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# Asthma Mortality in Spain From 1980 to 2019: Trends and Perspectives in the New Treatment Era

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## Abstract

*Background:* Previous studies suggest that asthma mortality rates in Spain have been decreasing in recent years. However, this trend is not homogeneous across age groups.
*Objective:* To analyze asthma mortality rates over a 40-year period, focusing on changes associated with the development of new therapeutic approaches.
*Methods:* Death records and mid-year population data were collected from the National Statistics Institute. Using the direct method, age-standardized mortality rates were calculated for the overall population and for each sex and age group. Significant changes in mortality trends were identified using joinpoint regression analysis. The independent effects of age, period, and cohort and potential years of life lost due to asthma were also analyzed.
*Results:* Age-standardized asthma mortality rates decreased in Spain from 7.38 to 2.03 deaths per 100 000 from the first to the last quinquennium of the study (1980-1984 to 2015-2019) for the whole population. This decrease was more intense among men, where a decrease from 10.37/100 000 to 0.91/100 000 was observed compared with 5.53 to 2.77/100 000 in women. Mortality decreased in all age groups. During the last 3 years, the decrease stabilized in patients aged >64 years but increased in those aged 35-64. Mortality has been decreasing rapidly since the 1990s in patients aged <35 years.
*Conclusion:* Asthma mortality rates began to decline in 1980. The decrease was observed among younger cohorts starting in the 1990s, thus confirming earlier trends. Improved diagnosis and development of new therapies for asthma may have played a role in the changes observed. Close monitoring of asthma mortality rates is necessary to confirm these trends.

Key words: Ecological studies. Mortality. Immunotherapy. Asthma. Therapy. Epidemiology. Age-period-cohort. Potential years of life lost.

## Resumen

*Introducción:* Estudios previos sugieren que las tasas de mortalidad en España han disminuido en los últimos años, aunque esta tendencia no se ha observado de forma homogénea en todos los grupos de edad.
*Objetivo:* Se analizan las tasas de mortalidad por asma de los últimos 40 años en España, centrándose en los cambios relacionados con el desarrollo de nuevas terapias.
*Métodos:* Se obtuvieron los registros de defunción y los datos de población del Instituto Nacional de Estadística. Se calcularon las tasas de mortalidad estandarizadas por edad utilizando el método directo para la población global y para cada sexo y grupos de edad. Se identificaron cambios significativos en las tendencias de mortalidad mediante modelos de regresión Joinpoint (puntos de cambio). También se analizaron los efectos de la edad, período y cohorte, y se calcularon los años potenciales de vida perdidos debido al asma.
*Resultados:* Las tasas de mortalidad estandarizadas por asma disminuyeron en España de 7,38 a 2,03 muertes por 100.000 entre el primer y el último quinquenio del estudio (1980-1984 a 2015-2019) para la población general. Esta disminución fue más intensa entre los hombres, donde se observó una disminución de 10,37/100.000 a 0,91/100.000 frente a 5,53 a 2,77 / 100.000 en las mujeres. Todos los grupos de edad han reducido su mortalidad globalmente en el periodo estudiado. Mientras que los mayores de 64 años han estabilizado su descenso y la población entre 35 y 64 incluso ha incrementado la mortalidad en los últimos 3 años, los menores de 35 años mantienen un rápido descenso desde la década de 1990.
*Conclusión:* Hay una disminución en las tasas de mortalidad por asma a partir de 1980, incluidas las cohortes más jóvenes a partir de la década de 1990, lo que confirma tendencias anteriores. Las mejoras en el diagnóstico y el desarrollo de nuevas terapias para el asma pueden tener un papel en estos hallazgos. Es necesario un estrecho seguimiento de las tasas de mortalidad por asma para confirmar estas tendencias.

Palabras clave: Estudios ecológicos. Mortalidad. Inmunoterapia. Asma. Epidemiología. Tratamiento. Epidemiología. Modelo edad-cohorte-periodo. Años potenciales de vida perdidos.

## Introduction

Bronchial asthma causes very high morbidity and mortality worldwide. Its prevalence varies widely from 2% in Tartu (Estonia) to almost 12% in Melbourne (Australia), and several studies have reported a gradual increase of around 13% from 1990 to 2015 [1,2]. Of an estimated 300 million asthma patients worldwide, more than 180 000 die from the disease annually [3]. Although prevalence tends to increase, the death rate for asthma in developed countries has been falling since its peak in the 1980s, with asthma mortality rates per 100 000 people ranging from 0.78 to 1 in the European Union [4].

Therapy for asthma has impacted positively on mortality rates. However, overuse of high-dose, potent, and poorly selective β2 agonists, such as isoprenaline and fenoterol, has resulted in an increase in asthma mortality. This trend has reversed owing to regulatory restrictions and withdrawal of these drugs in clinical practice. β2 agonists have been associated with long-term adverse effects, increasing the severity of asthma through worse bronchial hyperresponsiveness, reduced lung function, and cardiovascular-related adverse events linked to hypoxemia [5-9]. Awareness of the potential risks of overdependence on bronchodilator therapy and the efficacy of inhaled corticosteroids (ICS) in reducing the risk of morbidity and mortality in asthma led to a change in asthma treatment practice in the late 1980s. ICS are being increasingly used in many countries around the world, most recently in the form of combined ICS/long-acting β2 agonist therapy (LABA), in which the LABA component was basically a vehicle to improve adherence to ICS. The ICS-based management approach was associated with a generalized and progressive reduction in global asthma mortality of almost 63% [10-13].

To date, several epidemiological studies have focused on the prevalence and mortality of asthma in Spain. During the period 1980-1996, asthma mortality rates decreased in Spain, although this trend was not observed for younger age groups [14-17]. In this context, the GINA guidelines state that there is insufficient evidence to determine the exact causes of the variations in the prevalence of asthma within and between populations [18]. Although estimates of temporal trends in asthma epidemiology after the 1990s are frequently inhomogeneous in different parts of the world, trends in international asthma mortality rates provide a useful barometer of the burden of asthma and the impact of changes in asthma management [19]. Most previous Spanish studies have focused on large populations over 10- to 15-year study periods [14], and while this research has provided valuable information, longer observation periods are likely to provide a better understanding of temporal trends in asthma mortality. Based on this hypothesis, we used joinpoint analysis to describe asthma mortality rates in Spain over a 40-year period (1980-2019).

## Methods

Data on the mid-year population and death certificates for the period 1980-2019 were obtained from the Spanish National Statistics Institute (http://www.ine.es) in line with the methodology applied in previous epidemiological studies on mortality trends [20,21]. Ethics committee approval is not required for processing of data, since these are completely anonymous. This type of article is subject to the National Statistical Law, which only requires the data source to be mentioned. Death certificates in developed countries are a very reliable source of mortality data. We included all death records (obtained as microdata files) that showed asthma (International Classification of Diseases [ICD], Ninth Revision [ICD-9], 493; ICD-10, J45-46) to be the cause of death. Microsoft Excel and SPSS Statistics 25 (IBM Corp.) were used to process the microdata files, filter by cause of death, and build contingency tables according to age group, sex, and year of death.

Age-specific mortality rates by 5-year age groups were computed. Annual age-adjusted mortality rates were calculated using the direct method for the whole country and by stratifying according to sex and age groups (<35, 35-64, and >64 years). The new European standard population of 2013 was taken as the reference [22]. These results were obtained using Epidat 4.2 and expressed as deaths per 100 000 person-years. Likewise, the sex ratio was computed as the male mortality rate divided by the female mortality rate for each year.

Points of significant changes in mortality trends by sex and age group were assessed using joinpoint regression models, which analyze possible variations in the direction of the trend in various segments over a specific period. In these cases, the analysis of the trend is better characterized by the annual percent change for each of the segments. The joinpoint method chooses the appropriate number of inflection points (joinpoints) at which the rates of increase or decrease change significantly. The average annual percent change was also calculated using this method for the entire period. If there is no significant change in trend, there is no joinpoint, the model only chooses 1 segment, and annual percent change is constant and equals the average annual percent change.

For this purpose, we used the Joinpoint software application developed by the Surveillance Research Program of the US National Cancer Institute [23]. A maximum of 5 joinpoints were allowed in the analysis. The minimum number of years until the extremes of the observation periods was established at 2 years for both the beginning and the end of the periods.

Independent effects of age, period, and cohort factors (age-period-cohort effects [APC]) on mortality rates were also computed using the penalty functions proposed by Decarli and La Vecchia [24]. In this proposal, which is based on the Osmond and Garner models [25], APC models are estimated using Poisson regression, and the authors provide GLIM macros (APC package: Age-Period-Cohort Analysis version 1.3 for R) to perform the calculation. Data were analyzed based on 5-year periods. The goodness-of-fit of possible APC models was also compared.

Finally, potential years of life lost (PYLL) were computed to quantify premature mortality due to asthma in the population. Crude PYLL and PYLL standardized by age and sex were obtained, again using the 2013 European standard population as a reference.

## Results

Between 1980 and 2019, a total of 42 091 people died of asthma in Spain (14 590 men and 27 501 women). Although



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the overall age-adjusted rates of asthma mortality show a significant decline in the 40-year series analyzed (Figure 1A), rates began to stabilize from 2007 onward, with around 1000 deaths per year.

Table 1 shows the results of the analysis of standardized mortality rates between 1980-1984 and 2015-2019, as well as the key findings of the joinpoint regression analysis. Overall asthma mortality rates decreased from 7.38/100 000 to 2.08/100 000 between 1980-1984 and 2015-2019. This decrease was much more intense among men, where a decrease from 10.37/100 000 to 0.91/100 000 was observed compared with a more moderate decrease in women (from 5.53 to 2.77/100 000). In the joinpoint analysis, 2 cut-off points (3 periods) were observed in both sexes and 1 cut-off point (2 periods) in men and women, respectively. All these periods are characterized by a smaller decrease in the most recent periods than in the previous ones. In fact, overall, data were observed to stabilize from 2007 to the end of the series, with an average annual percent change of –1.2%.

Analysis by age group (Table 1, Figure 1B-D) revealed a different pattern. In the <35-year group, there was an increase at the beginning of the period, followed by a decrease from the 1990s onwards. In the 35- to 64-year group, there was a decrease from the beginning of the period analyzed (except in the case of women, where a slight rise was observed in the initial years up to 1987), with a shift toward an upward trend in recent years (nonstatistically significant rise for both sexes in the period 2016-2019). The group that experienced the most marked decrease in mortality was the >64-year group, where the highest mortality rates were observed and where the mortality curve was very similar to the global curve. This rapid decline from 1980 onwards flattened out in 1988 in women and 2004 in men, thus revealing 2 trend periods in both groups.

As mentioned, behavior between the sexes differed, both globally and by age groups; this illustrates an interesting change in the sex ratio (Figure 2). The most marked and constant change was observed in the >64-year group, where twice as many men died at the beginning of the period, thus reversing the trend from 1994, and ending the last decade at around 0.3. A similar but less marked trend was observed in the 35- to 64-year group, where deaths among men exceeded those among women until 1987, after which time the ratio remained unchanged between 0.8 and 0.6. Curiously, this pattern is reversed among the youngest individuals, where

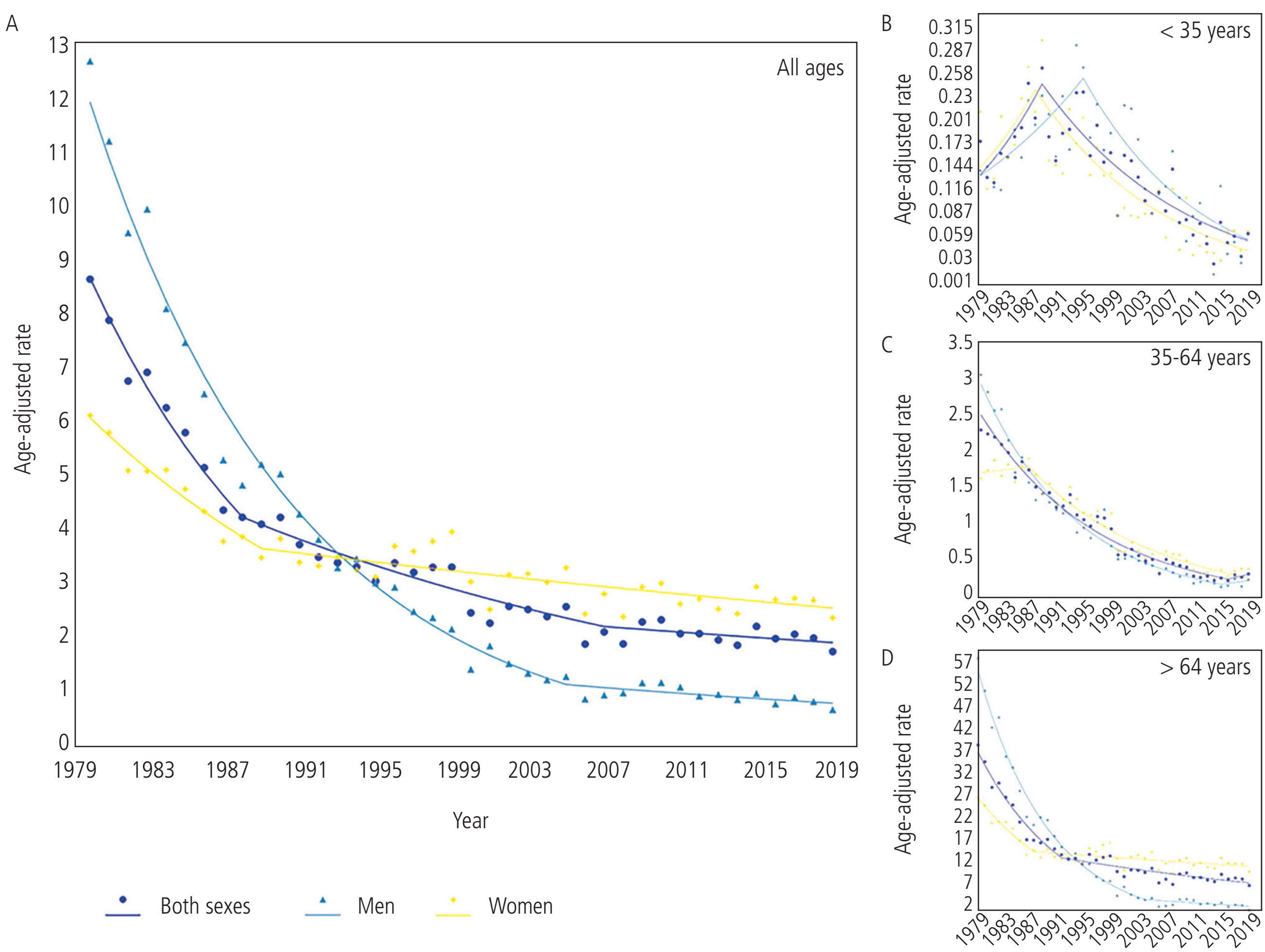


Figure 1. Joinpoint regression analysis (years 1980-2019) of the entire population (A), patients aged <35 years (B), patients aged 35-64 years (C), and patients aged >64 years (D).

 

Table 1. Age-adjusted Mortality Rates per 100 000 Inhabitants and Trend Analysis for Age and Sex

| | 1980-1984 ASMR (95%CI) | 2015-2019 ASMR (95%CI) | 1980-2019 AAPC (95%CI) | JP | Period(s) Years: APC (95 CI) |
|---|---|---|---|---|---|
| Both sexes | | | | | |
| All ages | 7.38 (6.98-7.80) | 2.08 (1.96-2.22) | –3.7 (–4.3 to –3.1)[a] | 2 | 1980-1988 –8.4 (–10.2 to –6.6)[a] 1988-2007 –3.3 (–3.9 to –2.6)[a] 2007-2019 –1.2 (–2.4 to 0.1) |
| <35 y | 0.16 (0.08-0.27) | 0.06 (0-0.13) | –2.1 (–3.4 to –0.9)[a] | 1 | 1980-1989 6.6 (2.2 to 11.3)[a] 1989-2019 –4.6 (–5.7 to –3.5)[a] |
| 35-64 y | 2.21 (1.94-2.50) | 0.34 (0.25-0.44) | –4.8 (–6.6 to –2.9)[a] | 1 | 1980-2016 -5.6 (–6 to –5.3)[a] 2016-2019 6.7 (–17.5 to 37.5) |
| >64 y | 32.93 (30.98-35.01) | 9.84 (9.23-10.48) | –3.6 (–4.1 to –3.1)[a] | 1 | 1980-1992 -7.7 (–9 to –6.3)[a] 1992-2019 –1.8 (–2.2 to –1.3)[a] |
| Men | | | | | |
| All ages | 10.37 (9.57-11.24) | 0.91 (0.75-1.07) | –6.5 (–7.1 to –5.9)[a] | 1 | 1980-2005 –8.7 (-9.2 to –8.3)[a] 2005-2019 –2.4 (–4.1 to –0.6)[a] |
| <35 y | 0.14 (0.06-0.27) | 0.07 (0.01-0.17) | –2.0(–3.6 to –0.4)[a] | 1 | 1980-1995 4.2 (1.0-7.5)[a] 1995-2019 –5.7 (–7.5 to –3.9)[a] |
| 35-64 y | 2.68 (2.26-3.14) | 0.26 (0.14-0.39) | –6.7 (–7.1 to –6.3)[a] | 0 | 1980-2019 –6.7 (–7.1 to –6.3)[a] |
| >64 y | 47.34 (43.39-51.74) | 3.99 (3.35-4.73) | –6.6 (–7.3 to –6.0)[a] | 1 | 1980-2004 –9.3 (-9.8 to –8.8)[a] 2004-2019 –2.2 (-3.8 to –0.05)[a] |
| Women | | | | | |
| All ages | 5.53 (5.08-6.00) | 2.77 (2.59-2.98) | –2.2 (–2.7 to –1.6)[a] | 1 | 1980-1989 –5.4 (–7.6 to –3.2)[a] 1989-2019 –1.2 (–1.5 to –0.08)[a] |
| <35 y | 0.17 (0.08-0.29) | 0.06 (0-0.17) | –2.8 (–4.3 to –1.3)[a] | 1 | 1980-1988 6.3 (0 to 13) 1988-2019 –5.1 (–6.2 to –3.9)[a] |
| 35-64 y | 1.80 (1.48-2.16) | 0.42 (0.29-0.57) | –4.2 (–5.0 to –3.4)[a] | 1 | 1980-1987 0.7 (–3.3 to 4.8) 1987-2019 –5.2 (–5.7 to –4.6)[a] |
| >64 y | 24.27 (22.17-26.56) | 13.21 (12.32-14.16) | –2.0(–2.7 to –1.3)[a] | 1 | 1980-1988 –6.7 (–9.8 to –3.5)[a] 1988-2019 –0.7 (–1.1 to –0.4)[a] |

Abbreviations: AAPC, annual average percentage change; APC, annual percentage change for each period; ASMR, age standardized mortality rate; JP, joinpoint.
[a]*P*<.05

the study began with more deaths among women than men, reversing from 1987 onwards, although since the 2010s, the ratio has inverted again.

The independent effects of the annual percent change on the mortality analysis show a constant and exponential increase with age (Figure 3). Important differences between the sexes were again observed with respect to the birth cohort: the risk of fatal asthma decreased significantly in males born from the end of the 19th century and up to 1950, stabilizing at low levels until the end of the 20th century. However, in the case of females, the mortality risk rose slightly among those born from the beginning of 1900 until about 1930 and then continued to decrease slowly and steadily until the end of the 20th century. The period effect was similar between the sexes, although slightly more marked in men than in women from the 1980s to the early 2000s, when a slight increase in both sexes was observed.

Table 2 shows the goodness of fit of the different APC models, with the 3-factor APC model being the best fit for both sexes and for men and women, since it has a lower Akaike information criterion and a narrower deviation.

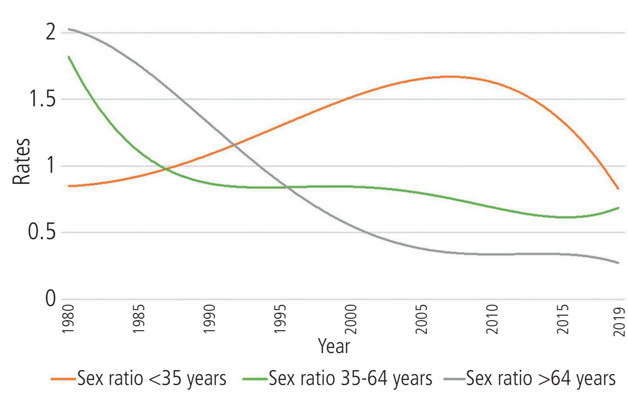


Figure 2. Trend in the sex ratio (men/women) over the years 1980-2019 by age group.



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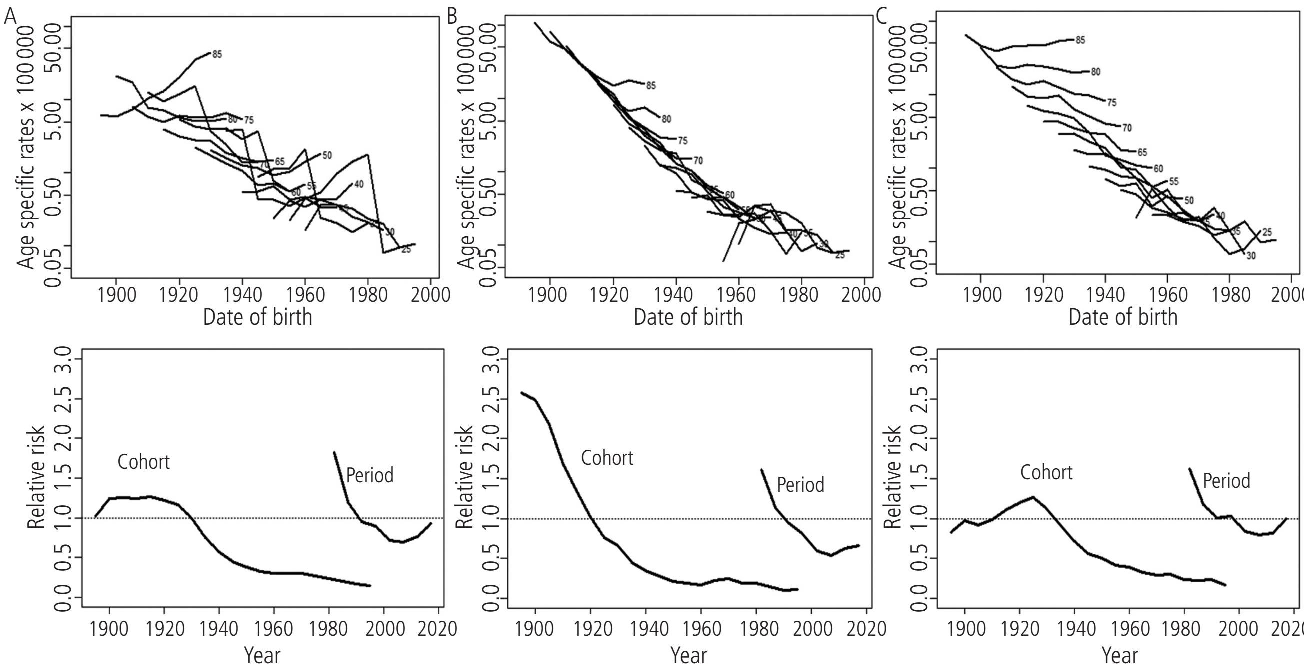


Figure 3. Analysis of the age-period-cohort effect for both sexes (A), men (B), and women (C). The upper graph shows the mortality rates for each 5-year age group; the lower graph shows the variation in the relative risk for the different cohorts and periods.

Table 2. Goodness-of-Fit Test for Different Age-, Period- and Cohort-Specific Models of Asthma in Spain, 1980-2019

| Model | df | Deviance | *P* Value | AIC |
|---|---|---|---|---|
| Both sexes | | | | |
| Age-Model | 98 | 10 510.58 | <.001 | 11 300.11 |
| Age-Drift Model | 97 | 3064.76 | <.001 | 3856.29 |
| Age-Period Model | 91 | 2154.45 | <.001 | 2957.98 |
| Age-Period-Cohort Model | 72 | 898.96 | <.001 | 1740.49 |
| Age-Cohort Model | 78 | 2272.38 | <.001 | 3101.91 |
| Men | | | | |
| Age-Model | 98 | 11 494.34 | <.001 | 12 180.14 |
| Age-Drift Model | 97 | 972.21 | <.001 | 1660.01 |
| Age-Period Model | 91 | 684.11 | <.001 | 1383.90 |
| Age-Period-Cohort Model | 72 | 435.44 | <.001 | 1173.24 |
| Age-Cohort Model | 78 | 706.33 | <.001 | 1432.12 |
| Women | | | | |
| Age-Model | 98 | 2637.65 | <.001 | 3362.96 |
| Age-Drift Model | 97 | 1625.44 | <.001 | 2353.75 |
| Age-Period Model | 91 | 1356.46 | <.001 | 2095.77 |
| Age-Period-Cohort Model | 72 | 338.40 | <.001 | 1115.71 |
| Age-Cohort Model | 78 | 780.33 | <.001 | 1545.63 |

Abbreviations: AIC, Akaike information criterion; df, degrees of freedom.

Asthma results in a significantly high PYLL. Although the adjusted rate declined significantly, especially in the 1980s and 1990s (Figure 4), it is still responsible for an average of more than 5000 PYLL lost each year in Spain (see eTable 1).

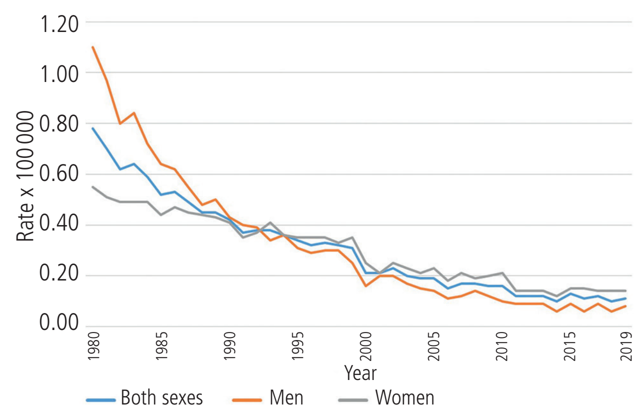


Figure 4. Rates of potential years lost per 100 000 person-years.

## Discussion

The present analysis of trends in asthma mortality over a 40-year period in Spain revealed a progressive increase in the 1980s, followed by a milder rise until the mid-1990s and subsequent stabilization with a pronounced decline in the middle of the last decade. However, these general trends are strongly influenced by mortality in asthma patients aged over 64 years. In younger asthmatics, mortality came to a halt in the 1980s and began to decline steadily, especially in the population under 35 years of age.

It is likely that the reduction in asthma mortality in patients younger than 65 years since the late 1980s is primarily due to the progressive and widespread increase in ICS therapy.

However, it is difficult to model mortality rates further to assess this hypothesis in the absence of robust contemporaneous data on asthma prevalence and pharmaceutical prescriptions over the same period. In any case, ICS have been very effective in reducing the frequency of days with symptoms, improving lung function, and reducing the frequency of hospitalization for asthma and the risk of life-threatening attacks [26,27]. Moreover, the regular use of low-dose inhaled corticosteroids is associated with a decreased risk of fatal asthma [28]. Although advances in asthma treatment are largely responsible for the magnitude of the decline in asthma-related mortality, other factors, such as the decline in smoking and better access to health care and medications, particularly in developed countries, may have also played a role [29].

In patients with chronic disease, such as asthma, mortality increases with age, thus reflecting the chronic nature of the disease, which is characterized by airway remodeling and, consequently, reduced response to classic asthma treatments in older people. On the other hand, elderly asthma patients may also be more sensitive to the adverse effects of ß-adrenergic agonists and corticosteroids, especially those receiving multiple drugs, and many have difficulty using inhalers correctly [30]. In fact, previous studies have associated advanced age with risk of poorer control in the future, asthma exacerbation, and a higher rate of hospitalization [31].

Whatever the reason for the apparent age difference in mortality, more research is needed into the increased frequency of fatal asthma in the older population. This is particularly pertinent, since many elderly patients with asthma are treated with drugs that have not been tested in older populations and older people with asthma are often excluded from clinical studies because of age-based inclusion criteria and comorbidities [32].

As seen in other studies, there is an association between age, sex, and asthma mortality. Older age and female sex, in general, are more likely to be associated with higher rates of severe asthma and asthma-related hospitalization and mortality [19,33]. The data collected in this study show that the decrease in mortality from asthma is less evident in women than in men, especially after 65 years of age. Previous studies have shown a higher prevalence of severe asthma in women [34], which is the group with the highest risk of exacerbations and death from asthma. The reasons for this remain obscure. The literature on hormonal and sex-related effects on the clinical course of asthma is conflicting. Rather than speculating on the many theoretically possible explanations, the results of this study show the need for further investigations as to why females with asthma experience more severe disease.

We observed a seasonal effect in the deaths from asthma included in the study, with a significant increase in the winter months, which could be correlated with the increase in viral infections, a fundamental cause of asthma exacerbations, especially in the elderly, whereas in young people, they are usually triggered by intense contact with allergens [31].

The limitations of the present study are typical of ecological studies. First, it was not possible to assess trends in specific age groups such as patients under 5 years of age, where mortality rates may be higher than in the 0- to 34-year group, or in school-age groups. This is because when small groups are analyzed, 1 or more years have a mortality equal to zero and the analysis cannot be performed using joinpoint regression. Second, our results may also be influenced by changes in the ICD version used over the period analyzed. The shift from ICD-9 to ICD-10 took place in 2000 in Spain. Nevertheless, there is no evidence of major changes associated with successive revisions of the ICD. Still, the reliability and validity of death certification from asthma remains open to discussion, with a possible shift from chronic obstructive pulmonary disease (COPD) and other cardiorespiratory conditions to asthma [35]. The prevalence of asthma and COPD overlap syndrome among adults with COPD or asthma ranges from 13% to 30%, and patients with the syndrome usually have severe disease, with increased rates of exacerbation, hospitalization, and death [36]. A third limitation of this research is the possible presence of bias with respect to collected mortality data based on death certificates. Notwithstanding, mortality records are postulated as much more reliable than incidence records, especially in Spain, where the available data are only partial [37].

In conclusion, asthma, which is considered a controllable disease and hence an avoidable cause of death, is currently responsible for about 1000 deaths per year in Spain. Consequently, further advances in asthma management would have major relevance and remain a public health priority.

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The authors declare that no funding was received for the present study.

### *Conflicts of Interest*

During the last 3 years, JD has served on advisory boards for Bial and Sanofi. He has also received speaker's honoraria from AstraZeneca, Bial, Chiesi, GlaxoSmithKline, Novartis, Sanofi, and TEVA and travel assistance to attend meetings from Sanofi.

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