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Trends in mortality due to osteoporosis in Spain: an analysis with Joinpoint regression.

Tendencias en la mortalidad por osteoporosis en España: un análisis con Joinpoint regression.

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CONTENTS

Table of contents

ABSTRACT

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Background: Osteoporosis is a major health problem, particularly in the elderly due to the burden in terms of fracture probability, disability and future health-related quality of life. The aim of this study is to identify the temporal trends in osteoporosis mortality in Spain from 1999 to 2015.

Methods: Data were obtained from the Spanish National Institute for Statistics. Age- and sex-specific mortality rates and age-adjusted mortality rates were estimated. Joinpoint regression was used to identify the years when changes in mortality trend and the annual percentage change in mortality rates took place.

Results: Women presented a greater globally rate decrease, though the mortality rate difference between gender was reduced by half at the end of the period. In women, significant trend changes were identified in three age groups while in men the only change in trend was identified in the youngest group. The average annual percentage change increases with age in women, while the change in the trend pattern was less clear in men.

Conclusion: Mortality caused by osteoporosis in Spain shows only a slight decrease despite the progress experimented in both diagnosis and treatment over the past two decades. Women in older cohorts show the faster decreases.

Keywords: osteoporosis, trends, mortality, bisphosphonates, non-adherence

INTRODUCTION

INTRODUCTION

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture(1).

In 2010, there were approximately 27.6 million men and women with osteoporosis in the EU27, being the prevalence of 22.1 % in women and 6.6% in men aged 50 years or more (2). In Spain, the prevalence of osteoporosis measured according to WHO´s criteria(1), is higher in women reaching 26% (3) and lower in men being of 4.15% (4) and it is estimated to increase with the population overaging. The age group ≥ 75 years presents a considerable difference between prevalence at hip and at lumbar spine osteoporosis, being of 24% and 40% respectively (3). Men older than 50 years present a prevalence of 4.4% at hip osteoporosis and of 4.8% at lumbar spine osteoporosis being much lower than women(3). In the USA, 2005–2008, the prevalence of osteoporosis at the lumbar spine ranges from 6.8 % in women aged 50 to 59 to 34.9 % in women aged 80 and older (5).

Osteoporotic fractures are widely considered to be the most important outcome of osteoporosis and an increased risk of death is well established in both women and men, especially after hip fracture (6). Taking into consideration the osteoporotic fractures repercussions, when analyzing world trends, studies in western populations have generally reported increases in hip fracture incidence through the second half of the last century, but those continuing to follow trends over the last two decades have found that rates stabilize, with age-adjusted decrease observed in Denmark as well as Austria and Germany between 1992-2004 and 2000-2005 respectively (7). Though few studies analyze osteoporosis trends, Azagra et al. described that in Spain the trend of hip fracture according to age groups and gender is clearly downward in women 65 to 80 years old remaining more or less the same in the 80-84 year-old group and presenting a significant increase in the 85 year-old groups. Nevertheless mortality rate dropped remarkably in both sexes (8).

Changes in osteoporotic fracture and mortality rates trend could be related to diagnosis and treatment improvements. Regarding the diagnosis, though Dual-energy X-ray absorptiometry (DXA) is the most widely used technique to assess bone mineral, there are others that include: quantitative ultrasound (QUS), quantitative computed tomography (QCT) applied both to the appendicular skeleton and to the spine, peripheral DXA, digital X-ray radiogrammetry, radiographic absorptiometry (9) and magnetic resonance imaging (MRI). Recent studies comparing these new diagnosis techniques with DXA show that MRI is a good predictor of femoral strength (10) and the thoracic and the lumbar QCT provide a similar and more sensitive method for detecting bone mineral loss (11).

In 2015, ISCD official position regarding bone strength calculated by QCT-based finite element analysis (FEA) of spine and hip, provide support for the use of homogenized FEA to predict spine and hip fractures while central DXA measurements at the spine

and femur are the preferred methods for making therapeutic decisions. Nevertheless, FEA cannot be used to diagnose osteoporosis using the current WHO T-score definition (12)

Moreover, since the use of risk factors add information on fracture risk, in 2008 was created the WHO fracture prediction tool FRAX, the web site being launched in 2008, visited about 180,000 visits per month in 2011 (13) and about approximately 225,000 calculations per month in 2016 (14). The fracture risk (FRAX) of a patient over 10 years can be estimated as low (< 10% in next 10 years), moderate (10 - 20% in next 10 years), or high (> 20% in next 10 years) using known risk factors and femoral neck bone mineral density (15). As well as the FRAX tool, other fracture risk calculators are available online which include the Garvan fracture risk calculator and QFracture, the last one including a history of falls as a different feature from the first one. (13)

Regarding the pharmacological interventions, they can be classified into anti resorptive agents that prevent the bone resorption and anabolic agents that help in the new bone formation. For many years the prevention of postmenopausal bone loss was marked by the use of hormone therapy estrogen + progestin (HT) or estrogen therapy (ET) (15) until in 2001, when Women's Health Initiative study finding the association between HT and several cancers was published, (16) leading to a progressive decline of the hormone replacement therapy presenting HT the higher decrease in 2004, of 31,7% respect the previous year (17) (18), and at the same time, changing the trends in pharmacological intervention towards bisphosphonates (19). The widespread use in the prescription of bisphosphonates in developed countries began in 2002. Since then an increasing use has been observed (19) being the marketing of bisphosphonates mostly represented by the alendronate (Fosamax®), which was the first oral bisphosphonate drug for treatment of osteoporosis in 1995, followed by risedronate (Actonel®) in 1998, and ibandronate (Boniva®) in 2005. The generic alendronate became available in 2008 and generic ibandronate in 2012 (20) (15). Nevertheless a trend of substantial decline in sales for osteoporosis treatment was observed for oral bisphosphonates since 2007–2008 and intravenous bisphosphonates since 2010 (20). Thus, studies to assess the effectiveness of the treatment in patient who do have adherence is needed since in Spain, the annual incidence of hip fractures in patients aged ≥ 65 years has been estimated at 36,000 (90.5 % of all hip fractures), and it is continuously increasing (21). The main objective of this study was to evaluate trends in the mortality rate of osteoporosis in Spain from 1999 until 2015 and its relationship to changes in diagnosis and treatment in the last decades.

METHODS

METHODS

Data extraction

Data on number of people dying from osteoporosis by sex and in 5- year-width age groups were obtained from the Spanish National Institute for Statistics, which obtained its data from national death certificates that listed osteoporosis as the cause of death.

Statistical analysis

To identify changes in mortality rate trends, joinpoint regression was estimated for every age and sex group by use of the Joinpoint Regression Program, Version 4.5.0.1 (Statistical Research and Applications Branch, National Cancer Institute). In brief, by using mortality rates as inputs, this method identifies the year(s) when a trend change is produced, it calculates the annual percentage change (APC) in rates between trend-change points, and it also estimates the average annual percentage change (AAPC) in the whole period studied.

To estimate the APC, the following model is used:

$\log(Y_x) = b_0 + b_1 x$ where $\log(Y_x)$ is the natural log of the rate in year *x*.

Then, the APC from year *x* to year *x+1* is:

$$APC = \frac{e^{b_0 + b_1 (x+1)} - e^{b_0 + b_1 x}}{e^{b_0 + b_1 x}} \times 100 = \left(e^{b_1} - 1\right) \times 100$$

When there are no join points (i.e., no changes in trend), APC is constant so it equals the AAPC. Otherwise, the whole period is segmented by the points with trend change. Then, AAPC is estimated as a weighted average of the estimated APC in each segment by using the segment lengths as weights. For instance, in 50- to 54-year-old men, joinpoint regression identifies two join points in 2003 and 2008, so the whole period is segmented in three periods: 1999–2003, 2003–2008, and 2008-2015, with APC equal to – 0.014, - 0.025, and – 0.015, respectively, and segment widths equal to 4, 5 and 7 years, respectively. Then, AAPC is estimated as:

$$AAPC = \left[Exp\left(\frac{-4 \times 0.014 - 5 \times 0.025 - 7 \times 0.015}{4 + 5 + 7} \right) - 1 \right] \times 100 = -1.8\%$$

An approximate 95% confidence interval for AAPC is: ($AAPC_L$,$AAPC_U$) where

$AAPC_L = \left\{ \exp\left[\log(AAPC + 1) - 1.96\sqrt{w_x^2 \sigma_x^2} \right] - 1 \right\} \times 100$

$AAPC_U = \left\{ \exp\left[\log(AAPC + 1) + 1.96\sqrt{w_x^2 \sigma_x^2} \right] - 1 \right\} \times 100$

and σ_x^2 is the estimate of the variance of b_x obtained from the fit of the joinpoint

model.

To further explore changes in trends related to events linked to diagnoses or treatment of osteoporosis in our country we have developed a point regression analysis adding the following specific dates: (1) 1997-2003 release and implementation of the Guide of Diagnosis and Treatment of Osteoporosis (#reference), (2) 2003-2008 the period of the bisphosphonates and (3) 2008-2015 the period of the generic bisphosphonates and FRAX introduction.

RESULTS

RESULTS

General Trend in mortality

Figure 1 displays the decreasing trend of the age-adjusted mortality rates by gender (please note that the y-axis is in log scale), which is more pronounced in women. During the period under study, the highest osteoporosis mortality rate registered in Spain was in 1999, both in women and men (23.14/100.000 in women and 17.72/100 000 in men), decreasing around 38% in women and 33% in men at the end of the period (2015). Though women presented a greater globally rate decrease, these differences were declining along the period reducing by half the mortality rate difference between women and men in 2015 (from 5.62/10000 in 2000 to 2.54/100000 in 2015).

Trend in mortality by age and sex

In order to explore changes in mortality trend by age, a joinpoint regression analysis was performed for every age and sex group. Table 1 shows trends in mortality caused by osteoporosis in Spain by gender.

Globally, a slight descent in the annual average percent change (AAPC) was observed for all age groups in both men and women. In women, the AAPC increases with age, while the change in the trend pattern was less clear in men. We identified two age groups (75-79 and ≥ 85 years) presenting a globally significant decrease over the 15 years of study, though no joinpoint could be identified (Figure 2 A-2B). In addition, we highlight the decrease observed in the men's mortality rate, in the 60-64 years group (-5.1% 95% CI -8.9 to -1.2).

On the other hand, several age groups show changes in trends during the period under study. In women, significant trend changes were identified in three age groups: 50-54 years (Figure 2C), 80-84 years (Figure 2D) and 60-64 years. The more pronounced decline was identified in the older group at the 2004-2015 period (6.50% (95% CI -7.9 to -5.2)), whereas in the youngest the higher decrease (-3.2% 95% CI -5.2 to -1.1) was in 2005-2009 . Finally, in the 60-64 years group an opposite trend was observed: increasing the annual percentage change (APC) between 1999-2002 (+2.9 95% CI (+0.6-5.1)) and decreasing afterwards (-3.4 CI95% (-4.1, -2.7)). In men the only change in trend was identified in the 50-54 years group, in which the pattern observed was quite similar to that of the women (identifying the same three joinpoints): until 2005 mortality decreased by 1.4% approximately; reaching a 3.20% decrease between 2005 and 2009, and in a less pronounced manner (1.2%) from 2009 on.

Trend in mortality by age and sex in specific periods

To explore the influence of changes in treatment or diagnosis on mortality trends, we have estimated the average APC in three predefined (Table 2): the first one (1999-2003) presented only a 1.4% decrease both in women and men in the 50-54 years age group. Nevertheless, in the second period (2003-2008) the same age group presented a more pronounced decline in both genders compared with the previous period (- 2.5 95% CI -3.6 to -1.3 in women and - 2.5 % 95% CI -3.5 to -1.5 in men). In addition,

women in the 80-84 years age group showed the higher significant decline (-5.2% (95% CI -6.4 to 4.0)). Finally, between 2008-2015 (third period) in the 50-54 age group the decrease was of 1.3% in women and 1.5% in men, being worthy of mention the 6.5% decrease observed in women in the 80-84 years age group.

DISCUSSION

DISCUSSION

Despite the progress experimented both in diagnosis and treatment over the past two decades (15) mortality caused by osteoporosis in Spain shows only a slight decrease. This trend seems to be on one hand less than the expected one if we take into account Lyles et al. and Wu et al. studies (22)(23). However, a Swedish study(24)showed an annual increase of 1.5% in people older than 75 years. The low adherence to both osteoporotic treatment at the time of fracture occurrence and DXA testing (25) support our results. In addition, this mild impact could be related to the great variability observed in osteoporosis treatment among general practitioners, who prescribe medication to a high percentage of women without a high FRAX risk while keeping untreated those women with a high FRAX risk (26). The deepest decline observed was around 5% in specific age groups (75-79 years old women and 60-64 years old in men). In the same line, Azagra et al, studying hip fractures (the most important cause of mortality) found that in women aged between 75-79 years, the incidence rates fell significantly by 7.7% (27). In the same fashion, men in the 75-79 years old group presented a globally significant decrease that could be related to the recommendation of DXA in men from 70 years on (28). Furthermore, screening rates were higher among men older than 75 years (29).

By analyzing changes in mortality trends, our study identified several joinpoints in three different age groups: 50-54, 60-64 and 80-84 years old. The largest decline in incidence rates (APC: -6.5 CI95% (-7.9, -5.2)) was observed in women aged 80-84 years old in the 2004-2015 period. This trend is consistent with the decrease observed in osteoporosis diagnosis (from 73% to 69%) between 2002 and 2012 (30). In this period, oral bisphosphonate initiation shifted towards older women and those with prior fracture (31), which corresponds with the increasing focus on primary and secondary fracture prevention of patients at elevated fracture risk given by WHO´s FRAX introduction. In addition, this age group is likely to represent patients with polyfarmacy which is associated with better treatment adherence (32). On the other hand, the lack of significant changes in tendency observed in men could be related to the fact that men were less likely to receive osteoporosis treatment (8%) compared with women (23.3%) after a hip fracture, as observed in a study between 2000 and 2010 (33). Our results are consistent with a meta-analysis published by Bolland et al, which shows a 10% decrease of the mortality risk associated with osteoporosis treatment in older population (34). However, some ecological studies developed in our country have failed to show correlation between the increasing use of antiresoptive therapy and the incidence of femoral fracture (35)(36).

On the other hand, in the youngest group (50-54 years) the greatest decrease on incidence (-3.2) was observed in the 2005-2009 period, which could be related to the decline of the prescription of the hormone replacement therapy (17) (18) and the increasing use of bisphosphonates (19). On the contrary, in the period 2009-2015 a slow decrease of mortality rate was observed. We hypothesize that this changes in trends may be associated with the release of generic bisphosphonates (18)(37). Regarding this point, in February 2008 the brand alendronate patent expired and

generic alendronate became available; four years later (2012) ibandronate was marketed as generic (20). At the same time practice guidelines in the UK and elsewhere recommended that generic alendronate should be viewed as the first-line treatment dominating nowadays many European markets (38). Since the introduction of generic bisphosphonates, reports have consistently concluded that its adherence is poorer than with the original brand (39)(21)(40). This poor adherence could be related to the higher rates of gastro-intestinal intolerance (41), lower increase of lumbar spine and total hip bone mineral density (BMD) (42) (43). In addition, age group 50-64 years present high level of treatment and low prevalence of risk factors (44)(45) . In Spain, primary treatment has been associated with lower adherences than secondary treatment (32). Treatment adherence represents a common problem in the osteoporosis treatment (40) and it is responsible for an increased risk of fracture of approximately 30% (36) and increases the cost-effectiveness ratio of osteoporosis screening strategies (31).

Finally, the different trends observed by sex in the 60-64 years old group must be stressed. In men a sharp decline of mortality trends was detected through the whole period, while women showed a less pronounced decrease. This finding does not seem to be related to changes in bisphosphonates treatment , given that men were less likely to receive osteoporosis treatment after a hip fracture compared with women (33). However, the improvement of the evaluation and treatment of glucocorticoid-induced osteoporosis (the most common cause of secondary osteoporosis in men) could be related to this descendent trend (46)(47)(48). On the other hand, two significant joinpoints were detected in women between 60-64 years old, showing opposite trends: an increase of mortality rate at the early years (1999-2002) and a markedly subsequent decline (2002-2009). The initial increase was probably related to the fact that hormone therapy was the most usually prescribed treatment in postmenopausal women before 2001 (15), while the later decline could probably be due to the introduction of bisphosphonates treatment from 2002 despite the decline of the proportion of women under 65 years old meeting treatment criteria applying FRAX since 2008 (14).

Despite the high prevalence of osteoporosis in older population, its impact on mortality has been scarcely studied. To the best of our knowledge, this is the first study evaluating trends on mortality caused by osteoporosis developed in Spain. However, our study has also some limitation. Firstly, Joinpoint regression consists in an ecological study, as a consequence of which causal relationship cannot be solved and our results require further confirmation at individual level. Secondly, databases of the Spanish National Institute of Statistics do not provide osteoporosis classification data so we are not able to determine which data corresponds to primary osteoporosis or secondary one. Thirdly, the scarce number of studies focused on osteoporosis mortality makes it difficult to compare our results and force us to contrast them with studies focused on osteoporotic fractures. However, we consider osteoporotic fractures an acceptable proxy to mortality because it has been demonstrated that general fractures, and especially hip fractures, are related to reducing personal autonomy through disability and dependence (49), influencing the quality of life (50)(51) and even mortality (52)(53).

In conclusion, osteoporosis mortality in Spain decreases faster in the older age cohorts especially in women. Several factors are to be taken into account to explain our results. Further observational studies to confirm our hypothesis are needed.

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TABLES AND FIGURES

TABLES AND FIGURES

Table 1. Trends in mortality caused by Osteoporosis in Spanish women and men: Year of change of trend, annual percentage change, and annual average percentage change

	Women		Men	
Age group, yrs	Period	APC (95% CI)	Period	APC (95%CI)
50-54	1999-2015	**-1.7 (-2.3 ,-1.1)***	1999-2015	**-1.8 (-2.3 ,-1.3)***
	1999-2005	**- 1.4 (-2.1,-0.7)**	1999-2005	**-1.4 (-2.1, -0.8)**
	2005-2009	**- 3.2 (-5.2,-1.1)**	2005-2009	**- 3.2 (-5, -1.3)**
	2009-2015	**- 1.0 (-1.8,-0.3)**	2009-2015	**- 1.2 (-1.8, -0.5)**
55-59	1999-2015	+1.2 (-3.5,+6.2)*	1999-2015	- 1.5 (-3.8, +1.0)*
60-64	1999-2015	**- 0.8 (-1.3, -0.3)***	1999-2015	-**5.1 (-8.9, -1.2)***
	1999-2002	**+2.9 (+0.6, +5.1)**	1999-2002	
	2002-2009	**-3.4 (-4.1, -2.7)**	2002-2009	
	2009-2015	+0.4 (-0.3, +1.2)	2009-2015	
65-69	1999-2015	-2.5 (-7.7, +3.1) *	1999-2015	+0.5 (-5.5, +6.9)*
70-74	1999-2015	-4.8 (-10.8,+1.6)*	1999-2015	- 0.4 (-4.3, +3.6)*
75-79	1999-2015	**-4.7 (-5.7, -3.7)***	1999-2015	**- 4.2 (-5.2, -3.1)***
80-84	1999-2015	**-4.4 (- 5.9, - 3.0)***	1999-2015	-2,4 (-6.5, +1,8)*
	1999-2004	+0.4 (-4.0, +5.0)	1999-2007	+0.1 (-3.4, 3.6)
	2004-2015	**-6.5 (-7.9, -5.2)**	2007-2011	- 13 (-25.7, +1.8)
			2011-2015	+4.0 (-5.7, +14.7)
85 +	1999-2015	**-3.4 (-4.2, -2.7)***	1999-2015	**- 2.90 (-3.8, -2.0)***

APC = annual percent change; CI = 95% confidence interval.

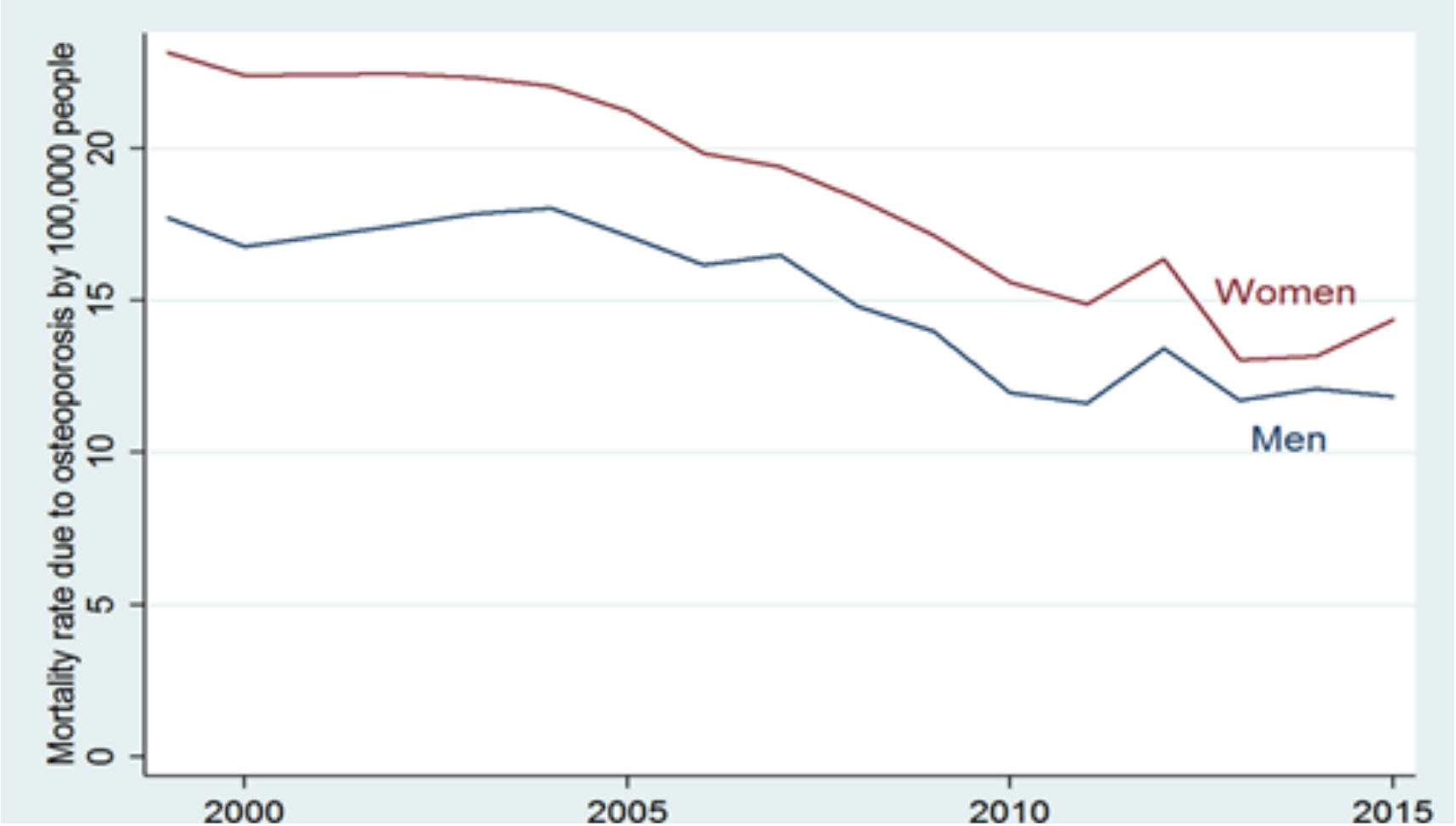
*AAPC = annual average percent change; CI = 95% confidence interval.

Table 2. Trends in mortality with predesigned joinpoint caused by Osteoporosis in Spanish women and men.

		Women		Men
Age group, yrs	Period	AAPC (CI)	Period	AAPC (CI)
50-54	1999-2003	**-1.4 (-2.1, -0.7)**	1999-2003	**-1.4 (-2.1, -0.8)**
	2003-2008	**-2.5 (-3.6, -1.3)**	2003-2008	**-2.5 (-3.5, -1.5)**
	2008-2015	**-1.3 (-1.9, -0.7)**	2008-2015	**-1.5 (-2.0, -0.9)**
60-64	1999-2003	+1.2 (- 0.2, +2,7)		
	2003-2008	**- 3.4 (- 4.1, -2.7)**		
	2008-2015	- 0.1 (- 0.7, +0.4)		
80-84	1999-2003	+0.4 (-4.0, +5.0)	1999-2003	+0,1 (-3.4, +3.6)
	2003-2008	**-5.2 (-6.4, -4.0)**	2003-2008	-2,7 (-6.2, +0.9)
	2008-2015	**-6.5 (-7.9, -5.2)**	2008-2015	-3,7 (-10.7, +3.9)

AAPC = annual average percent change; CI = 95% confidence interval.

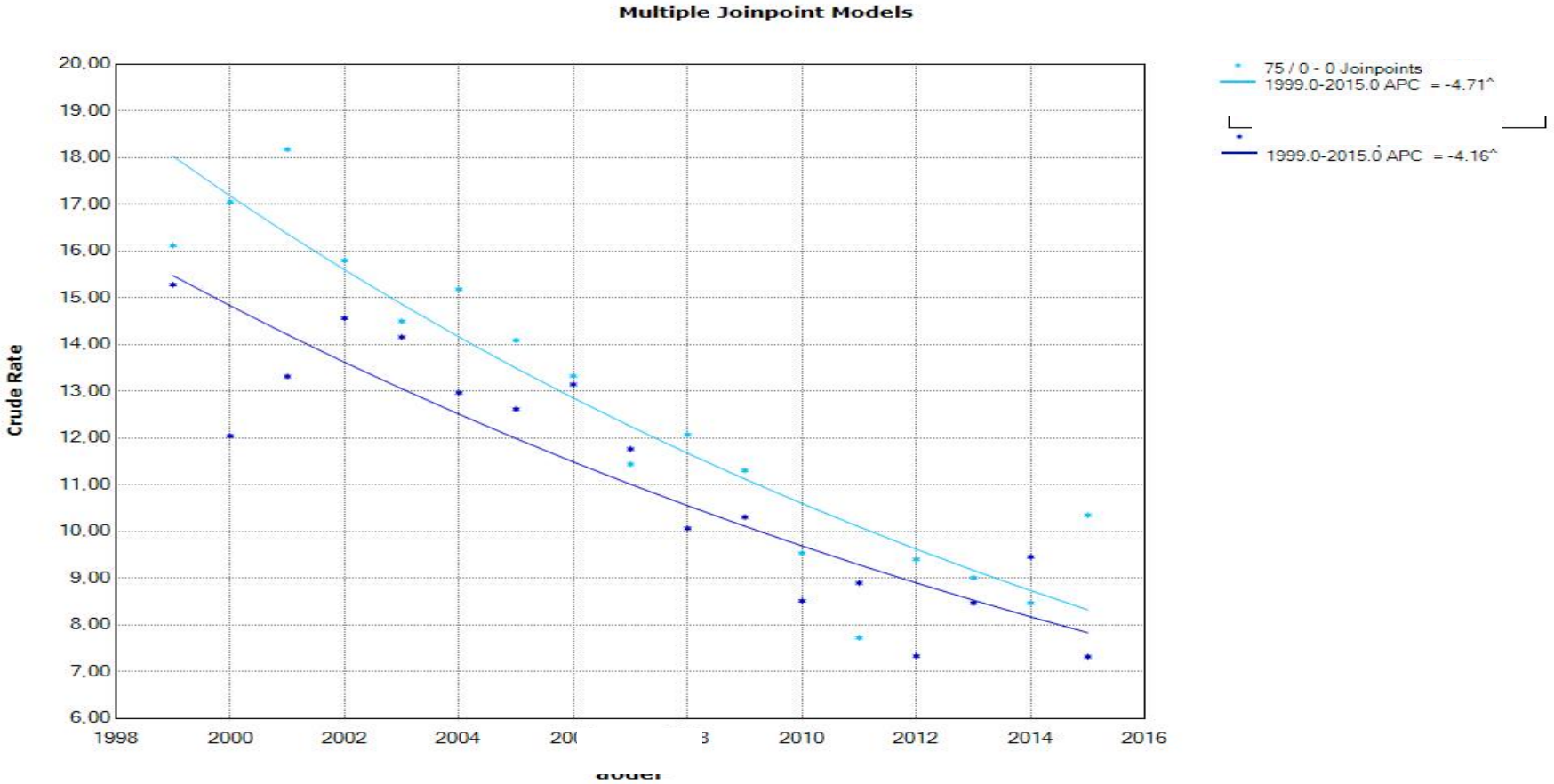
Figure 1 Age-adjusted mortality caused by Osteoporosis in Spain, 2000–2015; women (red line) and men (blue line)



Women 75-79 years

Men 75-79 years

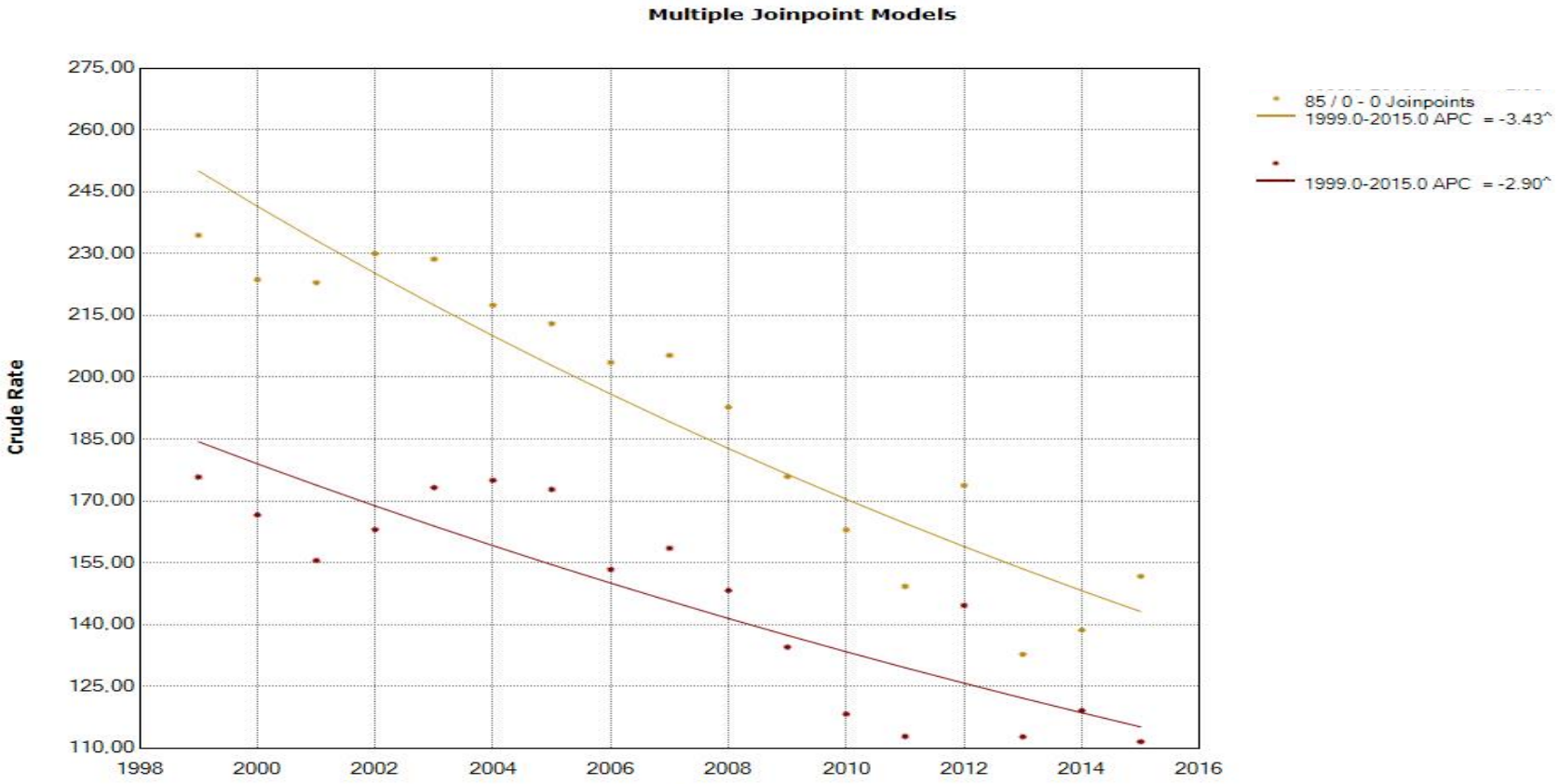
Figure 2 A Mortality caused by osteoporosis in Spanish people older than 75-79 years



Women +84 years

Men +84 years

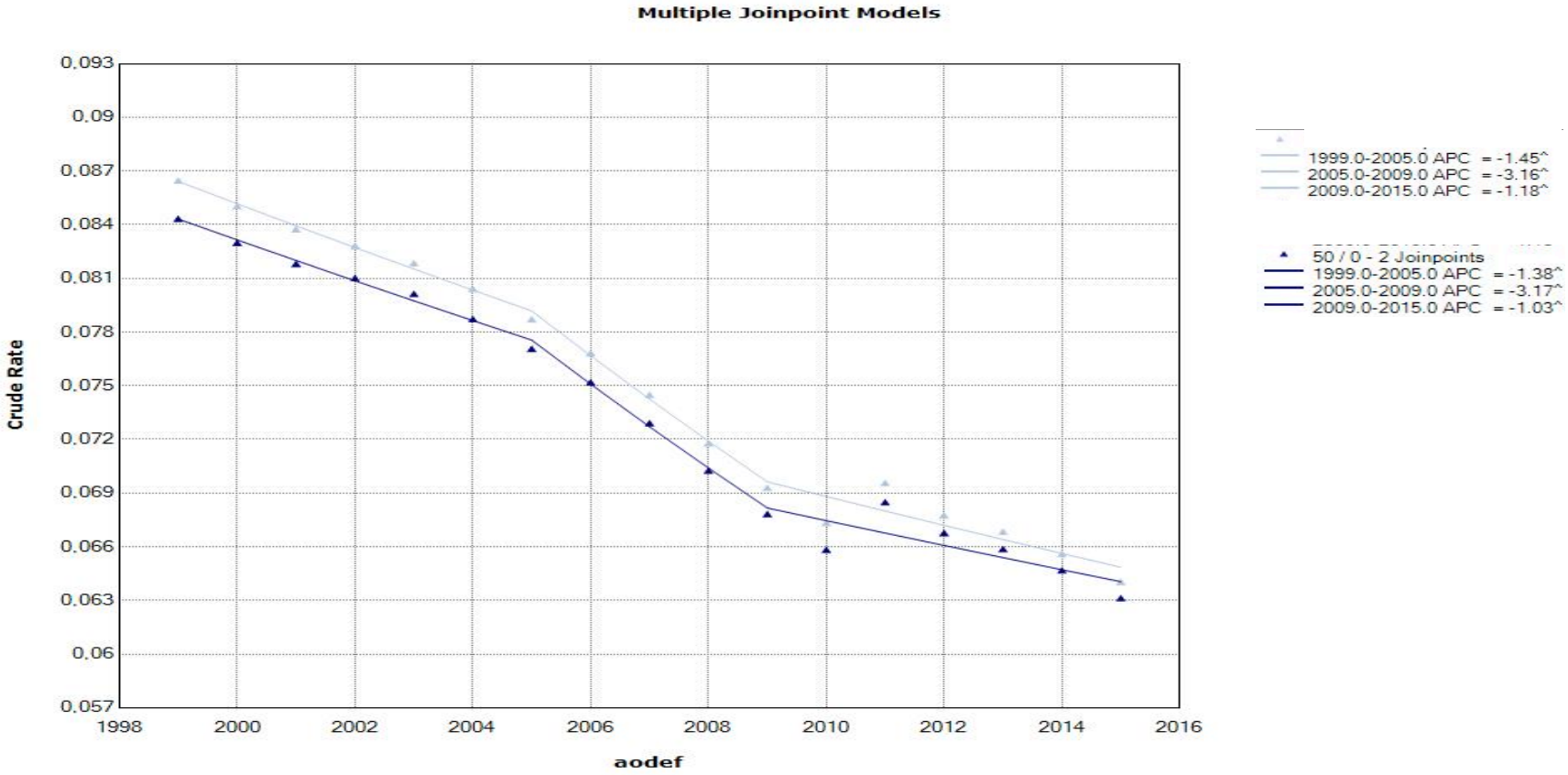
Figure 2 B. Mortality caused by osteoporosis in Spanish people older than 84 years



Men 50-54 years

Figure 2 C. Mortality caused by osteoporosis in Spanish people older than 50-54 years

Women 50-54 years



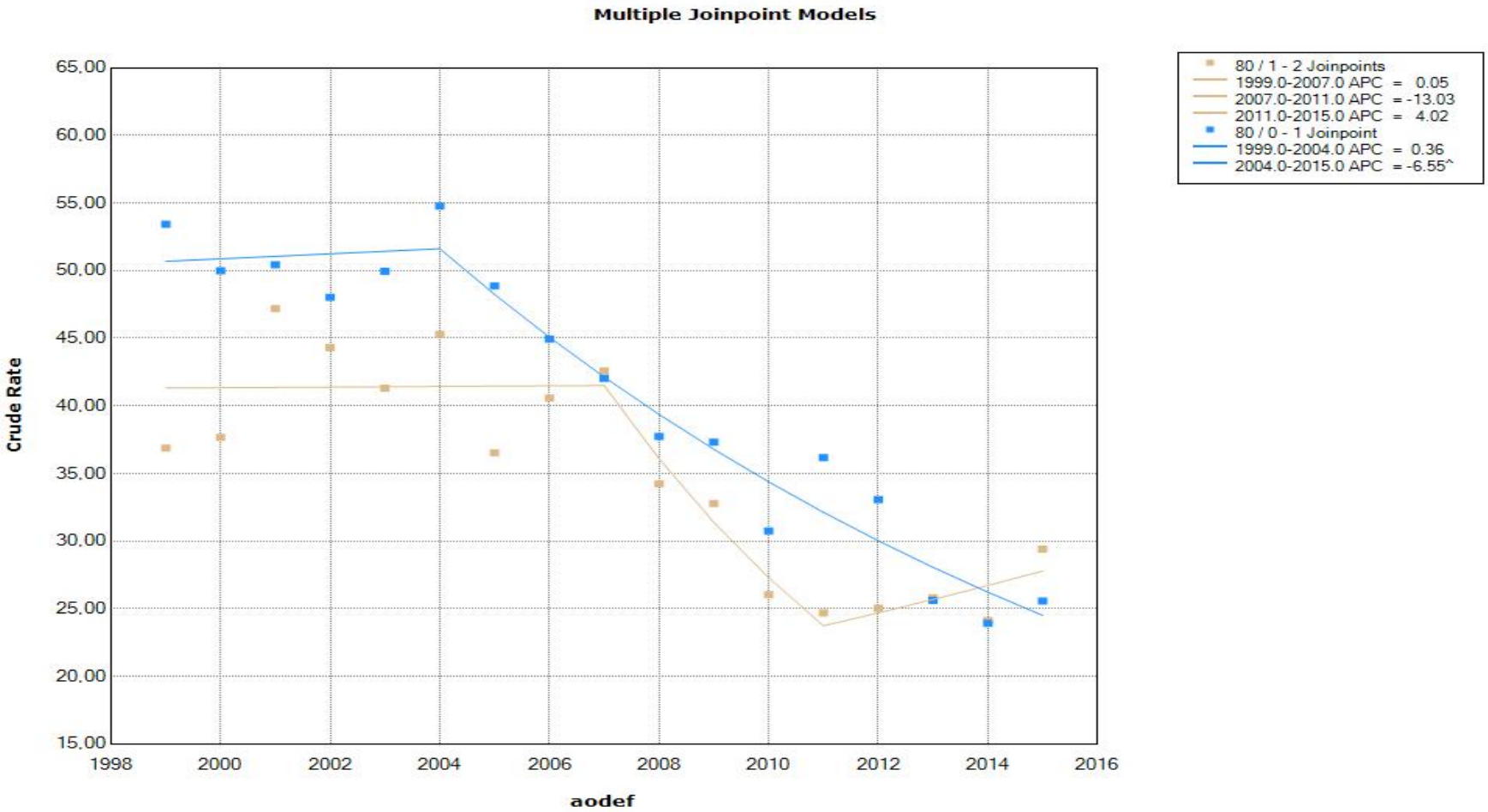
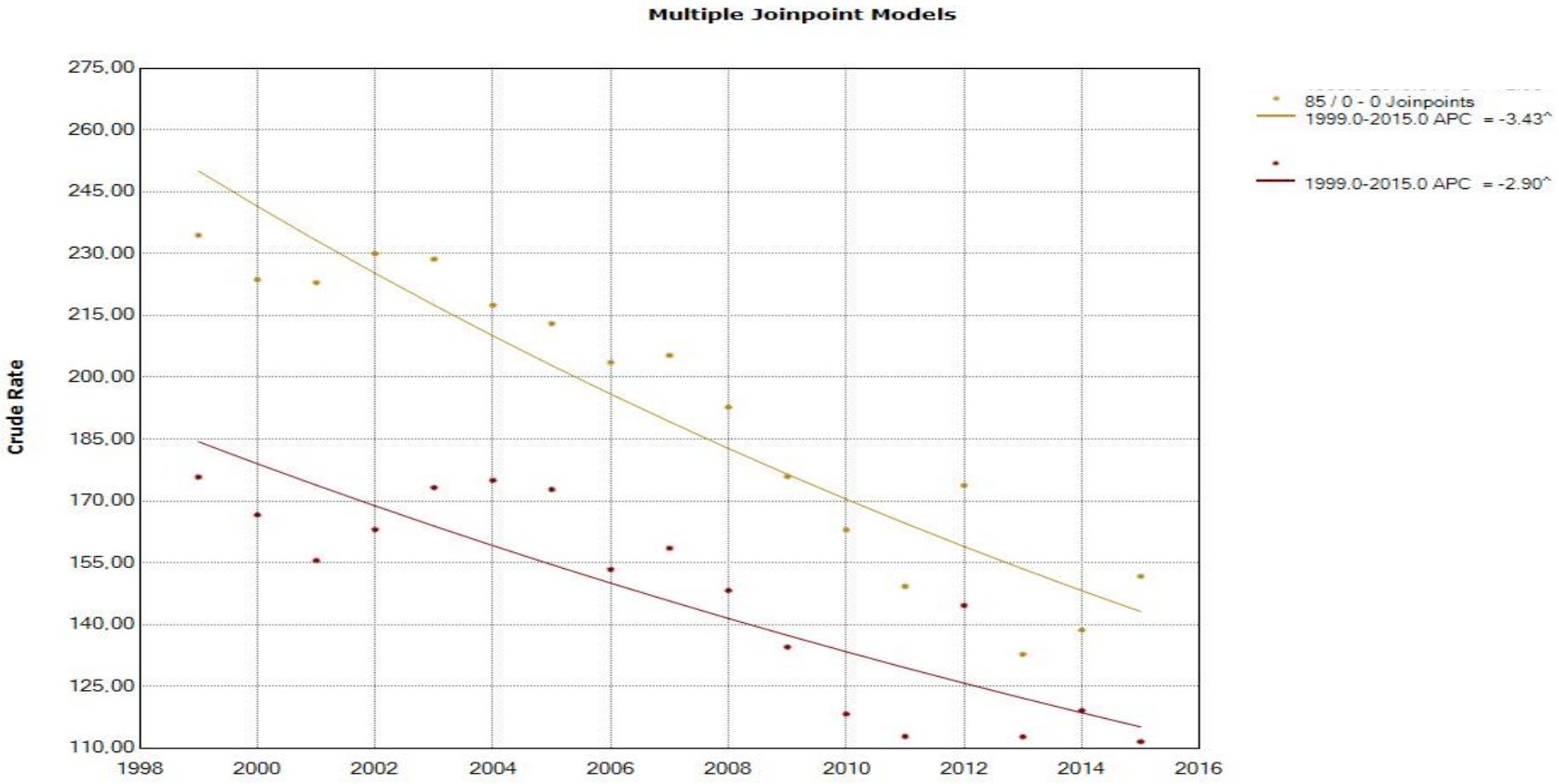


Figure 2 D. Mortality caused by osteoporosis in Spanish people older than 80-84 years

Women +84 years

Men +84 years

Figure 2: E. Mortality caused by osteoporosis in Spanish people older than 84 years



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