 and evaluated retrospectively because there was not annual comprehensive register of patients.
ANSWER: This study comprises 4 inclusion criteria for patients, one of which differs in the Balearic Islands with respect to Catalonia and Navarre. In the Balearic Islands, we selected patients allocated to Primary Health Care Team (PHCT) in 2013 and evaluated retrospectively all smoking-related data registered in their electronic health records (EHR) during the study period. In the Balearic Islands no annual comprehensive register of allocation of patients was available, and thus it was not possible to ascertain which patients were assigned to specific PHCT prior to 2013. In all three regions the information was collected from the EHR, but while in Catalonia and Navarre we selected patients allocated to the PHCT for the whole study period, in the Balearic Islands we selected the patients assigned to the PHCT only in 2013.

We have clarified this aspect in the methods section:
"Inclusion criteria for patients were: 1) Population allocated to the selected PHCT for the whole 2007-2013 period in Catalonia and Navarre; in the Balearic Islands, patients allocated to the selected PHCT in 2013 and evaluated retrospectively (no historical annual comprehensive register of allocation of patients was available). 2) Age ≥16 and ≤100 years in 2007 in Catalonia and Navarre, and 2010 in the Balearic Islands. 3) In order to have data in the EHR collected during the study period, a minimum of one visit to their PHCT during the 2007-2013 period in Catalonia and Navarre and 2010-2013 in the Balearic Islands; and 4) Information on smoking habit recorded in the EHR for the quarter prior to the onset of the study: last quarter of 2007 in Catalonia and Navarre and first quarter of 2010 in the Balearic Islands, to enable the adequate construction of the various variables".

Taking into account no updated electronic information during the period of study and the scarce number of date (three quarters) before the law came into force, it would be better to exclude this region from the analysis.
ANSWER: It is correct that the study period prior to the implementation of the Law is considerably shorter in the Balearic Islands (three quarters) compared to Catalonia and Navarre (twelve quarters). Unfortunately, the study just included the period 2010-2013 for the Balearic Islands because the EHR prior to 2010 were not sufficiently reliable. This was precisely one of the main reasons why the analyses were stratified by region. However, despite the limited study period, the information was completely updated. Moreover, all information in the EHR of participants from the Balearic Islands regarding smoking prior 2013 was also collected.

We have added a new sentence in the limitations:
"In view of the limited length of the study period, particularly in the Balearic Islands, we consider these results a first approximation to be succeeded by follow-up research. We should underscore that rather than just comparing two different periods, joinpoint analysis evaluates longitudinal trends, thus producing a more accurate assessment".

The design, based in a closed cohort where nobody is excluded after the study begins, is controversial. It is supposed that some patients will change of General Practitioner and PHCT due to social or work conditions.
ANSWER: In Catalonia and Navarre, participants had to be assigned to the same PHCT throughout the study period. Consequently, patients that moved and changed PHCT were excluded from the cohort. In addition, at least one consultation during the study period with primary health care (PHC) professionals was required. These selection criteria were established to avoid information gaps throughout the study period and to ensure comprehensive monitoring of smoking behaviour, thus maximizing the internal validity of the study.

We have modified different sentences in the discussion section:
"In addition, many patients were excluded from the study because of lack of baseline data on smoking (missing data is a common problem in studies based on EHR). In order to prevent bias caused by improved smoking records, we excluded the cases with no information at the beginning of the study. The selection criteria and the longitudinal design aimed to maximize the internal validity of the study."
"The results are only generalizable to PHC users".

From initial database, after excluding those patients <16 and >100 years old, patients with no PHC visit during 2007-2013 or 2010-2013, patients with no allocated PHCT for all years of the study, there is recorder information about smoking in the last quarter of 2007 or the 1st quarter of 2010 (Balearic Islands), in 40,1% of Catalonia, 39,2% of Navarre and 56,7% of Balearic Islands. The higher rate in recorded information on tobacco in the Balearic Islands suggests that it is related to an improvement in date collecting over time, a situation that could cause an artifact in the analysis of trends.
ANSWER: As the reviewer explains, many patients were excluded from the study because of lack of baseline data on smoking. Missing data is a common problem in studies based on EHR. In order to prevent bias caused by the improvement in recording smoking habits and to make certain that the data responded to changes in behaviour, we excluded the cases with no information at the beginning of the study, thus maximizing the internal validity of the study. While a considerable proportion of the initial population could not be included in the analysis, we succeeded in creating a large, stable cohort without loss of data.

We have clarified this aspect in the limitations section:
"In order to prevent bias caused by improved smoking records, we excluded the cases with no information at the beginning of the study. The selection criteria and the longitudinal design aimed to maximize the internal validity of the study."

Another aspect that suggests being conditioned by the data collection rather than self-selection bias, is the very low prevalence of ex-smokers, especially in Navarre and the Balearic Islands.
ANSWER: In comparison with previous studies, the lower age-adjusted smoking status prevalence rates are in all likelihood caused by the selection criteria of participants. As we explained in the limitations, young people might be underrepresented due to their lower use of PHC services. In consequence, the results might only be generalizable to PHC users.

We have modified the following sentence in the new version of the manuscript:
"The results are only generalizable to PHC users".

The information on smoking habit is a mix of clinical variables, codes from ICD 10, ICD 9 and ICP-2. This is confusing because some indicators (i.e. new ex-smokers, relapse) must be collected with ad-hoc questions.
ANSWER: PHC physicians and nurses use EHR in daily practice to register diagnoses, prescriptions, screenings, health advice and other clinical, management and administrative activities. The doctor or nurse obtain information on the smoking habit of the patient by means of specific questions made during the consultation and this information, together with subsequent measures taken, are recorded in the EHR as diagnostic codes and as clinical variables. For instance, in the medical records we might read that brief counselling for smoking cessation was given, which indicates that on the day of the consultation the patient was still smoking. In summary, for a complete construction of the dependent variables all information from clinical variables (number of cigarettes per day, history of smoking, history of advice for smoking cessation) and from the diagnostic codes of the international classification of

diseases (codes F17.0 to F17.9 and Z72.0 of the ICD-10, 305.1 of the ICD-9 and P17 of the ICPC-2) must be taken into account.

The update of information about smoking to estimate the prevalence each quarter is not clear. Few patients visit their GP every quarter, so authors say that if the EHR did not register smoking status at some point in time, the last observation was carried forward. This point should be clarified because it is probably that information about smoking is imputed in most quarters.
ANSWER: Table 1 describes the mean, median and interquartile range (IQR) PHC number of visits per patient and by region at the onset of the study. The visits consisted of consultations with the nurse or GP. As explained in the first paragraph of results, Catalonia presented the highest median number of visits (9, IQR: 3 -16), the Balearic Islands the second highest (7, IQR: 3-15) and Navarre the lowest (7, IQR: 3-12). In summary, the study population attend primary health care services frequently, thus facilitating continuity of smoking interventions.

We have previously explained that PHC professionals approach smoking in the consultation room in agreement with the recommendations of the Programme of Prevention Activities and Health Promotion (PAPPS) (2), the Consensus Document for the Clinical Care of Smoking in Spain (3) and current clinical guidelines. For instance, the PAPPS of the Spanish Society of Family and Community Medicine advises PHC practitioners to ask all people over 10 years of age about smoking at each consultation and to register cigarette consumption in the electronic medical records. Smoking screening should take place at least every 2 years. All smokers should be personally and clearly advised to quit smoking, should receive help to that end and follow up must be scheduled during the first weeks after quitting smoking. Moreover, since PHC professionals received annual financial incentives to register smoking habits, we should assume that the EHR were up to date and that they reflect real life.

In this study, we constructed the smoking status each trimester. The use of joinpoint for quarterly data analysis achieves results with greater precision than the analysis before-after the implementation of the law. The last recorded information closest to the end of each quarter was used to create the variable. This information could be recorded in the quarter under analysis or previously. We should emphasize that the lack of a quarterly entry in the EHR does not mean that the information is not up to date, rather, that no changes have taken place and thus the last entry is valid.

We have modified the following sentence in the methods section:
"Smoking status (three categories): 1) non-smoker: patient that has never been a tobacco consumer, 2) smoker: tobacco consumer or patient that has quit smoking for less than 12 months; and 3) ex-smoker: patient who used to smoke but has quit smoking for at least 12 continuous months. If the EHR did not contain a new entry related to smoking status, we assumed that no changes had taken place and thus the last observation was carried forward".

The longitudinal data analysis is performed like a cross-sectional study. Regarding that the outcomes are repeated measurements, this should be taking into account in the analysis, i.e. using Generalized Estimating Equations or mixed models (multilevel regression models). The authors **should discuss** about advantages and disadvantages of jointpoint analysis because most studies that have evaluated the impact of smoke-free policies have not chosen this method, using mostly Interrupted Time Series Analysis. Joinpoint is a useful method to describe changes in time series but generally requires changes in trend of a certain magnitude to detect a segment change. Furthermore, the position of joinpoints is not fixed by the researcher, but it is established on the basis of a statistical criterion. In addition, if the effect of regulations is immediate but not maintained over time, jointpoint may not be the best technique for analysis. Interrupted Time Series Analysis is a quasi-experimental design that can be applied to healthcare data to evaluate the effect of interventions, which involves the analyst pre-specifying the time point of interest in the data series.
ANSWER: This comment from Reviewer 4 (Iñaki Galán) is similar to comment 5 of Reviewer 2 (Anton Kunst). Both reviewers indicate that various statistical techniques can be used to evaluate the impact of the smoke-free legislation (SFL). In fact, prior studies have used either Interrupted Time Series Analysis (21–24) or Joinpoint regression analysis (10–13). Since, unfortunately, data prior to the implementation of the SFL are scarce, particularly from the Balearic Islands, we considered Joinpoint regression analysis better suited to the data available in view of the study objectives. Moreover, we believe that the point in time of the change should not be fixed, since factors other than the implementation of the Law influence smoking trends. Change in trends can be observed before and after the precise moment when the Law was implemented, and it is also possible to detect more than

one change in trend throughout the study period. Interestingly, in our study we did not limit the number of possible changes and we found up to 5 different trends (see Table 2). In conclusion, with Joinpoint we have been able to observe changes caused by the implementation of the Law that evolve with time.

We have added two sentences in the new version of the discussion section:
"We should underscore that rather than just comparing two different periods, joinpoint analysis evaluates longitudinal trends, thus producing a more accurate assessment. While other statistical models could have been used, we believe that joinpoint is a suitable method to achieve the study objectives with the available data, as shown in previous studies. [43-45]*"* (10,12,14)

Authors conclude that the introduction of the Spanish comprehensive Law 42/2010 does not significantly modify incidence and prevalence trends of smoking behaviour. However, when we see with detail tables S2 and S3 (results of Catalonia and Navarre) there is a strong change in no smoking prevalence just when the law came into force: the non-smokers prevalence decreases around 10% in the first quarter of 2011. Surprisingly, this important result (in case it was real) is not described in the text.

ANSWER: The design with a closed cohort and the definition of the variable non-smoker (patient that has never been a tobacco consumer) mean that the prevalence of non-smokers can either remain the same or decrease, but never increase, i.e., non-smokers can only remain non-smokers or become smokers and later on even ex-smokers. However, it is impossible to move from smokers or ex-smokers to non-smokers. Indeed, changes in our population are marked by changes in the prevalence and incidence of smokers and ex-smokers and these changes are accordingly highlighted in the manuscript. In contrast, the prevalence trend of non-smokers is not considered relevant, since it might be biased by the study design.

VERSION 2 – REVIEW

REVIEWER	Cristina Lidon Moyano Department of Public Health, University of California, Merced
REVIEW RETURNED	28-Feb-2018

GENERAL COMMENTS	The authors have properly address all my suggestions. Moreover, I agree with the authors that the manuscript has substantially improve. I specially appreciate the effort in obtaining the supplementary graphs for the trends. Therefore, I do recommend the acceptance of this manuscript.

REVIEWER	Kate Frazer University College Dublin Author of systematic reviews on smoking bans
REVIEW RETURNED	21-Mar-2018

GENERAL COMMENTS	Thank you for revising your paper and focusing on feedback from reviewers. The paper provides additional evidence of the impact of smoking bans at a population level. Acknowledges the limitations of study design. Statistical review required.

REVIEWER	Iñaki Galán Centro Nacional de Epidemiología, Madrid (España)
REVIEW RETURNED	26-Feb-2018

GENERAL COMMENTS	Although the paper has been improved, it maintains several weaknesses that can lead to a high risk of bias. Most of them are based on limitations of the source of information. Despite authors excluded a huge amount of cases with no information about smoking at the beginning of the study in order to

	increase the internal validity, there are important limitations about the homogeneous way of collecting information over time. As the authors claim, the lack of a quarterly entry in the EHR is replaced by imputations of the last recorded information, considering that no changes have taken place. But they do not describe how many values of the times series are imputed. Furthermore, the information on smoking habit is very confusing, a mix of clinical variables (codes from ICD 10, ICD 9 and ICP-2) and history of smoking. The authors do not explain clearly how the information to build the indicators is collected.
	The lack of accurate information on smoking indicators can be related to some inconsistencies in the results. For example, the very low prevalence of ex-smokers, especially in Navarre and the Balearic Islands taking into account that older people are overrepresented due to their higher use of PHC services; or the decrease in non-smokers prevalence, since the cohort is closed, where the authors recognize that it might be biased by the study design; or the very large changes in the prevalence of "new smokers" (Balearic Islands) and "ex-smokers relapse" (Balearic Islands and Catalonia) in the last quarters of the time series. Regarding that the outcomes are repeated measurements, this should be taking into account in the analysis, i.e. using Generalized Estimating Equations or mixed models (multilevel regression models) to allow for correlated observations.

REVIEWER	Rahim Moineddin University of Toronto Canada
REVIEW RETURNED	26-Apr-2018

GENERAL COMMENTS	This is study is a classical example of interrupted time series. I am not convinced that joint point analysis is the best method for analyzing interrupted time series. See for example James Lopez Bernal, Steven Cummins, Antonio Gasparrini . Interrupted time series regression for the evaluation of public health interventions: a tutorial. International Journal of Epidemiology, Volume 46, Issue 1, 1 February 2017, Pages 348. Authors need to justify the appropriateness of the jointpoint analysis or use another appropriate method for assessing the impacts of partial and full smoking ban in Spain using Primary Healthcare patients data.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1.Cristina Lidon Moyano
Department of Public Health, University of California, Merced

The authors have properly address all my suggestions. Moreover, I agree with the authors that the manuscript has substantially improve. I specially appreciate the effort in obtaining the supplementary graphs for the trends. Therefore, I do recommend the acceptance of this manuscript.
ANSWER: Thank you very much for this comment.

Reviewer: 3. Kate Frazer
University College Dublin

Thank you for revising your paper and focusing on feedback from reviewers. The paper provides additional evidence of the impact of smoking bans at a population level. Acknowledges the limitations of study design.

Statistical review required.
ANSWER: Thank you very much for this comment. We have improved the manuscript, as explained in the responses to the other reviewers.

Reviewer: 4. Iñaki Galán
Centro Nacional de Epidemiología, Madrid (España)

Although the paper has been improved, it maintains several weaknesses that can lead to a high risk of bias. Most of them are based on limitations of the source of information. Despite authors excluded a huge amount of cases with no information about smoking at the beginning of the study in order to increase the internal validity, there are important limitations about the homogeneous way of collecting information over time. As the authors claim, the lack of a quarterly entry in the EHR is replaced by imputations of the last recorded information, considering that no changes have taken place. But they do not describe how many values of the times series are imputed.

ANSWER: The databases that originate from primary care electronic health records (EHR) present a huge potential for epidemiological studies. This potential pivots on the wide population coverage, continuity of care and holistic approach of primary care services (1). For example, it is known that 70% of the Spanish population attend primary health care (PHC) services at least once a year, and that smokers attend more frequently than non-smokers (2). Nonetheless, as pointed out by the reviewer, the worthiness of these databases lies on the reliability and validity of the entries.

Information on smoking is registered in the EHR using diagnostic codes and clinical variables with their corresponding entry dates. Since smoking is not an acute condition (in contrast, for instance, with an episode of gastroenteritis, with a resolution date after just a few days), this information is considered valid until new information is entered.

In regular clinical practice, the first visit of a patient with her family doctor or primary care nurse includes a clinical interview that registers harmful habits like smoking. If due to constraints like lack of time these data are not registered during the first visit, a reminder system within the Prevention Activities and Health Promotion Programme (PAHPP) will alert the health professional to complete the data. The PAHPP recommends asking all adults about smoking when they attend appointments and also to provide advice on quitting smoking to smokers (clinical variables within the EHR also reflect this aspect). Two years is the minimum periodicity for asking about smoking habits and for providing smoking quitting advice (3). Most general practices routinely record smoking status at regular intervals as part of contractual financial objectives (4). Consequently, smoking status is regularly updated in patients that attend appointments in primary care centres (our study population). In contrast, data on people that do not attend primary care centres are not reliable, and this population was therefore not included in the study.

Imputation of missing values was not used in this study. Instead, we considered that the person had a specific smoking habit (collected during the consultation) until changes in this status appeared in the EHR. Swift behaviour changes are more easily detected when a smoker has attended the primary care centre on several occasions (and this was indeed the case for the population of this study). The information thus collected is real and rich in agreement with the Transtheoretical Model of Change (precontemplation, contemplation, action, maintenance and termination) (5). In addition, previous studies conclude that there is a good correlation between PHC registries of active smoking and data from National Health Surveys (6–8).

To avoid confusion, we have modified the following sentence in the methods section (variables):
"When the EHR did not contain a new entry related to smoking status (diagnostic codes or clinical variables), we considered that no changes in smoking status had taken place and thus that the last observation was still valid"

Furthermore, the information on smoking habit is very confusing, a mix of clinical variables (codes from ICD 10, ICD 9 and ICP-2) and history of smoking. The authors do not explain clearly how the information to build the indicators is collected.
ANSWER: Primary healthcare professionals use the EHR to register diagnoses, prescriptions, screenings, health advice and other clinical, management and administrative activities. Health

information can be stored as diagnostic codes and clinical variables, and this information is logged together with the entry date. Consequently, to understand the magnitude of a health issue such as smoking, we need to take into account the registers of the diagnostic codes and clinical variables related to smoking. If we look just for one type of variable we risk losing information. As a result, in this study the information from EHR has been retrieved as explained in the following Table:

Table S1: Information concerning smoking status in the electronic health records by region

Information from electronic health records	Catalonia	Navarre	Balearic Islands
Diagnostic codes related to smoking (with entry date)	Smoker: F17, F17.0, F17.1 F17.2, F17.5, F17.6, F17.7, F17.8, F17.9 in ICD-10	Smoker: code P17 in ICPC-2	Smoker: 305.1 in ICD-9
	Ex-smoker: Z72.0		
Clinical variables related to smoking in the medical history (with entry date)	Smoking habit: 0: non-smoker. 1: smoker. 2: ex-smoker		
	Number of cigarettes per day: 0 to 300		
	Smoking cessation advice: 1: yes 0: no		

Abbreviations: ICPC-2, International Classification of Primary Care, second edition; ICD-9 and 10, International Classification of Diseases, 9th and 10th revision.

Based on this information, and taking into account entry dates, we created the dependent variables of the study. The first variable calculated was "smoking status", which we used as the basis to calculate the remaining dependent variables.

We have added modifications in the section Variables of the new version of the manuscript and included Table S1 in the supplementary files (Supplementary File Table S1) for clarification:

"Information on smoking is registered in the electronic health records using diagnostic codes to classify diseases (codes F17.0 to F17.9 and Z72.0 of the ICD-10, 305.1 of the ICD-9 and P17 of the ICPC-2), and also clinical variables (number of cigarettes per day, history of smoking, advice for smoking cessation). This information is stored with the entry date (Supplementary File Table S1). With the information on smoking status and entry date we created the following dependent variables at the end of each quarter of the study period:"

The lack of accurate information on smoking indicators can be related to some inconsistencies in the results. For example, the very low prevalence of ex-smokers, especially in Navarre and the Balearic Islands taking into account that older people are overrepresented due to their higher use of PHC services; or the decrease in non-smokers prevalence, since the cohort is closed, where the authors recognize that it might be biased by the study design; or the very large changes in the prevalence of "new smokers" (Balearic Islands) and "ex-smokers relapse" (Balearic Islands and Catalonia) in the last quarters of the time series.

ANSWER: Before reflecting on the results of the study, we would like to underscore that in this study overrepresentation by older people does not bias the results, since in order to control for the possible effect of age, age-standardized incidence and prevalence rates were calculated for each trimester using the direct method based on the European Standard Population.

As the reviewer points out, the prevalence of ex-smokers, especially in Navarre and the Balearic Islands, is low when compared with data from health surveys (9). Ramos *et al.* (2012) (1) suggested that the lower prevalence of ex-smokers observed in their study could be attributed to the misclassification of long-term ex-smokers as non-smokers during the computerization process of health records. Marston *et al.* (2014) also conclude that the misclassification of ex-smokers as non-smokers is likely to occur in people who quit smoking at an early age or a long time ago (7).

Regarding the decrease of non-smokers prevalence, the design with a closed cohort (where no new participants are recruited) and the definition of the variable non-smoker (patient who has never been a cigarette consumer) mean that the prevalence of non-smokers can either remain the same or decrease, but never increase, i.e., non-smokers can only remain non-smokers or become smokers and later on even ex-smokers. However, it is impossible to move from smokers or ex-smokers to non-smokers.

With regard to the extensive changes in "new smokers" (Balearic Islands) and "ex-smokers relapse" (Balearic Islands and Catalonia) in the last quarters of the study period, we should highlight that they refer to incidence (as opposed to prevalence) rates. As pointed out by the reviewer, some variability exists amongst the quarterly incidence rates in the last quarters of the time series, although this variability of the last quarters does not translate into a statistically significant change of the trend. In the Balearic Islands, the overall trend of new smoker incidence rates remained stable during the whole period, and the overall trend of ex-smokers relapse incidence did not significantly decrease in the last quarters of 2013. However, in Catalonia a non-significant, decreasing trend was observed in the overall ex-smokers relapse incidence and in women from January 2008 to March 2012. This trend becomes increasing and significant from March 2012 to April 2013, perhaps due to the impact of the financial crisis on the mental health of the population (anxiety and depression), as pointed out in the discussion. The lack of significance in the Balearic Islands might be due to random changes, since the baseline rates for new smokers are much lower. Also, the study period is shorter than for the other two regions of the study.

In addition, we should mention that there is variability of results amongst the 3 regions. As reported in previous studies carried out in Spain, this variability could be explained by socio-economic differences. In a study by Galan *et al.* (2017) (10), the effect of the smoke-free legislation in COPD-related admissions was found to be higher in provinces with lower socioeconomic development. In another article on cardiovascular disease, Galan observed high regional variability that did not originate from the information source or methods of analysis, and the authors attributed this variability to the different implementation of smoke-free legislation and to a lower index of economic development (11). This variability amongst regions led us to present the results stratified by region.

To clarify these aspects, we have added the following sentences in the discussion:
"We should underscore that other studies that use health surveys as information source have a higher prevalence of ex-smokers than the prevalence we obtained in this study, especially for Navarre and the Balearic Islands[31] (9). This discrepancy could be explained by the misclassification of long-term ex-smokers as non-smokers during the process of computerization of medical records in the cases where the smoking habit was not sufficiently investigated[32] (1)".

We observed a gradual decline in new smoker incidence trends in Catalonia and Navarre throughout the study period, whereas incidence trends remained stable in the Balearic Islands (possibly due to the shorter study period or lower rates).

The incidence trend in ex-smoker relapses increased in Catalonia and declined in Navarre throughout the whole period, particularly for women, but the overall trend remained stable in the Balearic islands (most likely because of the shorter study period).

In addition, we have added the following sentences in the methods- data analyses section:
"Because the three regions used different EHR systems (different standards and computer programs), have different socioeconomic characteristics, different complementary measures to the SFL and also due to the shorter study period in the Balearic Islands, we performed a stratified analysis per region, overall and by sex."

"The trend of non-smoker prevalence rates was not calculated because the study consisted of a closed cohort where no new participants are recruited, and thus the prevalence of non-smokers can either remain the same or decrease, but never increase".

Regarding that the outcomes are repeated measurements, this should be taking into account in the analysis, i.e. using Generalized Estimating Equations or mixed models (multilevel regression models) to allow for correlated observations.

ANSWER: This comment from Reviewer 4 (Iñaki Galán) is similar to the comment of Reviewer 5 (Rahim Moineddin). As we explained in the previous letter, various statistical techniques can be used to evaluate the impact of smoke-free legislation (SFL). In fact, prior studies in the literature regarding SFL have used either Interrupted Time Series Analysis (12–15) or Joinpoint Regression Analysis (16–19). During the design of the study, we reviewed and pondered about the most adequate type of analysis, taking into account the characteristics of the project. We finally decided to use jointpoint analysis due to the following reasons:

- Data prior to the implementation of the SFL are scarce, particularly from the Balearic Islands, where only 3 quartiles were available before the smoke-free legislation.
- Because we are analysing smoking status, we believe that the point in time of the change should not be fixed, since factors other than the implementation of the Law influence smoking trends. In addition, quitting smoking is not an immediate process, it takes time as patients undergo the different phases of change. Thus, the effect of the Law on smoking status can be relatively slow, similarly to its effect on exposure to secondhand smoke. Joinpoint identifies the point in time when significant changes in the trend occur, and it estimates the magnitude of the increase or decrease observed in each interval through the calculation of the annual percentage change (APC).
- It is possible to detect more than one change in smoking trends throughout the study period. Interestingly, in our study we did not limit the number of possible changes and we found up to 5 different trends (see Table 2).
- Other confounders were not available and we had to carry out the analysis with age-standardized prevalence and incidence rates. Joinpoint regression analysis is used to identify when a significant change in the rates takes place and crucially, to determine if changes are statistically significant.

In order to clarify these arguments we have modified the following sentence in the new version of the discussion:

"We should underscore that rather than just comparing two different periods, joinpoint analysis evaluates longitudinal trends, thus producing a more accurate assessment. The following characteristics of the study were taken into consideration: scarcity of data prior to the implementation of the SFL; delayed changes in smoking status; possibility of detecting more than one change in smoking trends; and influence of unanticipated factors. While other statistical models could have been used, we believe that joinpoint is a suitable method to achieve the study objectives, as shown in previous studies.[43-45]"

Reviewer: 5. Rahim Moineddin
University of Toronto, Canada

This is study is a classical example of interrupted time series. I am not convinced that joint point analysis is the best method for analyzing interrupted time series. See for example James Lopez Bernal, Steven Cummins, Antonio Gasparrini . Interrupted time series regression for the evaluation of public health interventions: a tutorial. International Journal of Epidemiology, Volume 46, Issue 1, 1 February 2017, Pages 348. Authors need to justify the appropriateness of the jointpoint analysis or use another appropriate method for assessing the impacts of partial and full smoking ban in Spain using Primary Healthcare patients data.

ANSWER: This comment from Reviewer 5 (Rahim Moineddin) is similar to the comment of Reviewer 4 (Iñaki Galán). As we explained in the previous letter, various statistical techniques can be used to evaluate the impact of smoke-free legislation (SFL). In fact, prior studies in the literature regarding SFL have used either Interrupted Time Series Analysis (12–15) or Joinpoint Regression Analysis (16–19). During the design of the study, we reviewed and pondered about the most adequate type of analysis, taking into account the characteristics of the project. We finally decided to use jointpoint analysis due to the following reasons:

- Data prior to the implementation of the SFL are scarce, particularly from the Balearic Islands, where only 3 quartiles were available before the smoke-free legislation.
- Because we are analysing smoking status, we believe that the point in time of the change should not be fixed, since factors other than the implementation of the Law influence smoking trends. In addition, quitting smoking is not an immediate process, it takes time as patients undergo the different phases of change. Thus, the effect of the Law on smoking status can be relatively slow, similarly to its effect on exposure to secondhand smoke. Joinpoint identifies the point in time when

significant changes in the trend occur, and it estimates the magnitude of the increase or decrease observed in each interval through the calculation of the annual percentage change (APC).

- It is possible to detect more than one change in smoking trends throughout the study period. Interestingly, in our study we did not limit the number of possible changes and we found up to 5 different trends (see Table 2).
- Other confounders were not available and we had to carry out the analysis with age-standardized prevalence and incidence rates. Joinpoint regression analysis is used to identify when a significant change in the rates takes place and crucially, to determine if changes are statistically significant.

In order to explain these reasons, we have modified the following sentence in the new version of the discussion:

"We should underscore that rather than just comparing two different periods, joinpoint analysis evaluates longitudinal trends, thus producing a more accurate assessment. The following characteristics of the study were taken into consideration: scarcity of data prior to the implementation of the SFL; delayed changes in smoking status; possibility of detecting more than one change in smoking trends; and influence of unanticipated factors. While other statistical models could have been used, we believe that joinpoint is a suitable method to achieve the study objectives, as shown in previous studies.[43-45]"

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VERSION 3 – REVIEW

REVIEWER	Iñaki Galán Centro Nacional de Epidemiología. Instituto de Salud Carlos III
REVIEW RETURNED	27-Jun-2018

GENERAL COMMENTS	The authors have made a big effort to improve the manuscript and to answer the questions raised by reviewers, adding supplementary data. However, I keep having doubts about the homogeneous way of collecting information over time, especially how many of quarterly values entry in the EHR are replaced by imputations (last recorded information), considering that no changes have taken place. Without discussing if Joinpoint regression is as well method as interrupted time series, it should be taking into account in the analysis that the outcomes are repeated measurements and control the correlation. I think this deserves a specialist statistical review.

REVIEWER	Rahim Moineddin University of Toronto, Canada
REVIEW RETURNED	02-Jul-2018

GENERAL COMMENTS	In the abstract authors wrote "The overall standardized smoker prevalence rate showed a significant downward trend (higher in men than women) and the overall standardized ex-smoker

	prevalence rate showed a significant increased trend (higher in women than men) in the three regions. (line 21)" And then in the conclusions they wrote "Trends on smoking behaviour in Primary Health Care patients remain unchanged after the implementation of comprehensive smoke-free legislation. (Line 30)". The results and conclusions look contractive. Page 10 line 31, add per 10,000 population, "The overall standardized smoker prevalence rates per 10,000 population were … If the change in rates are for 10,000 population authors need to modify the results. For example authors need to write (page 10, line 38) "A significant downward overall trend of smoker prevalence age standardized rates per 10,000 population was found in Catalonia (AAPC=- 2.02), Navarre (AAPC= -1.40) and the Balearic Islands (AAPC= -1.75); this downward trend was higher for men than for women in the three regions. In Catalonia, the most significant reduction occurred during the period 2010.3-2011.2 (APC= -8,77), similarly to the Balearic Islands (2010.2-2012.4; APC= -2.11), whereas in Navarre it occurred between 2008.1-2011.3 (APC= -1.69)". Similarly in the entire paper. If the reported results in tables 2, 3, and 4 are for age standardized rates per 10,000 population authors should modify the titles including in the titles both age standardized and 10,000 population.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 4. Iñaki Galán
Centro Nacional de Epidemiología, Madrid (España)

The authors have made a big effort to improve the manuscript and to answer the questions raised by reviewers, adding supplementary data. However, I keep having doubts about the homogeneous way of collecting information over time, especially how many of quarterly values entry in the EHR are replaced by imputations (last recorded information), considering that no changes have taken place.

ANSWER: Thank you for your comment. The data were collected retrospectively. The study included three closed cohorts, where nobody was added nor excluded after the start of the study, since patients with no available information on their smoking habit and not allocated to the selected Primary Health Care teams (PHCT) in the whole period study were excluded, as specified in the inclusion criteria. Information on smoking habit was registered in the electronic health records (EHR) using diagnostic codes and clinical variables with their corresponding entry dates. Since smoking is not an acute condition, this information is considered valid until new information is entered. A minimum of one visit to the PHCT during the study period was required for inclusion. Consequently, we did not use imputation of missing values. Instead, we considered that the person had a specific smoking habit (collected during the consultation) until changes appeared in the EHR.

We have added the following sentence in the methods section (inclusion criteria) to clarify this issue:
4) Information on smoking habit recorded in the EHR for the quarter prior to the onset of the study: last quarter of 2007 in Catalonia and Navarre and first quarter of 2010 in the Balearic Islands, to enable the adequate construction of the various variables. *Since smoking is not an acute condition, this information was considered valid until new information was entered.*

Without discussing if Joinpoint regression is as well method as interrupted time series, it should be taking into account in the analysis that the outcomes are repeated measurements and control the correlation. I think this deserves a specialist statistical review.
We agree that the outcomes are repeated measurements and that we need to control for the correlation. We repeated all the analyses controlling for the correlation and changed the values of Tables 2-4 and Figures S1-S2 accordingly.

We have also introduced the following sentence in "Data analyses" (page 7, line 7 of the second paragraph):
"Because the outcomes originate from repeated measurements, control for autocorrelation errors was used"

However, the results of the new analyses controlling for the correlation did not substantially change any previously obtained outcome.

Reviewer: 5. Rahim Moineddin

University of Toronto, Canada

In the abstract authors wrote "The overall standardized smoker prevalence rate showed a significant downward trend (higher in men than women) and the overall standardized ex-smoker prevalence rate showed a significant increased trend (higher in women than men) in the three regions. (line 21)" And then in the conclusions they wrote "Trends on smoking behaviour in Primary Health Care patients remain unchanged after the implementation of comprehensive smoke-free legislation. (Line 30)". The results and conclusions look contractive.

ANSWER: We are aware that the results and conclusions might appear contractive due to the word limit of the abstract. In short, despite upward and downward trends in some variables throughout the study period, Law 42/2010 did not influence these trends. Indeed, if this Law had influenced these variables, a change of trend would have been observed from the first quarter of 2011, when the Law was first enforced. However, as Figure S1 and S2 in Supplementary Data illustrate, no subsequent leaps were observed in prevalence nor incidence trends. We can therefore conclude that Law 42/2010 failed to modify the trends that preceded its implementation.

To avoid confusion, we have modified the following sentence in the conclusions section of the abstract:

"Trends on smoking behaviour in Primary Health Care patients remain unchanged after the implementation of comprehensive smoke-free legislation. The impact of the comprehensive SFL might have been lessened by the effect of the preceding partial SFL."

In addition, we have included further modifications in the results section for a closer definition of the trends of some incidence rates:

The overall trend of new smoker incidence rates decreased significantly in Catalonia (AAPC= -10.39) and Navarre (AAPC= -9.49); additionally, the decline was similar for men and women. In contrast, the overall trend remained stable in the Balearic Islands despite a decrease until 2012.4 (APC= -46.20), and a considerable increase from 2012.4 to 2013.4 (APC= 1054.2) (Tables 2, 3, 4, Supplementary File Figure S2).

The overall trend of ex-smoker relapse incidence rates showed significant increases in Catalonia (AAPC= 18.60), particularly in women (AAPC= 14.56), although a decrease from 2008.1 to 2012.3 was observed (APC= -8.40). In contrast, Navarre showed significant decreases (AAPC= -11.42) (Tables 2, 3, 4, Supplementary File Figure S2).

Page 10 line 31, add per 10,000 population, "The overall standardized smoker prevalence rates per 10,000 population were …

If the change in rates are for 10,000 population authors need to modify the results. For example authors need to write (page 10, line 38) "A significant downward overall trend of smoker prevalence

age standardized rates per 10,000 population was found in Catalonia (AAPC=- 2.02), Navarre (AAPC= -1.40) and the Balearic Islands (AAPC= -1.75); this downward trend was higher for men than for women in the three regions. In Catalonia, the most significant reduction occurred during the period 2010.3-2011.2 (APC= -8,77), similarly to the Balearic Islands (2010.2-2012.4; APC= -2.11), whereas in Navarre it occurred between 2008.1-2011.3 (APC= -1.69)". Similarly in the entire paper.

ANSWER: Following the reviewer's recommendation, in the results section we have added per 10,000 inhabitants to all rate-related information.

If the reported results in tables 2, 3, and 4 are for age standardized rates per 10,000 population authors should modify the titles including in the titles both age standardized and 10,000 population.

ANSWER: Following the reviewer's recommendation, we have added for age-standardized in the titles of Tables 2, 3 and 4, but not per 10,000 population to avoid confusion, since the trends are expressed in percentages. The trends are based on rates for 10,000 population, but the unit of change is the percentage (APC, annual percentage change; and AAPC, average annual percent change).

VERSION 4 – REVIEW

REVIEWER	Iñaki Galán
	National Centre for Epidemiology. Institute of Health Carlos III
REVIEW RETURNED	24-Oct-2018

GENERAL COMMENTS	I do not have any additional comments

REVIEWER	Rahim Moineddin
	University of Toronto, Canada
REVIEW RETURNED	22-Oct-2018

GENERAL COMMENTS	I have no further comments.