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Original article

Estimations of smoking-attributable mortality in Spain at a regional level: comparison of two methods☆

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Purpose: To estimate and discuss smoking-attributable mortality (SAM) for the 17 regions in Spain among the population aged ≥35 years in 2017, using two methods.
Methods: A descriptive analysis of SAM was conducted using two methods, the prevalence-independent method (PIM) and the prevalence-dependent method (PDM). Observed mortality was obtained from the National Institute of Statistics; smoking prevalence from three National Health Surveys; lung cancer mortality rates from the Cancer Prevention Study-II; and relative risks from five US cohorts. SAM and percentages of change were estimated for each region overall, by sex, age and cause of death.
Results: In 2017, tobacco caused 56,203 deaths in Spain applying the PIM. Using the PDM the number of deaths was 4.4% (95% CI: 3.4–5.5) lower (53,825 deaths). Except in four regions, the PIM estimated a higher overall SAM and the maximum percentage of change was 18.6%. Overall percentages of change were higher for women (15.7% 95% CI: 12.6–19.0) and for cardiovascular diseases–diabetes mellitus (13.8%; 95% CI: 11.5–16.2).
Conclusions: At the national level, both methods estimate similar figures for SAM. However, the difference in estimates appears at the subnational level. Differences were higher in subgroups with lower smoking prevalence and for causes of death with periods of induction shorter than those for lung cancer.

Introduction

Tobacco consumption is one of the greatest threats to human health worldwide. The latest Surgeon General's report has identified more than 20 tobacco-related causes of death [1]. However, it is suspected that even more diseases, such as breast cancer, could be caused by tobacco [1].

Tobacco is recognized as an important risk factor for health. Therefore, it is essential to estimate the burden of disease caused by tobacco at the population level. To this end, various calculation procedures have been developed to quantify smoking-attributable mortality (SAM) [2,3]. The main difference between the two most widely methods for estimating-smoking related mortality is whether smoking prevalence or lung cancer mortality rates are used. Hereafter, we will refer to them as the prevalence-dependent method (PDM) or prevalence-independent method (PIM).

Until the 1980s, the estimation of SAM was not very frequent. One of the first estimation methods used was the PDM based on the calculation of population-attributable fractions (PAFs) [2]. Different formulas can be used to calculate PAFs. However, one of the most commonly used was the one proposed by Levin in 1953 [4] and later adapted by Lilienfeld [5]. This formula takes into account the prevalence of smokers, ex-smokers, and never-smokers. Therefore, to

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use the PDM it is necessary to ensure good quality data on smoking prevalence [6]. The PIM was developed by Peto et al. and was published in 1992 [7]. Unlike the previous method, this method is based on the use of lung cancer mortality rates as a proxy for smoking prevalence [7]. Therefore, it might be useful when there are unreliable or inexistent data on smoking prevalence in a given population.

In general, the choice of methodologies varies depending on the available data. If the smoking prevalence is unknown, the PIM is the only alternative. However, when prevalence data are available, a choice should be made. This decision should take into account the underlying assumptions of the methods and their relative accuracy in different scenarios [2,3,8].

Uncertainty arises, for instance, when estimating SAM in different regions within a country where there is not a survey with a sufficient sample size to estimate smoking prevalence by region, sex, and age. This scenario complicates the use of a PDM and is this the situation in Spain. In this case, one option would be to increase the sample size by appending data from two or more chronologically adjacent surveys. This option would allow for a precise estimation of the prevalence of tobacco consumption by age and sex at the local level. Another option would be to use the PIM.

These two methods have been compared in previous studies [9–14]. Although most of these comparisons apply national data [9–11,13,14] there is only one which uses regional data [12]. Both methods have been assessed by previous studies and no method seems to prevail [9–14]. However, having different calculation procedures available can cause uncertainty regarding which method should be applied.

The aim of this study was to estimate SAM in the 17 regions of Spain among the population aged 35 years and over in 2017 by applying both the PDM and the PIM and to critically ascertain the differences in the estimations obtained.

Materials and methods

Data sources and variables

Cause-specific observed mortality data, defined as deaths by diseases causally related to tobacco consumption in the population 35 years old and over, were obtained from the National Statistics Institute for each region for 2017 by age and sex [15]. The tobacco-related diseases analyzed were grouped into three broad categories according to the cause of death (cancer, cardiovascular diseases–diabetes mellitus, and respiratory diseases) [1]. The specific causes included in each category are shown below accompanied, in parentheses, by their code according to the 10th edition of the International Classification of Diseases (ICD-10). *Cancer*: trachea or bronchus or lung (C33-34), lips, oral cavity, pharynx (C00-C14), esophagus (C15), stomach (C16), colon and rectum (C18-20), liver cells (C22), pancreas (C25), larynx (C32), cervix uteri (C53), urinary bladder (C67), kidney and renal pelvis (C64-65), and acute myeloid leukemia (C92.0); *Cardiovascular diseases–diabetes mellitus*: ischemic heart disease (I20-25), rheumatic heart disease (I00-02/I05-09), cardiopulmonary and other heart diseases (I26-28/I30-51), cerebrovascular disease (I60-69), atherosclerosis (I70), aneurysms (I71-78), and diabetes mellitus (E10-14); *Respiratory diseases*: influenza, pneumonia (J09-18), tuberculosis (A15-19), and chronic obstructive pulmonary disease (J40-44). The observed mortality figures can be found in the Supplementary Material Tables S1 and S2.

Prevalence of smokers, ex-smokers, and never-smokers by sex and age group (35–54, 55–64, 65–74, 75 years and over) were obtained from the joint analysis of three representative surveys at a national and regional level: the Spanish Health Survey of 2011 [16] and 2017 [17] and the European Health Survey for Spain carried out in 2014 [18]. In the three surveys, the same question was asked to determine the smoking prevalence and participants were classified according to their smoking pattern as smokers (daily or occasional smokers), ex-smokers (persons who do not currently smoke but have smoked before), and never smokers (persons who have never smoked regularly) [16–18]. These prevalences can be consulted in a previous study [19].

Relative risks (RRs) were drawn from the follow-up of 956,765 subjects included in five cohort studies conducted in the USA. For the PDM, three categories of consumption were considered: smokers, ex-smokers, and never smokers, and for the prevalence-independent two: smokers versus never-smokers [1]. The RRs used can be found in Table S3 of the Supplementary Material.

Lung cancer mortality rates in the Spanish population were calculated for 2017, being the study population of the residents in Spain on July 1, 2017 [20]. Lung cancer mortality rates in the reference population for smokers and never-smokers were taken from Cancer Prevention Study Phase II (CPS-II), which is a cohort study of more than 1.2 million Americans followed for 6 years (1982–1988) [21]. The lung cancer mortality rates used can be found in Table S4 of the Supplementary Material.

Calculation procedure

Prevalence-dependent method

This method is based on the smoking prevalence in the target population and relies on the calculation of the PAF, taking into consideration three levels of exposure.

$$PAF = \frac{(P_0 + P_1 RR_1 + P_2 RR_2) - 1}{P_0 + P_1 RR_1 + P_2 RR_2}$$

where P represents the prevalence of never smokers (0), smokers (1), and ex-smokers (2); RR refers to the risk of death of smokers (1) and ex-smokers (2), using the reference category of the never smokers (0).

The SAM is estimated as the product of observed mortality due to the causes associated with tobacco consumption and PAF. To calculate the SAM, the recommendations of the STREAMS-P (STrengthen the design and REporting of Attributable Mortality Studies using a Prevalence-based method) tool were followed [6].

Prevalence-independent method

This method, proposed by Peto et al. [7], uses the lung cancer mortality rate as a proxy for tobacco consumption. The calculation methodology is divided into two processes: SAM is estimated, first, for lung cancer and, subsequently, for the remaining causes associated with tobacco consumption [8].

Lung cancer SAM was calculated based on the difference between the overall lung cancer mortality rate in the Spanish population and the lung cancer mortality rate in never smokers among the US population (CPS-II). The use of a US population instead of the Spanish population is due to the fact that in Spain we do not have lung cancer mortality rates according to tobacco consumption. To estimate SAM in relation to the remaining causes causally related to tobacco consumption the smoking impact ratio (SIR) was calculated. The SIR compares lung cancer rates in a study population (Spanish population) with those of a reference population (CPS-II). The SIR is calculated as follows:

$$SIR = \frac{C_{LC} - N_{LC}}{S^*_{LC} - N^*_{LC}}$$

where C_{LC} and N_{LC} express the lung cancer mortality rate in overall terms and for never smokers in the study population, respectively. Since lung cancer mortality rates in Spain are not available according to smoking consumption, we have used the rates of never smokers (N_{LC}) from the CPS-II. S^*_{LC} and N^*_{LC} express the lung cancer mortality

Table 1
Smoking-attributable mortality (SAM) estimated using the prevalence-dependent method (PDM) and the prevalence-independent method (PIM) and the percentage of change accompanied by their 95% confidence intervals (95% CI)

	Overall					Men					Women				
Regions	PDM	PIM	% Of change			PDM	PIM	% Of change			PDM	PIM	% Of change		
Andalusia	9469	9095	−3.9	−6.3	−1.5	8218	8347	1.6	−0.8	4.0	1251	748	−40.2	−45.2	−34.7
Aragon	1805	2065	14.4	8.3	20.8	1550	1706	10.1	4.3	16.2	256	359	40.5	20.4	63.4
Asturias	1616	1878	16.2	9.8	23.0	1357	1460	7.6	1.6	14.0	258	417	61.6	39.6	87.2
Balearic Islands	1173	1262	7.6	0.6	15.0	942	976	3.6	−3.3	11.0	231	286	23.8	5.4	45.4
Canary Islands	2298	2295	−0.2	−4.8	4.8	1831	1757	−4.1	−8.8	0.9	467	538	15.2	2.8	29.1
Cantabria	755	895	18.6	9.2	28.7	635	706	11.1	2.4	20.8	119	189	58.3	28.0	97.0
Castile and Leon	3256	3443	5.7	1.4	10.3	2856	2857	0.0	−4.0	4.3	400	586	46.4	29.6	65.5
Castile La Mancha	2488	2773	11.5	6.4	16.8	2260	2410	6.7	2.0	11.4	228	363	59	35.7	86.9
Catalonia	8283	8996	8.6	5.9	11.4	7129	7180	0.7	−1.8	3.3	1154	1816	57.4	46.8	68.7
Valencia	5968	6264	5.0	1.8	8.2	5031	5170	2.7	−0.3	5.9	936	1094	16.8	7.6	27.0
Extremadura	1562	1641	5.1	−1.0	11.5	1426	1511	5.9	0.3	11.9	136	130	−4.3	−24.4	20.8
Galicia	3618	4133	14.2	9.9	18.8	3099	3333	7.5	3.5	11.8	519	800	54.3	38.7	71.3
Madrid	6310	6012	−4.7	−7.5	−1.8	4818	4655	−3.4	−6.4	−0.3	1492	1357	−9	−15.0	−2.6
Murcia	1446	1604	11.0	4.4	17.9	1289	1339	3.9	−2.1	10.2	157	266	69.3	40.2	104.7
Navarre	716	759	5.9	−2.9	15.7	593	651	9.7	0.6	19.8	123	108	−12.5	−31.3	12.2
Basque Country	2738	2784	1.7	−2.8	6.4	2208	2275	3.0	−1.6	7.9	529	508	−3.9	−14.3	7.7
La Rioja	325	306	−5.8	−18.0	8.1	277	260	−6.2	−18.3	7.9	48	46	−3.4	−35.1	41.5
Spain	**53,825**	**56,203**	**4.4**	**3.4**	**5.5**	**45,519**	**46,591**	**2.4**	**1.3**	**3.4**	**8305**	**9612**	**15.7**	**12.6**	**19.0**

SAM estimated with PDM was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the PIM.

rate in smokers and never smokers in the reference population, respectively [8].

The PAF was calculated for each cause of death associated with tobacco consumption, except for lung cancer. This indicator depends on the SIR calculated in the previous step and which is common to the remaining causes of death according to year, sex and age group, and on the RRs which are specific to each cause of death according to sex and age group. Thus, the formula for calculating the PAF for each cause of death was:

$$PAF = \frac{SIR\,(RR - 1)}{1 + SIR(RR - 1)}$$

where RR refers to the risk of death from tobacco-related diseases in smokers with respect to never smokers.

The SAM is estimated as the product of observed mortality due to the causes associated with tobacco consumption, except from lung cancer, and each PAF.

Analysis

SAM was estimated for each region overall, by sex, age and cause of death. To compare the estimates between the two methods, the percentage of change (PC) of the PAF overall, by sex, age and cause of death were calculated, accompanied by their 95% confidence intervals (CI). The PC was calculated as follows:

$$PC = \frac{(PAF_I - PAF_D) * 100}{PAF_D}$$

Where PAF_I is the PAF calculated with the PIM and PAF_D with the PDM. As the PAF is the proportion of SAM over the observed mortality, a Wald CI for the log-transformed proportion ratio PAF_I/PAF_D was obtained [22] and, from which, the CI limits of the PC were derived. Both PC and confidence limits are expressed in percentages.

Analyses were performed with the statistical package Stata v14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

Results

Tobacco consumption is estimated to have caused 56,203 deaths in Spain in 2017 when calculated with the PIM and, 53,825 deaths when applying the PDM; the PC between methods was 4.4% (95% CI [3.4–5.5]). For men, both methods yield similar SAM values (PC: 2.4% 95% CI [1.3–3.4]), whereas for women the PC between methods reached 15.7% (95% CI [12.6–19.0]) (Table 1). According to age group, the greatest differences were observed in the 35–54 age group (PC: −23.2% 95% CI [−26.0 to −20.3]) and in the 75 and over age group (PC: 14.4 95% CI [12.7–16.1]) (Table 2). Cancer reflected the least PC between methods, below 1% (PC: −0.8% 95% CI [−2.0 to 0.5]), while cardiovascular diseases–diabetes mellitus showed the largest difference, 13.8% (95% CI [11.5–16.2]) (Table 3). By sex, the highest PC between methods was observed in women due to cardiovascular diseases–diabetes mellitus (PC: 41.9% 95% CI [35.2–49.0]).

The PIM estimated higher mortality rates in 13 out of 17 regions, 18.6% being the highest PC. The PDM shows higher mortality in the remaining four regions, with PC over 6%. For males, the PC between regions does not exceed 11%, and the PIM estimated a higher SAM in 14 out of the 17 Spanish regions—lower in the Canary Islands, Madrid, and La Rioja. For women, the PIM yields a greater SAM in 11 out of the 17 regions with PC over 70% in some regions. In the remaining six regions, the PDM estimated a higher SAM, having Andalusia with the highest PC (−40.2%) (Table 1).

The PDM estimated higher SAM in the younger age group in the 17 regions, whereas the PIM did so in the older age group. Cantabria, Castile and Leon, and Madrid were the regions with the highest PC in the 35–54 age group, and Cantabria and Murcia in the 75 and older age group (Table 2).

The estimations of SAM by cardiovascular diseases–diabetes mellitus vary the most between methods. Thus, in regions such as Cantabria, Asturias, or Aragon the PIM estimates at least 35% more SAM than the PDM. On the other hand, these values are never higher than 10% for cancer and 14% for respiratory diseases in any region (Table 3). In men, the PC between methods is lower for cancer and respiratory diseases, under 7% in all regions (Fig. 1 and Table S5 of the Supplementary Material). For women, PC due to cause of death varies between −32% and 17% in the case of cancer and between −50% and 173% for cardiovascular diseases–diabetes mellitus (Fig. 2 and Table S6 of the Supplementary Material).

Discussion

The results show that SAM in Spain and in its 17 regions can differ depending on the use of the PIM or PDM, though global results are quite similar. Overall, the PIM estimates higher SAM in most regions. The differences found in the estimations appear to be

Table 2
Smoking-attributable mortality (SAM) estimated using the prevalence-dependent method (PDM) and the prevalence-independent method (PIM) and the percentage of change accompanied by their 95% confidence intervals (95% CI), overall and by age group

	35–54					55–64					65–74					75 +				
Regions	PDM	PIM	% Of change			PDM	PIM	% Of change			PDM	PIM	% Of change			PDM	PIM	% Of change		
Andalusia	809	624	−22.9	−28.9	−16.3	1661	1536	−7.5	−12.1	−2.7	2593	2593	0.0	−4.1	4.3	4405	4342	−1.4	−5.1	2.4
Aragon	120	107	−10.8	−26.3	7.9	294	304	3.4	−7.5	15.6	464	457	−1.5	−10.4	8.2	927	1197	29.1	19.5	39.5
Asturias	115	94	−18.3	−33.8	0.9	279	320	14.7	2.6	28.3	435	464	6.7	−3.2	17.6	787	1000	27.1	16.8	38.2
Balearic Islands	102	98	−3.9	−22.0	18.3	202	201	−0.5	−13.7	14.8	345	370	7.2	−3.5	19.1	524	594	13.4	2.1	25.9
Canary Islands	198	155	−21.7	−33.7	−7.6	444	443	−0.2	−9.3	9.7	624	596	−4.5	−12.4	4.1	1032	1101	6.7	−1.0	15.0
Cantabria	43	29	−32.6	−54.1	−0.8	157	181	15.3	−0.3	33.3	192	206	7.3	−7.7	24.7	362	479	32.3	17.2	49.4
Castile and Leon	192	107	−44.3	−54.2	−32.1	506	461	−8.9	−16.9	−0.1	832	790	−5.0	−11.7	2.2	1727	2086	20.8	14.0	28.0
Castile La Mancha	183	155	−15.3	−28.1	−0.3	348	333	−4.3	−14.2	6.7	578	590	2.1	−6.2	11.1	1379	1695	22.9	15.4	31.0
Catalonia	614	465	−24.3	−31.1	−16.7	1360	1276	−6.2	−11.3	−0.8	2169	2104	−3.0	−7.3	1.5	4140	5151	24.4	20.0	29.0
Valencia	492	404	−17.9	−25.8	−9.1	1022	996	−2.5	−8.5	3.7	1659	1582	−4.6	−9.4	0.4	2795	3282	17.4	12.2	22.9
Extremadura	109	90	−17.4	−33.1	1.9	242	230	−5.0	−16.2	7.8	411	429	4.4	−5.5	15.2	800	892	11.5	2.3	21.5
Galicia	243	205	−15.6	−27.0	−2.4	579	620	7.1	−1.4	16.3	933	965	3.4	−3.5	10.8	1864	2343	25.7	18.9	32.8
Madrid	385	217	−43.6	−51.0	−35.2	937	835	−10.9	−16.7	−4.6	1571	1453	−7.5	−12.4	−2.4	3416	3506	2.6	−1.5	7.0
Murcia	129	110	−14.7	−29.9	3.8	244	217	−11.1	−22.3	1.7	402	381	−5.2	−14.8	5.4	670	896	33.7	22.2	46.4
Navarre	43	31	−27.9	−50.3	4.6	124	128	3.2	−12.8	22.2	208	197	−5.3	−18.1	9.5	342	403	17.8	3.4	34.2
Basque Country	215	173	−19.5	−30.9	−6.3	458	474	3.5	−5.4	13.3	707	740	4.7	−3.0	13.0	1358	1396	2.8	−3.9	9.9
La Rioja	26	23	−11.5	−42.1	35.2	57	45	−21.1	−41.6	6.7	78	68	−12.8	−32.7	13.0	165	170	3.0	−15.4	25.5
Spain	**4017**	**3085**	**−23.2**	**−26.0**	**−20.3**	**8915**	**8600**	**−3.5**	**−5.6**	**−1.4**	**14,201**	**13,986**	**−1.5**	**−3.2**	**0.2**	**26,691**	**30,531**	**14.4**	**12.7**	**16.1**

SAM estimated with PDM was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the PIM.

greater among women, in the younger and older population, and for cardiovascular diseases–diabetes mellitus.

Overall, the PC between methods is not substantial, although we found that the PIM estimates higher mortality, as shown in other studies [10,12]. This may be because the PIM estimates tobacco consumption from lung cancer mortality rates, whereas the PDM uses current prevalences. The use of current prevalences may not be a good indicator of smoking hazards accumulated in previous years, as current prevalence does not take into account years of active smoking exposure and smoking history [3,8].

According to sex, the PC is higher in women than in men. However, these differences are not reflected in the overall SAM, as for women SAM is very low in comparison to men. This difference has also been observed in previous studies [10,11,13]. One explanation for the higher PC in women may be related to the evolution of the tobacco epidemic in men and women. In Spain, until the 1960s it was unusual for women to smoke [23,24], whereas men had already started smoking decades earlier. This led to a different evolution of smoking prevalence in both sexes. While in men the smoking prevalence decreased since the 1970s [23], in women, it was not until the beginning of the 21st century that a slight decrease began to occur [25].

Most of the regions that achieved higher SAM estimates with the PIM like Cantabria, Cataluña, or Galicia, presented the lowest prevalence of women smokers in 2017 [17], while also having some of the highest mortality rates due to lung cancer [15,20]. This reinforces the fact that the differences observed between the two methods cannot be completely explained by the evolution of tobacco consumption in women. Therefore, other lung cancer risk factors such as secondhand smoke, radon, indoor air pollution (e.g. biomass or cooking fumes), or occupational agents (e.g. asbestos or arsenic) may explain these differences [26,27].

In men, the PC between methods is smaller. The regions with the greatest variation, such as Cantabria, Aragon, Asturias, and Galicia,

Table 3
Smoking-attributable mortality (SAM) estimated using the prevalence-dependent method (PDM) and the prevalence-independent method (PIM) and the percentage of change accompanied by their 95% confidence intervals (95% CI), overall and by cause of death

	Overall														
	Cancer					Cardiovascular diseases–diabetes mellitus					Respiratory diseases				
Regions	PDM	PIM	% Of change			PDM	PIM	% Of change			PDM	PIM	% Of change		
Andalusia	4420	4246	−3.9	−7.0	−0.8	2960	2859	−3.4	−7.9	1.3	2088	1990	−4.7	−8.7	−0.5
Aragon	923	966	4.7	−2.3	12.1	469	639	36.2	21.9	52.3	414	460	11.1	0.9	22.4
Asturias	835	903	8.1	0.6	16.2	447	615	37.6	22.9	54.1	334	360	7.8	−2.9	19.6
Balearic Islands	612	631	3.1	−5.0	11.9	320	375	17.2	2.1	34.5	240	256	6.7	−5.1	19.9
Canary Islands	1101	1069	−2.9	−8.8	3.4	710	733	3.2	−6.0	13.4	487	493	1.2	−7.4	10.7
Cantabria	417	456	9.4	−1.1	20.9	188	268	42.6	19.9	69.4	149	170	14.1	−2.4	33.4
Castile and Leon	1674	1638	−2.2	−7.3	3.3	884	1058	19.7	10.1	30.2	699	748	7.0	−0.8	15.5
Castile La Mancha	1194	1232	3.2	−2.9	9.7	574	752	31.0	18.3	45.1	719	788	9.6	1.9	17.9
Catalonia	4047	4052	0.1	−3.2	3.6	2104	2584	22.8	16.4	29.6	2132	2360	10.7	6.4	15.2
Valencia	3001	2973	−0.9	−4.7	2.9	1741	2001	14.9	8.3	22.0	1225	1289	5.2	−0.4	11.2
Extremadura	792	804	1.5	−5.7	9.3	420	488	16.2	2.9	31.2	351	349	−0.6	−11.0	11.1
Galicia	1853	1940	4.7	−0.4	10.1	961	1282	33.4	23.3	44.3	804	911	13.3	5.8	21.3
Madrid	3202	2958	−7.6	−11.1	−4.0	1654	1632	−1.3	−7.4	5.1	1454	1421	−2.3	−7.3	3.1
Murcia	677	689	1.8	−6.1	10.4	386	496	28.5	13.5	45.5	382	420	9.9	−0.2	21.2
Navarre	374	381	1.9	−8.8	13.7	184	213	15.8	-3.7	39.2	158	165	4.4	−10.5	21.9
Basque Country	1491	1487	−0.3	−5.6	5.4	726	781	7.6	−2.1	18.2	520	516	−0.8	−9.2	8.4
La Rioja	162	147	−9.3	−24.3	8.8	94	92	−2.1	−25.4	28.5	69	67	−2.9	−23.6	23.4
Spain	**26,774**	**26,572**	**−0.8**	**−2.0**	**0.5**	**14,823**	**16,868**	**13.8**	**11.5**	**16.2**	**12,228**	**12,763**	**4.4**	**2.6**	**6.2**

SAM estimated with PDM was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the PIM.

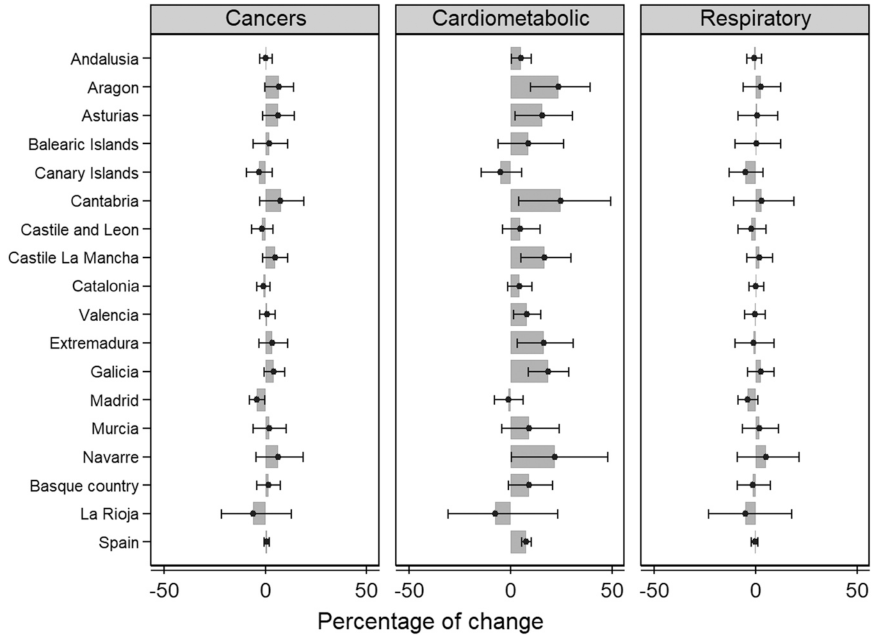

Fig. 1. Percentage of change between the prevalence-dependent and prevalence-independent methods, in MEN, by region and cause of death, in 2017. Smoking attributable mortality estimated with the prevalence-dependent method was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the prevalence-independent method.

for which the PIM estimated a higher SAM, present the highest mortality rates due to lung cancer in 2017 [15,20]. On the other hand, in the Canary Islands, La Rioja, and Madrid, for which the PIM yielded lower SAM, the rates of mortality caused by lung cancer are the lowest [15,20].

In relation to age groups, the greatest differences were observed in the most extreme groups. In the 35–54 age group, the differences could be because this age group has the smallest number of SAM. Therefore, a difference of 10 deaths may translate into a greater PC. In the 75 and older age group, these differences may be because this age group has the lowest smoking prevalence. Furthermore, in relation to the regions where the greatest differences were found, the same pattern seems to be seen regarding sex. Thus, when smoking prevalences are lower but lung cancer mortality rates are higher or vice versa is where more PC is observed. Both the PIM and the PDM have placed cancer as the main cause of death associated with tobacco consumption with a very low PC between methods, under 1%. Cardiovascular diseases–diabetes mellitus show the greatest difference between methods (13.8%). The results obtained are similar to those found in studies carried out in Lithuania, USA and Vietnam [9,10,14]. These differences between the causes of death were also observed in the detailed analysis by sex and region,

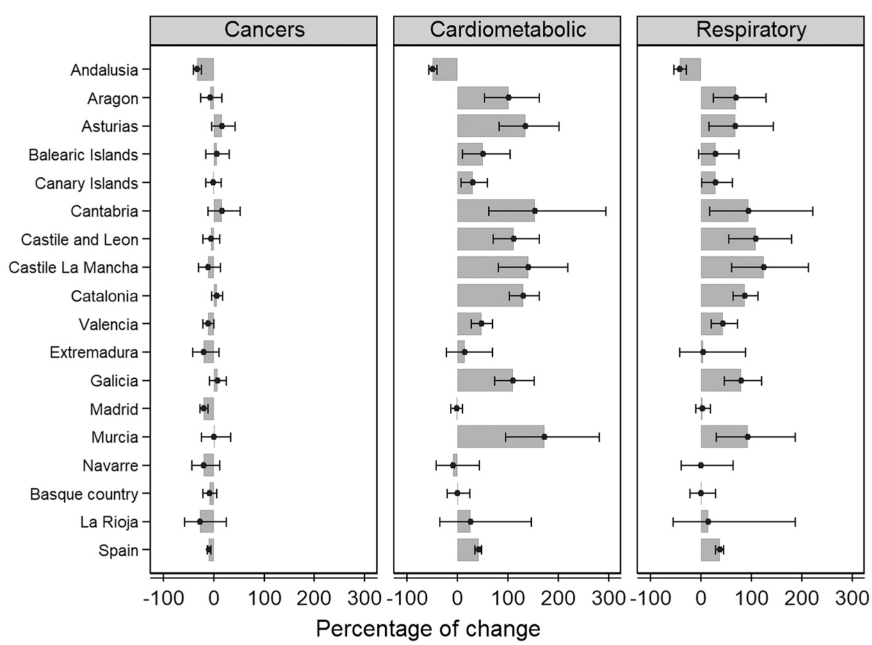

Fig. 2. Percentage of change between the prevalence-dependent and prevalence-independent methods, in WOMEN, by region and cause of death, in 2017. Smoking attributable mortality estimated with the prevalence-dependent method was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the prevalence-independent method.

with no consistent results obtained within the different regions. When estimating SAM for cancer, the PDM almost always reveals higher rates among women, but this is not the case for cardiovascular diseases–diabetes mellitus or respiratory diseases. In women, the PIM is associated with higher mortality for cancer in six regions and yields the highest rates in Asturias and Cantabria, with percentages of change of 17.0% and 16.8%, respectively. Both are the regions with the greatest mortality rates for lung cancer in women [15,20].

The greater variations in SAM for cardiovascular diseases might be due, in part, to the fact that tobacco is the main risk factor for lung cancer [27] and because it plays a key part in the genesis of the other cancers associated with its consumption. This is not the case for cardiovascular diseases, since smoking is one of the most important risk factors, it is not the only one [28,29], therefore, changes in the prevalence of other cardiovascular risk factors may have an impact on mortality rates. In past years, therapeutical advances and the promotion of healthy lifestyles have improved the prognosis and evolution of cardiovascular diseases [29], which has caused a reduction of around 10,000 deaths in Spain since the 1990s [15]. This reduction is not seen in the case of cancer, for which mortality rates almost doubled from 1980 to 2020 (1980: 58,481 deaths vs. 2020: 112,741 deaths) [15,30], and which will probably keep growing overcoming cardiovascular disease as the main cause of death in Spain. On the other hand, one of the methods of estimating SAM uses lung cancer as a proxy for tobacco consumption; the PIM. Lung cancer is a disease that takes several years to develop from the start of tobacco consumption. In fact, it is estimated that the time lapse between the use of tobacco products and the onset of lung cancer is approximately 30 years [31]. However, the development of cardiovascular diseases is shorter and, thus, the impact of any changes in the prevalence of their risk factors is shown sooner, too [32].

The estimations obtained in this study are subject to several limitations which are not commonly contemplated when estimating SAM. When using the PDM, the calculations are performed as if the study had a cross-sectional design, obtaining prevalence and observed mortality for the same year. However, when employing the PIM, this limitation is overcome as lung cancer is used as a "marker" of the tobacco epidemic. However, this means assuming that the induction time for the diseases for which mortality is analyzed must be the same. Despite these limitations associated with the PDM, a study conducted in Oregon concluded that estimates of SAM obtained using the PDM were comparable to mortality reports kept by physicians [33]. The PIM also has limitations as it is based on RRs and lung cancer mortality rates from another population. Other similar PIMs, such as that proposed by Preston et al. [34], also have limitations. In this case, specifically, it only allows the estimation of SAM in the population aged 50 years and older. There are also limitations regarding the sources of data. In Spain, mortality rates for lung cancer in relation to tobacco consumption are not available. This means that, for the PIM, we had to use lung cancer mortality rates for American never smokers and assume that they are similar to those in Spain. These estimations might differ depending on the evolution of smoking habits in the different regions, although, we do not expect these differences to change results substantially. In addition, combining three surveys to obtain prevalence data according to sex and age could misrepresent the figures and impact their true value. The main advantage of the present study may be perhaps the fact of having applied both methods in the same population, for the same period, and using the same data on observed mortality.

Appendix A. Supporting information

See Tables S1-S6.

In view of the results obtained, in the absence of prevalence data, the independent method provides similar estimations of the overall burden of SAM at both the national and subnational levels. However, when analyzing the estimates according to the cause of death, we should be careful since the burden of mortality from cardiovascular diseases varies between methods. This is noteworthy among women and in the extreme age groups where prevalences suffer greater changes.

Conclusion

The overall estimation of SAM on a national level in Spain was very similar using the PIM or the PDM. When the attributed mortality data were disaggregated by region according to sex, the differences between methods became more evident in women. In relation to causes of death, in spite of the differences in calculation procedures, the SAM by cancer and lung cancer are almost the same when applying both methods. However important differences were found for cardiovascular diseases–diabetes mellitus, especially when data were disaggregated according to sex. Despite the differences found between the two methods in some subgroups, both methodologies can be applied in the estimation of SAM. Furthermore, in cases in which prevalence data are not available, the independent prevalence method is an effective alternative in the estimation of SAM.

CRediT authorship contribution statement

Julia Rey-Brandariz: Conceptualization, Planification, Methodology, Formal analysis, Writing – original draft. Ana Blanco-Ferreiro: Planification, Methodology, Formal analysis, Writing – review and editing. Leonor Varela-Lema: Conceptualization, Planification, Methodology, Writing – review and editing. María Isolina Santiago-Pérez: Conceptualization, Methodology, Formal analysis, Writing – review and editing. Alberto Ruano-Ravina: Conceptualization, Planification, Writing – review and editing. Iñaki Galán: Conceptualization, Planification, Writing – review and editing. Cristina Candal-Pedreira: Conceptualization, Writing – review and editing. Mónica Pérez-Ríos: Conceptualization, Planification, Methodology, Writing – review and editing, Supervision, Funding acquisition.

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Ethical approval statement

Based on the "Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos", we do not need formal ethics approval since this study is not performed on human participants including identifiable human material or identifiable data and no human intervention is performed.

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Table S1
Observed mortality in 17 regions of Spain in menmen by cause of death in 20172017

Regions	Men								
	Lung cancer	Other cancers*	Ischemic heart disease	Other heart disease†	Cerebrovascular disease	Other vascular disease‡	Diabetes mellitus	Influenza/pneumonia/ tuberculosis	Chronic obstructive pulmonary disease
Andalusia	2939	4301	3555	3238	2366	516	689	925	1872
Aragon	625	933	608	681	456	106	205	226	369
Asturias	531	891	631	529	355	88	106	162	311
Balearic Islands	396	520	402	333	217	43	139	86	193
Canary Islands	667	1021	886	602	361	104	191	245	376
Cantabria	266	421	208	279	185	52	28	69	136
Castile and Leon	1048	2000	1278	1246	768	222	333	408	652
Castile La Mancha	842	1279	759	809	550	130	248	355	705
Catalonia	2585	4270	2581	2699	1591	493	798	755	1966
Valencia	1932	2868	2267	1894	1239	341	462	590	1064
Extremadura	544	770	524	505	369	77	91	248	295
Galicia	1224	2159	1336	1578	840	227	263	350	743
Madrid	1864	3049	1913	1649	915	281	287	771	1116
Murcia	466	701	543	486	337	72	142	176	370
Navarre	249	396	231	253	165	43	76	76	144
Basque Country	906	1550	799	916	588	182	171	237	426
La Rioja	96	214	126	145	95	29	28	28	66

* Other cancers include: lip, oral cavity and pharynx, esophagus, stomach, colon and rectum, liver and intrahepatic bile ducts, pancreas, larynx, cervix uteri, urinary bladder, kidney-renal pelvis and acute myeloid leukemia.
† Other heart diseases include: rheumatic heart diseases, cardiopulmonary diseases, other types of heart disease.
‡ Other vascular diseases: atherosclerosis, aortic aneurysm and other arterial diseases.

Table S2
Observed mortality in 17 regions of Spain in womenwomen by cause of death in 20172017

Regions	Women								
	Lung cancer	Other cancers*	Ischemic heart disease	Other heart disease†	Cerebrovascular disease	Other vascular disease‡	Diabetes mellitus	Influenza/pneumonia/ tuberculosis	Chronic obstructive pulmonary disease
Andalusia	643	2346	2604	5011	3036	348	952	847	381
Aragon	149	548	429	925	620	59	241	217	110
Asturias	175	505	529	857	503	55	156	147	61
Balearic Islands	133	322	254	487	257	34	140	81	84
Canary Islands	240	537	560	733	427	70	235	251	130
Cantabria	89	243	142	324	255	30	46	65	50
Castile and Leon	282	1131	873	1853	1036	124	431	366	155
Castile La Mancha	162	654	613	1250	666	94	338	366	146
Catalonia	781	2441	1742	3807	2088	318	925	756	636
Valencia	532	1636	1469	2952	1635	187	578	537	310
Extremadura	92	416	371	787	468	41	149	224	33
Galicia	337	1321	933	2329	1334	179	332	374	301
Madrid	691	1994	1431	2808	1345	231	420	800	355
Murcia	114	354	357	726	453	53	181	166	77
Navarre	65	226	139	315	222	35	78	70	34
Basque Country	308	838	501	1235	794	92	207	263	170
La Rioja	27	114	92	205	122	12	35	27	17

* Other cancers include: lip, oral cavity and pharynx, esophagus, stomach, colon and rectum, liver and intrahepatic bile ducts, pancreas, larynx, cervix uteri, urinary bladder, kidney-renal pelvis and acute myeloid leukemia.
† Other heart diseases include: rheumatic heart diseases, cardiopulmonary diseases, other types of heart disease.
‡ Other vascular diseases: atherosclerosis, aortic aneurysm and other arterial diseases.

Table S3
Relative risks in smokers (S) and ex-smokers (ExS) by sex, age group and cause of deathdeath

	Men								Women							
	35–54		55–64		65–74		≥75		35–54		55–64		65–74		≥75	
Cause	S	ExS	S	ExS	S	ExS	S	ExS	S	ExS	S	ExS	S	ExS	S	ExS
Lung cancer	14.33	4.40	19.03	4.57	28.29	7.79	22.51	6.46	13.30	2.64	18.95	5.00	23.65	6.80	23.08	6.38
Other cancers*	1.74	1.36	1.86	1.31	2.35	1.49	2.18	1.46	1.28	1.24	2.08	1.28	2.06	1.26	1.93	1.27
Coronary heart disease	3.88	1.83	2.99	1.52	2.76	1.58	1.98	1.32	4.98	2.23	3.25	1.21	3.29	1.56	2.25	1.42
Other heart diseases†	2.40	1.07	2.51	1.51	2.22	1.32	1.66	1.15	2.44	1.00	1.98	1.10	1.85	1.29	1.75	1.32
Cerebrovascular disease	2.40	1.07	2.51	1.51	2.17	1.23	1.48	1.12	2.44	1.00	1.98	1.10	2.27	1.24	1.70	1.10
Other vascular diseases‡	2.40	1.07	2.51	1.51	7.25	2.20	4.93	1.72	2.44	1.00	1.98	1.10	6.81	2.26	5.77	2.02
Diabetes mellitus	2.40	1.07	2.51	1.51	1.50	1.53	1.00	1.06	2.44	1.00	1.98	1.10	1.54	1.29	1.10	1.06
Influenza, pneumonia, tuberculosis	4.47	2.22	15.17	3.98	2.58	1.62	1.62	1.42	6.43	1.85	9.00	4.84	1.75	1.28	2.06	1.21
COPD	4.47	2.22	15.17	3.98	29.69	8.13	23.01	6.55	6.43	1.22	9.00	1.34	38.89	15.72	20.96	7.06

COPD, Chronic obstructive pulmonary disease.
* Other cancers include: lip, oral cavity and pharynx, esophagus, stomach, colon and rectum, liver and intrahepatic bile ducts, pancreas, larynx, cervix uteri, urinary bladder, kidney-renal pelvis and acute myeloid leukemia.
† Other heart diseases include: rheumatic heart diseases, cardiopulmonary diseases, other types of heart disease.
‡ Other vascular diseases: atherosclerosis, aortic aneurysm and other arterial diseases.

Table S4
Lung cancer mortality rates per 100.000 inhabitants from the Cancer Prevention Study II, by sex and age groupgroup

Age (y)	Men		Women	
	Never smokers rate*	Smokers rate*	Never smokers rate*	Smokers rate*
35–39	2	0	2	7
40–44	3	23	3	12
45–49	5	35	4	49
50–54	7	114	7	71
55–59	10	227	10	136
60–64	14	375	14	195
65–69	20	599	19	310
70–74	27	899	26	339
75–79	35	1168	34	429
80–84	46	1191	44	400
≥85	46	1191	44	400

* Source: Peto R, Boreham J, Lopez AD, Thun M, Heath C. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet 1992;339(8804):1268–78.

Table S5
Smoking-attributable mortality (SAM) estimated using the prevalence-dependent method (PDM) and the prevalence-independent method (PIM) and the percentage of change accompanied by their 95% confidence intervals (CI 95%), in menmen and by cause of deathdeath

	Men														
	Cancers					Cardiovascular diseases–diabetes mellitus					Respiratory diseases				
Region	PDM	PIM	% Of change	CI 95%		PDM	PIM	% Of change	CI 95%		PDM	PIM	% Of change	CI 95%	
Andalusia	3843	3855	0.3	−2.7	3.4	2485	2617	5.3	0.4	10.5	1890	1875	−0.8	−4.4	2.9
Aragon	795	847	6.6	−0.3	13.9	393	486	23.8	9.9	39.2	362	372	2.8	−6.0	12.4
Asturias	693	737	6.4	−1.2	14.4	365	422	15.6	2.2	30.8	299	301	0.7	−8.6	10.9
Balearic Islands	495	505	2.2	−6.2	10.9	257	280	8.8	−6.0	26.3	190	191	0.3	−10.2	12.6
Canary Islands	881	854	−3.1	−9.2	3.5	553	526	−4.8	−14.2	5.5	397	377	−5.1	−12.9	3.5
Cantabria	342	368	7.8	−2.9	19.2	162	202	24.9	4.1	49.3	131	135	2.5	−10.6	18.8
Castile and Leon	1452	1428	−1.6	−6.7	3.7	761	799	4.9	−3.9	14.7	643	630	−2.0	−8.6	5.0
Castile La Mancha	1076	1127	4.8	−1.2	11.0	508	594	16.9	5.3	29.8	676	689	2.0	−4.3	8.6
Catalonia	3455	3422	−1.0	−4.2	2.4	1799	1879	4.4	−1.3	10.6	1874	1879	0.2	−3.2	3.9
Valencia	2517	2542	1.0	−2.8	4.9	1443	1561	8.2	1.6	15.1	1071	1067	−0.4	−5.3	4.8
Extremadura	721	747	3.7	−3.2	10.9	374	435	16.3	3.2	31.0	331	328	−0.8	−10.0	9.1
Galicia	1606	1675	4.3	−0.7	9.5	802	950	18.4	8.9	28.8	691	708	2.4	−3.8	9.1
Madrid	2499	2393	−4.2	−8.0	−0.4	1153	1140	−1.2	−8.0	6.2	1166	1122	−3.8	−8.6	1.3
Murcia	595	606	1.8	−5.9	10.2	342	373	9.2	−4.1	24.1	352	359	2.2	−6.5	11.2
Navarre	312	332	6.1	−4.6	18.7	146	178	21.8	0.4	48.1	134	141	4.8	−9.0	21.6
Basque Country	1211	1229	1.5	−4.1	7.4	578	632	9.2	−1.0	20.7	420	415	−1.2	−9.0	7.3
La Rioja	136	128	−6.2	−21.6	13.0	79	73	−7.9	−30.7	23.3	62	59	−4.3	−23.1	17.7
Spain	**22,629**	**22,796**	**0.7**	**−0.60.6**	**2.0**	**12,201**	**13,147**	**7.8**	**5.4**	**10.1**	**10,690**	**10,648**	**−0.40.4**	**−2.02.0**	**1.2**

SAM estimated with PDM was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the PIM.SAM estimated with PDM was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the PIM.

Table S6
Smoking-attributable mortality (SAM) estimated using the prevalence-dependent method (PDM) and the prevalence-independent method (PIM) and the percentage of change accompanied by their 95% confidence intervals (CI 95%), in womenwomen and by cause of deathdeath

Region	Women														
	Cancers					Cardiovascular diseases–diabetes mellitus					Respiratory diseases				
	PDM	PIM	% Of change	CI 95%		PDM	PIM	%Of change	CI 95%		PDM	PIM	% Of change	CI 95%	
Andalusia	577	392	−32.2	−39.6	−23.6	475	242	−49.1	−56.3	−40.6	198	114	−42.3	−53.6	−28.5
Aragon	128	119	−7.4	−25.9	16.6	76	153	101.0	53.9	163.4	52	88	69.9	24.5	130.0
Asturias	141	165	17.0	−4.0	42.7	82	193	135.0	83.1	202.6	35	59	68.9	16.3	144.4
Balearic Islands	118	125	6.5	−14.6	31.4	63	95	51.2	10.8	105.2	50	65	29.7	−3.6	75.3
Canary Islands	219	216	−1.7	−15.9	15.7	157	206	31.1	7.6	60.0	90	116	28.7	1.8	63.2
Cantabria	75	88	16.8	−10.2	53.4	26	66	149.2	63.0	295.4	18	35	99.0	17.2	222.6
Castile and Leon	222	210	−5.3	−20.5	12.5	122	259	111.7	71.9	162.2	56	117	107.9	55.6	180.5
Castile La Mancha	118	105	−11.0	−30.3	13.6	66	159	138.6	81.6	219.5	44	99	126.7	61.2	214.0
Catalonia	591	630	6.5	−3.6	17.9	305	705	131.3	102.8	163.5	258	482	86.7	63.8	113.1
Valencia	484	432	−10.9	−20.5	0.2	298	440	47.6	28.0	70.4	154	222	44.4	20.2	73.0
Extremadura	71	57	−19.9	−42.1	11.2	46	53	15.4	−22.0	70.1	20	21	6.0	−41.6	88.9
Galicia	248	266	7.3	−8.5	25.7	158	332	109.5	74.6	152.9	113	203	80.0	46.5	120.3
Madrid	703	565	−19.6	−27.1	−11.4	500	492	−1.6	−12.7	10.9	289	300	3.8	−9.7	19.3
Murcia	82	83	1.2	−23.3	33.5	45	123	175.4	95.5	282.1	31	60	96.6	30.3	187.4
Navarre	61	49	−20.2	−42.8	12.8	38	35	−8.5	−41.2	44.2	24	24	0.7	−39.1	64.3
Basque Country	281	257	−8.3	−21.1	6.1	148	149	1.0	−19.3	25.6	100	101	0.9	−20.7	28.7
La Rioja	26	19	−27.3	−57.6	25.8	15	19	28.8	−34.8	146.2	7	8	16.9	−54.7	188.0
Spain	**4145**	**3776**	**−8.98.9**	**−12.412.4**	**−5.25.2**	**2622**	**3721**	**41.9**	**35.2**	**49.0**	**1538**	**2116**	**37.5**	**29.8**	**45.9**

SAM estimated with PDM was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the PIM.SAM estimated with PDM was used as a reference; thus, the percentage of change refers to the changes in mortality estimated with the PIM.