












## Lung cancer mortality attributable to smoking: a multi-scenario analysis with variable lag periods

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### ABSTRACT

**Purpose:** The estimation of smoking-attributable mortality (SAM) is subject to the acceptance of different assumptions that may influence the estimates. We aimed to assess lung cancer mortality attributable to smoking by using both a prevalence-independent method (PIM) and a prevalence-dependent method (PDM) with different lags between exposure (smoking prevalence) and outcome (lung cancer mortality).

**Methods:** We estimated the population attributable fractions (PAF) and the lung cancer SAM by sex and age group (35–64, 65–84 years), year-by-year from 2011 to 2020, in four scenarios in Spain. In three of these scenarios, a PDM was applied using different lags: no lag, a 15-year lag and a 20-year lag. In the fourth scenario, a PIM was applied.

**Results:** In the period 2011–2020 in Spain, the SAM was higher when the 20-year lag PDM was considered (173,526 deaths) and lower when no lag PDM or a PIM was applied (161,249 and 157,390 deaths, respectively). In men, the PAFs were similar between the no lag PDM and the PIM (86.7 % and 87.3 %, respectively). However, when a PDM 15-year or 20-year lag was considered, the PAF increased to 91.0 % and 92.3 %, respectively. In women, the lowest PAF was obtained with the PIM (57.3 %), and the highest with the PDM 20-year lag (79.4 %).

**Conclusions:** SAM estimates differ depending on the methods and lags used. Applying a 15-year or 20-year lag PDM yields higher SAM estimates than when no lag PDM or a PIM is used. Therefore, when feasible, smoking prevalence data that incorporate a lag of 15 or 20 years between exposure and result should be used for accurate estimates.

### Introduction

To allocate resources for public health interventions, decision makers require information on the prevalence and the health impact of a

risk factor in a given population. In a smoking control context, smoking prevalence and smoking-attributable mortality (SAM) are the key indicators used to describe the evolution of the tobacco epidemic in a population. Prevalence and SAM estimations are based on underlying

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assumptions, which must be established and accepted to ensure confidence in the results generated [1].

When estimating smoking prevalence, inputs are based on individual self-reported data, under the assumption that self-reporting is an optimal method for estimating prevalence [2,3]. For the estimation of SAM, the assumptions are specific to data sources and the estimation method. The prevalence-dependent method [4] is the most commonly used. This method requires data on smoking prevalence, as well as data on observed mortality and death smoking-related risks. Applying this method, the lag between exposure to the risk factor and the appearance of the outcome tends to be ignored, and contemporaneous data for smoking prevalence and mortality are used. For example, when estimating the 2020 SAM, both mortality and smoking prevalence in 2020 would be applied, ignoring the time sequence principle. Contemporaneous smoking prevalences are commonly used for estimating SAM for two reasons: first, a lack of knowledge of the lag time between smoking and the more than 20 related causes of death; and second, the absence of a historical series of smoking prevalence. Another method used for estimating SAM is the prevalence-independent method. In this method, lung cancer mortality rates are used as a proxy for smoking prevalence and indirectly account for a lag [5,6]. As a consequence, decreases or increases in lung cancer mortality reflect decreases or increases in smoking prevalence in previous years.

In the context of smoking, lung cancer is the main marker of the tobacco epidemic, making the study of lung cancer mortality crucial. Several studies have set the lag between smoking and lung cancer mortality at approximately 15–20 years, i.e., the prevalence of smoking at a given time is linked to lung cancer mortality approximately 15–20 years later [7,8]. Accordingly, when estimating lung cancer SAM, smoking prevalence should precede mortality data by approximately 15–20 years. It should be mentioned that, in Spain, as in most developed countries, the overall prevalence of smoking has decreased [9]. This decrease has an impact on SAM, and if the prevalence-dependent method is applied without considering the lag between prevalence and mortality, SAM would be underestimated.

The aim of this study was to assess how the estimation of lung cancer mortality attributable to smoking in a population aged 35–84 years is influenced by applying: (i) a prevalence-dependent method with different lags between exposure (smoking prevalence) and outcome (lung cancer mortality), and (ii) a prevalence-independent method.

## Material and methods

We estimated lung cancer mortality attributable to smoking in Spain, by sex and age group (35–64 and 65–84 years), for each year of the period 2011–2020. We applied the prevalence-dependent method, and the prevalence-independent method proposed by Peto et al. [5].

### Data source

Observed mortality (OM) was obtained from the statistics on causes of death, sourced from the National Statistics Institute [10]. We considered deaths due to cancer of trachea, bronchus and lung (codes C33–C34 of the ICD-10) occurring in Spain during the period 2011–2020, by year, sex, and age.

For the calculation of lung cancer mortality rates, the population on 1 July each year was used as the reference population [11].

Annual prevalence of smokers, ex-smokers and never smokers, by sex and five-year age group, were obtained from a reconstruction of smoking prevalences for the period 1991–2020. Smoking prevalence estimates were obtained fitting a multinomial logistic mixed model with random area and time effects, based on aggregated smoking-related data and auxiliary information, as described in previous studies [12,13]. Data were sourced from the National Health Surveys (NHS) (*Encuesta Nacional de Salud de España*) and the European Health Surveys (EHS) (*Encuesta Europea de Salud en España*), which follow similar

methodologies. To ensure consistency, we harmonized prevalence data by applying a standardized definition of current smoking across all surveys. To reconstruct annual prevalence series, it was essential to retrieve each participant's smoking history, including age of initiation and cessation. While only the 2017 NHS and the 2009, 2014, and 2020 EHS partially captured this information, we addressed gaps by applying Multivariate Imputation by Chained Equations (MICE) [14] to estimate initiation and cessation ages for smokers and ex-smokers, using data from other surveys where this information was available. Using eight NHS and three EHS rounds, we reconstructed individual-level smoking histories for each year between 1991 and 2020. Based on these reconstructions and direct prevalence estimates, we fitted a multinomial logistic mixed model with random area and time effects to improve estimate precision. Further details on model covariates, assumptions, and analytical procedures can be found elsewhere [12].

Relative risks (RR) of lung cancer mortality in smokers and ex-smokers, compared with never smokers, were obtained from a follow-up study of five United States (U.S.) cohorts comprising 956,765 individuals [15,16]. These risks varied by sex and age group (35–54, 55–64, 65–74, and 75 years and over).

### Estimation of attributable mortality

The prevalence-dependent method estimates SAM as the product of OM multiplied by the population attributable fraction (PAF) [17], as follows:

$$\text{SAM} = \text{OM} \times \text{PAF}, \text{ with } \text{PAF} = 1 - \frac{1}{P_0 + P_1 \text{RR}_1 + P_2 \text{RR}_2}$$

where  $P_0$ ,  $P_1$  and  $P_2$  are the prevalence of never smokers, ex-smokers and smokers, respectively, and  $\text{RR}_1$  and  $\text{RR}_2$  are the relative risks of lung cancer mortality in ex-smokers and smokers compared with never smokers.

SAM was calculated for each year, sex, and five-year age group, and the results were then pooled.

Regarding smoking prevalence, three scenarios were considered, based on the results of a previous study [7]:

- (1) no lag: we applied smoking prevalence data for the same year as OM and in the same age group;
- (2) 15-year lag: for a specific year of OM at a specific age group, we applied smoking prevalence data from 15 years before in the age group 15 years younger. For example, for OM in 2011 in the 35–39 age group, we used the 1996 prevalence in the 20–24 age group; and
- (3) 20-year lag: for a specific year of OM at a specific age group, we applied smoking prevalence data from 20 years before in the age group 20 years younger.

The prevalence-independent method [5] estimates SAM on the basis of lung cancer mortality rates in the study population. Specifically, lung cancer mortality attributable to smoking is obtained as follows:

$$\text{SAM} = \text{OM} \times \frac{C_{\text{LC}} - N_{\text{LC}}}{C_{\text{LC}}}$$

where  $C_{\text{LC}}$  is the overall lung cancer mortality rate, and  $N_{\text{LC}}$  is the lung cancer mortality rate in never smokers.  $C_{\text{LC}}$  was estimated for each year based on lung cancer deaths in Spain.  $N_{\text{LC}}$  was obtained from the Cancer Prevention Study Phases (CPS) I and II [18].

All statistical calculations were performed using the Stata v.17 computer software program.

## Results

In the period 2011–2020 in Spain, 193,494 individuals died due to lung cancer, of which 80 % were men. This amounts to a mean of

approximately 19,000 deaths per year; 15,000 in men and 4000 in women.

Lung cancer mortality attributable to smoking, estimated using the prevalence-dependent method and applying prevalence data concurrent with the year of mortality (no lag), was estimated at 161,249 deaths (PAF: 83.3 %). Assuming a 15-year lag between smoking prevalence and the year of mortality, the PAF rose to 88.2 %, with an estimated 170,566 attributable deaths. This amounts to an additional 9317 deaths. When a 20-year lag was considered, the PAF was 89.7 % and SAM increased to 173,526 deaths, 7.6 % higher than the estimate with no lag. The independent method yielded an estimate of 157,390 deaths, amounting to a PAF of 81.3 %, two percentage points lower than the PAF with no lag.

Table 1 shows the OM, SAM, and PAF for each year of the study period, in each of the scenarios, by sex. Among men, the PAF estimated with no lag for the period 2011–2020 was slightly lower than that obtained with the independent method (86.7 % versus 87.3 %), but the difference between these two PAFs decreased over time. The difference between PAFs was 1.9 percentage points in 2011, and negative in 2020 (-0.5). When a 15-year or a 20-year lag was applied, this yielded a PAF of 91.0 % and 92.3 %, respectively. Similar values were observed year-by-year. A similar pattern was observed by age group, with the lowest PAFs for no lag and the independent-method, and the highest PAFs for 15-year and 20-year lags (Fig. 1). Among women, the lowest overall PAF was obtained with the independent method (57.3 %), followed by the prevalence-dependent method with no lag (69.9 %). The highest PAF was obtained when a 20-year lag was applied, reaching a PAF of almost 80 %. Contrary to the results in men, in women the PAFs obtained with any method displayed a rising trend throughout the period. This trend is due to the growth of the PAF in the 65–84 age group (Fig. 2).

Discussion

In countries where the prevalence of smoking has varied appreciably in recent decades, the estimation of SAM varies when a lag between smoking prevalence and mortality is applied. The impact is most pronounced in women, for whom estimates of SAM would otherwise be underestimated. The results obtained in this study for Spain may reflect the situation in other developed countries.

Table 1

Observed mortality due to lung cancer (OM), number of deaths attributable to tobacco smoking (SAM), and population attributable fraction (PAF), considering four scenarios in the Spanish population aged 35–84 years, by sex, in each year of the period 2011–2020.

|              | OM             | No lag         |             | 15-year lag    |             | 20-year lag    |             | Independent method |             |
|--------------|----------------|----------------|-------------|----------------|-------------|----------------|-------------|--------------------|-------------|
|              |                | SAM            | PAF (%)     | SAM            | PAF (%)     | SAM            | PAF (%)     | SAM                | PAF (%)     |
| <b>Men</b>   |                |                |             |                |             |                |             |                    |             |
| 2011         | 15,957         | 13,776         | 86.3        | 14,580         | 91.4        | 14,776         | 92.6        | 14,082             | 88.2        |
| 2012         | 16,046         | 13,965         | 87.0        | 14,643         | 91.3        | 14,803         | 92.3        | 14,146             | 88.2        |
| 2013         | 15,870         | 13,788         | 86.9        | 14,573         | 91.8        | 14,634         | 92.2        | 13,950             | 87.9        |
| 2014         | 15,496         | 13,490         | 87.1        | 14,189         | 91.6        | 14,292         | 92.2        | 13,564             | 87.5        |
| 2015         | 15,477         | 13,449         | 86.9        | 14,108         | 91.2        | 14,256         | 92.1        | 13,529             | 87.4        |
| 2016         | 15,768         | 13,687         | 86.8        | 14,363         | 91.1        | 14,545         | 92.2        | 13,801             | 87.5        |
| 2017         | 15,376         | 13,379         | 87.0        | 13,932         | 90.6        | 14,161         | 92.1        | 13,395             | 87.1        |
| 2018         | 15,232         | 13,131         | 86.2        | 13,780         | 90.5        | 14,103         | 92.6        | 13,230             | 86.9        |
| 2019         | 14,948         | 12,901         | 86.3        | 13,530         | 90.5        | 13,795         | 92.3        | 12,915             | 86.4        |
| 2020         | 14,678         | 12,685         | 86.4        | 13,261         | 90.3        | 13,493         | 91.9        | 12,618             | 86.0        |
| <b>Total</b> | <b>154,848</b> | <b>134,250</b> | <b>86.7</b> | <b>140,956</b> | <b>91.0</b> | <b>142,859</b> | <b>92.3</b> | <b>135,229</b>     | <b>87.3</b> |
| <b>Women</b> |                |                |             |                |             |                |             |                    |             |
| 2011         | 3077           | 1953           | 63.5        | 2223           | 72.2        | 2326           | 75.6        | 1482               | 48.2        |
| 2012         | 3329           | 2208           | 66.3        | 2453           | 73.7        | 2532           | 76.1        | 1717               | 51.6        |
| 2013         | 3567           | 2401           | 67.3        | 2639           | 74.0        | 2730           | 76.5        | 1943               | 54.5        |
| 2014         | 3512           | 2418           | 68.8        | 2623           | 74.7        | 2762           | 78.7        | 1882               | 53.6        |
| 2015         | 3758           | 2635           | 70.1        | 2853           | 75.9        | 3006           | 80.0        | 2120               | 56.4        |
| 2016         | 3921           | 2786           | 71.1        | 3025           | 77.1        | 3118           | 79.5        | 2271               | 57.9        |
| 2017         | 4201           | 3024           | 72.0        | 3226           | 76.8        | 3370           | 80.2        | 2543               | 60.5        |
| 2018         | 4270           | 3014           | 70.6        | 3327           | 77.9        | 3464           | 81.1        | 2598               | 60.9        |
| 2019         | 4401           | 3190           | 72.5        | 3528           | 80.2        | 3598           | 81.8        | 2708               | 61.5        |
| 2020         | 4610           | 3370           | 73.1        | 3713           | 80.5        | 3760           | 81.6        | 2895               | 62.8        |
| <b>Total</b> | <b>38,646</b>  | <b>26,999</b>  | <b>69.9</b> | <b>29,610</b>  | <b>76.6</b> | <b>30,667</b>  | <b>79.4</b> | <b>22,160</b>      | <b>57.3</b> |

OM: observed mortality; SAM: smoking attributable mortality; PAF: population attributable fraction.

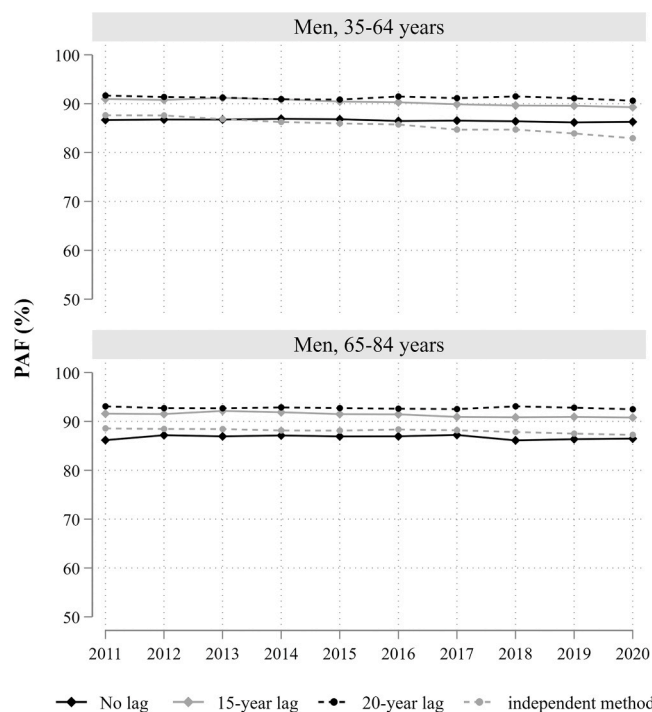


Fig. 1. Population attributable fraction (PAF) of lung cancer mortality in Spanish men aged 35–84 years, by age group, across the period 2011–2020, considering four scenarios.

In Spain, as in other countries, it is not possible to accurately characterize smoking history based on survey data. The main reason being that smoking surveillance is part of national health surveys. These surveys gather data on multiple risk factors or preventive practices at irregular intervals. In Spain, the first NHS for which microdata are available was conducted in 1987. Since then, its periodicity has been irregular and its number limited to certain years. Hence, for a period of 34 years (1987–2020), ten surveys are available, seven NHS and three

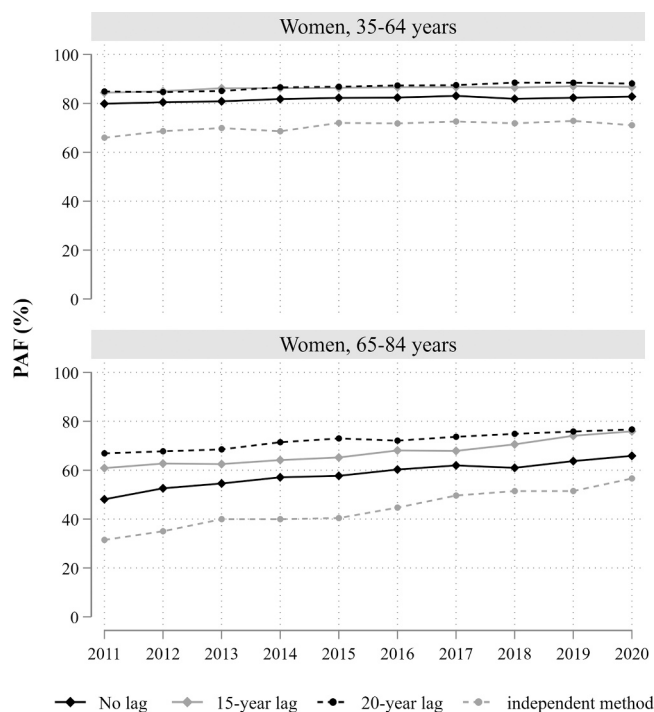


Fig. 2. Population attributable fraction (PAF) of lung cancer mortality in Spanish women aged 35–84 years, by age group, across the period 2011–2020, considering four scenarios.

EHS. In order to characterize the history of smoking in Spain, various studies have reconstructed the prevalence series by applying different methodologies and accepting different assumptions [12,19–21]. The most recent reconstruction shows that smoking in Spain has steadily declined among men across all age groups since 1991. Among women, however, the trend varies according to age group. In general, since 1991 the prevalence of smoking has decreased among the youngest women, whereas in those aged 55 and over, the prevalence of smoking has grown and continues to rise [12]. When a prevalence-dependent method with no lag is applied, these changes in prevalence are not accurately reflected in the SAM estimations.

Previous studies that assessed the evolution of the smoking epidemic in Spain on the basis of a detailed analysis of SAM showed that the SAM rate in men has fallen since the latter part of the 1990s and has risen in women since 1990 [22]. The results of our study show a stabilization of lung cancer mortality attributable to smoking in men, but an important increase in women. This similar trend in the two indicators (smoking prevalence and lung cancer mortality) supports the use of lung cancer as a marker of the tobacco epidemic.

Previous SAM analyses performed in Spain have already found evidence of the variation in the figures of SAM obtained after applying the prevalence-dependent and the independent method [23,24]. The variation was greatest in women, and it was concluded that this difference was essentially because the dependent method failed to consider a lag between smoking and mortality. When a lag time is considered, the variation between methods increases further still. Estimation of SAM by applying the prevalence-independent method assumes that the application of lung cancer mortality rates approximates the lag between smoking and mortality [5,6]. The results of our analysis do not confirm this assumption. By applying the independent method, SAM in men, and especially in women, is underestimated when compared against estimates obtained from the prevalence-dependent method applying lags. The variation is greatest with a 20-year lag, i.e., the PAF obtained for women on applying the independent method is 57.3 % versus 79.4 % when using a 20-year lag. The greater underestimation observed among women may be explained by the different evolution of the tobacco

epidemic between sexes in Spain, as described previously. Regarding age groups, no differences in PAFs for lung cancer were observed among men. This could be explained by the prevalence of smoking and the relative risks for each age group. Among men aged 35–64 years, the prevalence of smoking is higher but relative risk of lung cancer mortality is lower, whereas among men aged 65–84 years, the opposite pattern is found. In contrast, among women, PAFs in this study were 10–30 percentage points lower in the older age group. The explanation might be because the prevalence of smoking was lower (< 7 %) in women over 65 years old compared to younger women (16–30 %) during the period under study.

Differences have also been observed in previous studies comparing estimations of SAM using the prevalence-independent method versus the lag prevalence-dependent method. Specifically, a study conducted in China estimated a higher PAF when applying the prevalence-independent method versus a 10-year lag prevalence-dependent method [25]. A similar pattern was observed in a Canadian study employing a 15-year lag [26]. In the former study, the discrepancy may be attributed to the shorter lag time used compared to ours. In the Canadian study, the authors suggested that their results could be explained by a greater than 10 % decline in smoking prevalence over the preceding two decades. Conversely, results from a Korean study with a 20-year lag align with our findings for men but diverge for women [27]. An explanation for this difference could be the misclassification of causes of death among Korean women.

It should be noted that, in Spain, lung cancer mortality is not differentiated by smoking status. Therefore, mortality rates specific to never smokers are not available. Consequently, when applying the prevalence-independent method, we were required to use lung cancer mortality rates among never smokers derived from the U.S. population (CPS-I and CPS-II cohorts) [18]. It is important to recognize that lung cancer mortality rates among never smokers in the U.S. may differ from those in the Spanish population due to variations in exposure to different risk factors for lung cancer, such as radon, secondhand tobacco smoke or occupational carcinogens [28,29].

Another important limitation is that this analysis focuses exclusively on lung cancer. The lag time to be applied to the estimation of SAM due to other smoking-related cancers, cardiovascular or respiratory diseases vary and remain unknown [30]. In addition, the decision to analyze lag times of 15, and 20 years was based on previous evidence [7,8]. Although evaluating longer periods, such as 25 or 30 years, would be valuable it was not feasible in this analysis due to data limitations. Another limitation is the inability to provide confidence intervals for either the absolute number or the proportion of lung cancer deaths attributable to smoking. While the inclusion of such intervals would improve the interpretability and robustness of the estimates, the nature of the underlying data prevents their calculation. Finally, the lack of consistent timing of the NHS in Spain required us to work with smoking prevalence estimates derived from model-based estimations [12]. Consequently, these estimated prevalences may not fully reflect the real smoking prevalence. Nevertheless, since smoking prevalence typically changes gradually from year to year, and due to the robustness of the applied statistical method, we do not expect this limitation to have a significant impact on the reliability of our estimates.

This analysis is the first to describe the impact of smoking on lung cancer mortality using two different approaches and taking lag times into account. In essence, performing this detailed analysis by focusing on lung cancer is justifiable, since smoking is the principal risk factor for this disease and lung cancer is the main marker for the tobacco epidemic. This is borne out by the results of this analysis, which indicate that by eliminating smoking in a population, 90 % of lung cancer mortality could be prevented in men and 80 % in women.

Previous analyses placed the lag between smoking and lung cancer mortality at 15–20 years [7]. However, the results of our analysis highlight the fact that using a lag of either 15 or 20 years in the estimation of SAM does not decisively impact the estimates obtained, as the

differences in the SAM burden between these two scenarios are minimal.

## Conclusion

Accurate estimation of smoking attributable mortality is essential for achieving and understanding the impact of tobacco use at the population level, as well as for informing public health decision-making. Thus, when these estimates are communicated effectively, they can improve the implementation of the WHO MPOWER strategy [31] by supporting its key components: monitoring tobacco use and its health consequences (M: monitoring), strengthening tobacco control policies (E: enforce bans), and warning the public about the dangers of tobacco (W: warn). To maximize their impact, future efforts should focus not only on refining smoking attributable mortality estimations methods but also on integrating these results into national health policies and public health messages.

Estimations of lung cancer mortality attributable to smoking, whenever possible, should be based on prevalence data that account a plausible lag between exposure and mortality. The influence of lag time in SAM estimations in Spain may be extrapolated to other countries in a similar epidemic situation. In Spain, smoking caused 173,000 lung cancer deaths across the period 2011–2020 taking a 20-year lag into account. The estimates obtained with no lag set mortality at 160,000. It should still be noted that both estimates rank smoking as an important risk factor at a population level. These estimates indicate the need to implement primary and secondary prevention measures, along with legislative improvements based on integrated smoking control policies.

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## CRediT authorship contribution statement

**Carla Guerra-Tort:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation. **María Isolina Santiago-Pérez:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Lucía Martín-Gisbert:** Writing – review & editing. **Esther López-Vizcaíno:** Writing – review & editing, Visualization. **Guadalupe García:** Writing – review & editing. **Ana Teijeiro:** Writing – review & editing. **Alberto Ruano-Ravina:** Writing – review & editing, Supervision. **Julia Rey-Brandariz:** Writing – review & editing, Visualization. **Mónica Pérez-Ríos:** Writing – original draft, Visualization, Supervision, Funding acquisition, Conceptualization.

## Declaration of Competing Interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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