

Regional variability in population acute myocardial infarction cumulative incidence and mortality rates in Spain 1997 and 1998

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Abstract

Background: Myocardial infarction (MI) incidence and mortality display a high geographic variation. **Aims:** The objective of the present study was to analyze MI mortality, cumulative incidence rate variability in seven regions of Spain from 1997 to 1998. **Methods and Results:** Standardized methods were used to identify, find, register, and classify MI cases that were classified as *definite*, *possible*, *insufficient-data*MI, and *non-MI*. The total population of the seven monitored regions was 7,364,682 inhabitants. Of the 11,256 cases fulfilling eligibility criteria to investigate, 10,660 were selected to calculate MI rates: 6554 (61.5%) *non-fatal definite* MI, 1179 (11.1%) *fatal definite* MI, 1859 (17.4%) *fatal possible* MI, 1068 (10.0%) *fatal* cases with *insufficient data*. The IBERICA 25–74 years age-standardized cumulative incidence rates for men and women, were 207 (range: 175–252) and 45 (range: 36–65) per 100,000, respectively. The age-standardized mortality rates for men and women, were 73 (range: 62–94) and 20 (range: 13–29) per 100,000, respectively. Age-standardized case-fatality was 31.4 and 24.2% in men aged 25–74 and 35–64 years, respectively, and 32.7 and 27.0%, respectively, in women. **Conclusions:** MI cumulative incidence and mortality rates are low compared with other industrialized countries but, vary considerably among regions in a Mediterranean country like Spain.

Key words

Coronary disease, Cumulative incidence rate, Mortality rate, Myocardial infarction, Registry

Introduction

Although, coronary heart disease (CHD) mortality rates appear to have decreased and stabilized in the last 30 years in Spain [1, 2], CHD is expected to continue to be the leading cause of death in Spain, as in other industrialized countries, in the next two decades [3]. However, low event rates are observed in Spain as compared with other industrialized countries [4, 5].

There are some studies showing a considerable differences of MI event rates among countries [6, 7], which arises interesting issues on the determinants of such a variability, taking into account that the low incidence rates in southern Europe Mediterranean countries contrasts with the high cardiovascular risk factor prevalence observed [8–14]. MI incidence data were scarce in Spain owing to the difficulty of recording out-of-hospital fatal MI cases, and the only population data came from two neighboring areas in the north-eastern part of the country [4, 5].

The objective of the present study was to determine and compare MI event rates in a prospective population registry in seven Spanish regions in 1997–1998.

Methods

The Investigación Búsqueda Específica y Registro de Isquemia Coronaria Aguda (IBERICA) study was designed to prospectively monitor and compare the MI cumulative incidence and mortality rates and 28-day case-fatality observed in seven regions of Spain (i.e. Castilla-La Mancha, Gerona, Majorca, Murcia, Navarra, Basque Country and Valencia) among residents aged 25–74, in 1997 and 1998.

Identical methods have been used in all areas to detect MI events, and to record demographic and clinical characteristics, and complications including death occurred within 28 days of onset of symptoms.

Subjects

The study was designed as a population registry of patients aged 25–74 years with a MI in the seven regions of the IBERICA study. The reference population of the participating areas included in average 3,638,940 men and 3,725,742 women according to official projections for the 1997–1998 period [15]. There were 99 hospitals of all levels operating in these areas.

Case-finding procedures and sources

Case-finding procedures for hospitalized patients included: (1) A “hot pursuit” during admission was used in all hospitals with a reference coronary care or intensive care unit (CCU); (2) to identify patients not admitted to a CCU, all medical records of patients with a discharge diagnosis code 410–414 of the international classification of diseases 9th revision (ICD-9) were reviewed in all hospitals of the area (“cold pursuit”); (3) the medical records of those patients with the diagnosis ICD-9 410–414 in emergency room of all hospitals were also reviewed by cold pursuit; and (4) the records of secondary medically attended transportation were also screened to identify possible MI cases referred to medical centers out of the area.

To identify out-of-hospital MI fatal cases all the death certificates containing suggestive ICD-9 410–414 codes were investigated by reviewing medical records, interviewing physicians who signed the selected death certificate or assigned general practitioner, and relatives or witnesses when deemed necessary by using a standardized questionnaire.

Event classification

Each event was classified according to the MONICA algorithm [16], which takes into account the type of symptoms, electrocardiographic (ECG) findings, cardiac enzyme values, and history of ischaemic heart disease and necropsy interpretation in fatal cases. Each event was classified into one of the following diagnostic categories:

- (a) Non-fatal *Definite* MI patients with serial ECGs showing either: (1) progression from no Q wave to Q wave, or (2) ST-segment depression, developing ST segment elevation or progressive T-wave inversion, or (3) persistent ST-segment elevation with progressive T-wave inversion, or (4) patients with other ECG characteristics and cardiac enzyme levels at least twice the normal limit (creatin-phosphokinase, and creatin-phosphokinase-MB fraction), either with typical symptoms (chest pain lasting at least 20 min which cannot be definitely attributable to non-coronary heart disease pathologies) or non-typical symptoms. ECG findings were analyzed by trained medical, but non-cardiologist, investigators using standardized criteria.
- (b) Fatal *Definite* MI if they satisfied non-fatal *definite* criteria or if autopsy showed recent myocardial infarction or coronary thrombosis.
- (c) Non-fatal *Possible* MI events with typical symptoms although without the electrocardiographic or enzymatic criteria to be defined as definite MI, but no other definite cause of death.
- (d) Fatal *Possible* MI involved suggestive terminal symptoms, or a CHD history in the absence of an autopsy, or autopsy findings of chronic occlusive CHD or old infarction but no other pathological finding suggestive of a fatal disease.
- (e) Fatal *Insufficient* data events was used when a patient had no record of suggestive symptoms, or previous CHD, or an autopsy, and were therefore unclassifiable.
- (f) *No myocardial infarction or coronary death* when another cause of death was implied by the clinical history or at autopsy. Also 28-day cardiac arrest survivors from CHD without criteria to be defined as definite or possible, were included in this category.

Rates for *fatal* and *non-fatal definite* and *fatal possible* MI are presented alone and together with *insufficient-data fatal cases*.

Quality control

All field investigators were trained together in a 2-day course before starting the study. Agreement in case classification among them was assessed by a set of cases that had to be independently categorized and included some duplicate cases. All investigators had to reach an intraindividual agreement and an agreement with the standard classification provided by the coordinating center (i.e. Multiple Kappa statistics value ≥ 0.94) to obtain proper accreditation.

Moreover, all registered events were blindly reclassified into one of the above-mentioned categories in the coordinating center, and all discrepancies were discussed with field and local investigators until a consensus category was reached.

The number of the investigated deaths in the study was also compared with the number of coronary heart disease deaths in official statistics of each area. The study-to-official rate (i.e. coverage) was calculated [17]. Results ranged from 0.95 to 1.23, but all except one had values >1 . Data were entered in an ad hoc computer program which automatically warned against out-of-range values and checked internal consistency of individual information.

Statistical analysis

Rates were standardized by age using the world standard population weights for the 25–74 and 35–64 age intervals [16]: 25–34 (14/50), 35–44 (12/50), 45–54 (11/50), 55–64 (8/50), 65–74 (5/50) in order to facilitate comparability with other registers. Case fatality at 28 days was standardized by age for the 35–64 age interval using the MONICA data center weights: 35–44 (1/11), 45–54 (3/11) and 55–64 (7/11). For the 25–74 age interval the following weights were used: 25–34 (1/100); 35–44 (7/100); 45–54 (16/100); 55–64 (26/100); 65–74 (50/100).

Aggregated data for 1997–1998 are presented in tables and figures broken down by area, decades of age, and sex. Crude and age-standardized cumulative incidence and mortality rates are presented per 100,000 inhabitants. The study includes 1997–1998 data for all centers excepted Valencia which includes only 1998 data. Standardized rates are presented with 95% confidence intervals calculated according to the normal approximation of the Poisson distribution. Standardized mortality and cumulative incidence ratios with 95% confidence intervals were used to compare each participant region event rate with the IBERICA average in the 25–74 years population.

Results

Between 1997 and 1998, 11,256 cases fulfilling eligibility criteria were investigated. The distribution by diagnostic category and sex is shown in Table 1. Rates were calculated using 10,660 cases (8412 men, 2248 women) with non-fatal and fatal *definite* MI, fatal *possible* MI, and fatal cases with *insufficient data*. The proportion of *insufficient data* cases in all regions was in average 10.0% of total cases, and 26.0% of fatal cases.

Table 1. Distribution of investigated and included cases by diagnostic categories and sex. Aggregated data from 1997 to 1998 in the IBERICA Study (Spain). Age groups 25–74 years

Diagnostic categories	Investigated cases		Investigated fatal cases		Included cases	
	Men N (%)	Women N (%)	Men N (%)	Women N (%)	Men N (%)	Women N (%)
<i>Definite</i> MI	6195 (55.0)	1538 (13.7)	893 (20.6)	286 (6.6)	6195 (58.1)	1538 (14.4)
Possible MI	1638 (14.6)	463 (4.1)	1454 (33.6)	405 (9.4)	1454 (13.6)	405 (3.8)
Insufficient data	767 (6.8)	307 (2.7)	763 (17.6)	305 (7.1)	763 (7.2)	305 (2.9)
Not an MI ^a	263 (2.3)	85 (0.7)	162 (3.7)	58 (1.3)	—	—
Total	8863 (78.7)	2393 (21.3)	3272 (75.6)	1054 (24.4)	8412 (78.9)	2248 (21.1)

MI: Myocardial infarction.

^a After investigating the medical records and interviewing the physician who signed the death certificate and/or the patient relatives

The 1997–1998 crude and age-standardized cumulative incidence and mortality annual rates per 100,000 inhabitants by age groups, for all *definite* and fatal *possible* MI, and with the fatal *insufficient data* category added are presented in Tables 2 and 3, for men and women, respectively. Age-standardized cumulative incidence, for the 35–64 and 25–74 years population, were 206 and 207 in men, and 32 and 45 in women, respectively (Tables 2 and 3). Rates increased smoothly with age in men, while a sharp increase appeared in women after the age of 55. Age-adjusted cumulative incidence rates for the 25–74 years population are presented by sex and region in Figure 1. Two regions had a standardized incidence rates significantly over the average, and three regions had rates under the average in men. One was over and two under the IBERICA average in women (Figure 1).

Table 2. Myocardial infarction cumulative incidence and mortality rates per 100,000 men by age and diagnostic categories. Aggregated data from 1997 to 1998 in the seven regions of the IBERICA Study (Spain)

Age	Population	NF1+F1+F2 Annual rate per 100,000 inhabitants		NF1+F1+F2+F9 Annual rate per 100,000 inhabitants	
		Cumulative incidence (N=7649)	Mortality (N=2347)	Cumulative incidence (N=8412)	Mortality (N=3110)
25–34	986,992	9	2	9	2
35–44	851,083	66	14	70	18
45–54	710,668	201	39	215	53
55–64	581,897	365	102	398	135
65–74	508,300	678	264	762	348
25–74 ^a	3,638,940	210	64	231	85
25–74 ^b	3,638,940	189 (184–193)	55 (53–57)	207 (202–211)	73 (70–76)
35–64 ^b	2,143,648	191 (185–197)	46 (43–48)	206 (200–212)	61 (57–64)

F1: NF1: Fatal and non-fatal *definite* myocardial infarction.

F2: Fatal *possible* myocardial infarction.

F9: Fatal *insufficient data*.

^a Crude rate.

^b Age-standardized rate using world population weights. Rate (95% confidence interval).

N: Number of cases

Table 3. Myocardial infarction cumulative incidence and mortality rates per 100,000 women by age and diagnostic categories. Aggregated data from 1997 to 1998 in the seven regions of the IBERICA Study (Spain)

Age	Population	NF1+F1+F2 Annual rate per 100,000 inhabitants		NF1+F1+F2+F9 Annual rate per 100,000 inhabitants	
		Cumulative incidence N=1943	Mortality N=691	Cumulative incidence N=2248	Mortality N=996
25–34	958,214	1	0	1	0
35–44	846,396	7	1	8	2
45–54	709,940	19	4	22	6
55–64	612,337	74	25	84	35
65–74	598,855	215	84	251	120
25–74 ^a	3,725,742	52	19	60	27
25–74 ^b	3,725,742	39 (38–41)	13 (12–15)	45 (44–47)	20 (18–21)
35–64 ^b	2,168,673	28 (26–31)	8 (7–9)	32 (30–35)	12 (11–13)

F1: NF1: Fatal and non-fatal *definite* myocardial infarction.

F2: Fatal *possible* myocardial infarction.

F9: Fatal *insufficient data*.

^a Crude rate.

^b Age-standardized rate using world population weights. Rate (95% confidence interval).

N: Number of cases

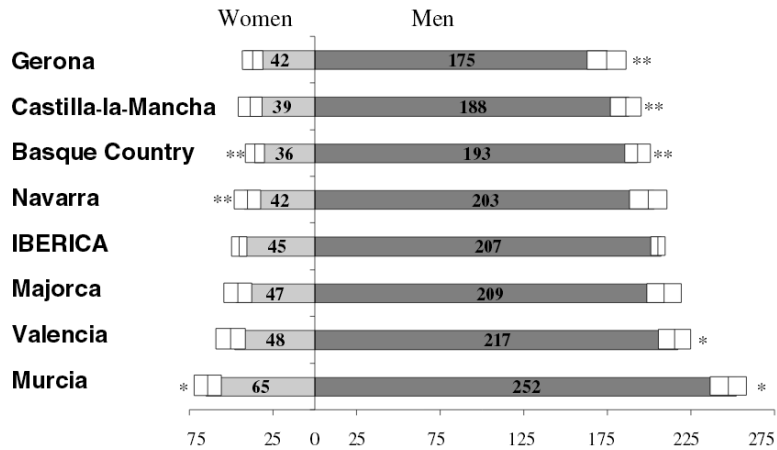


Figure 1. Myocardial infarction age-standardized cumulative incidence annual rate per 100,000 inhabitants in seven regions of Spain, 1997–1998, in patients aged 25–74 in the IBERICA Study. Fatal and non-fatal *definite*, fatal *possible* and fatal *insufficient data* myocardial infarction cases alone are presented. * Standardized cumulative incidence rate significantly higher than the IBERICA average. ** Standardized cumulative incidence ratio significantly lower than the IBERICA average. □□95% Confidence interval.

Age-standardized mortality annual rates per 100,000 inhabitants for the 25–74 years population were 73 and 20 in men and women, respectively, and are presented by age groups, for all *definite* and fatal *possible* MI alone, and with the fatal *insufficient data* category in Tables 2 and 3. Age-standardized mortality rates for the 25–74 years population are presented by sex and region in Figure 2. Two regions had standardized mortality ratios significantly over the IBERICA average, and four regions had ratios under the average in men (Figure 2). These figures were two and one, respectively in women.

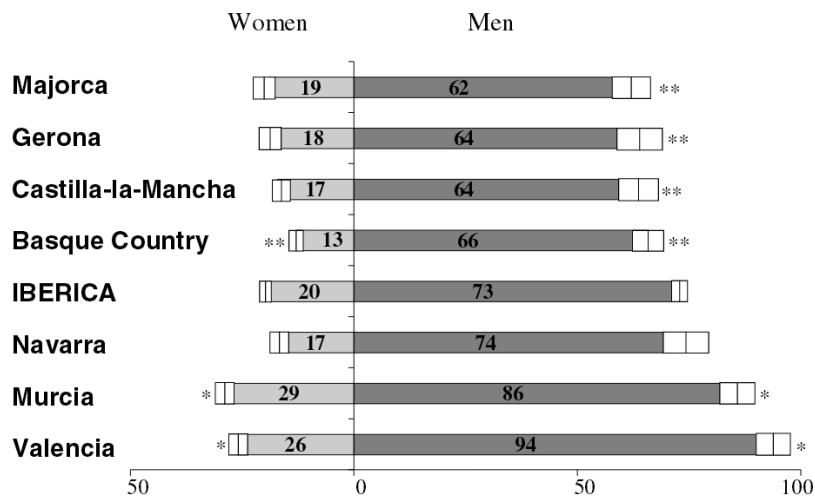


Figure 2. Myocardial infarction age-standardized mortality annual rate per 100,000 inhabitants in seven regions of Spain, 1997–1998, in patients aged 25–74 in the IBERICA Study. Fatal and non-fatal *definite*, fatal *possible* and fatal *insufficient data* myocardial infarction cases alone are presented. * Standardized mortality rate significantly higher than the IBERICA average. ** Standardized mortality ratio significantly lower than the IBERICA average. □□95% Confidence interval

The number of autopsies was 633 (19.0% of all fatal cases). Crude case-fatality was 30.7% (2347/7649) in men aged 25–74 years and 35.6% (691/1943) in women for all *definite* and fatal *possible* MI. With the fatal *insufficient data* category added the figures were 37.0 and 41.4%, respectively. Age-standardized case-fatality was 31.4 and 24.2% in men aged 25–74 and 35–64 years, respectively, and 32.7 and 27.0%, respectively, in women. These figures increased to 37.7 and 29.7%, and to 44.2 and 35.6%, respectively, the fatal *insufficient data* category was added.

Discussion

The present study shows the seven regions of Spain analyzed to be areas with low MI cumulative incidence and mortality rates close to those of other southern Europe Mediterranean countries, and much lower than the average WHO-MONICA study (see a comparison of selected world regions in Figure 3). This fact is noteworthy, since cardiovascular risk factors prevalence in Spain is relatively high [11–14]. The possible explanations for this apparent paradox may be related to differing environmental factors (i.e. physical activity and antioxidant-rich diet) and their interaction with genetic characteristics of the population [10]. Nonetheless, the proportion of mortality due to ischaemic heart disease was 12.1% in men (the main individual cause of death) and 10.2% in women (third individual cause of death), in Spain in 1997–1998 [1]. Ischaemic heart diseases will have claimed more than 39,000 lives in year 2002 in Spain [18].

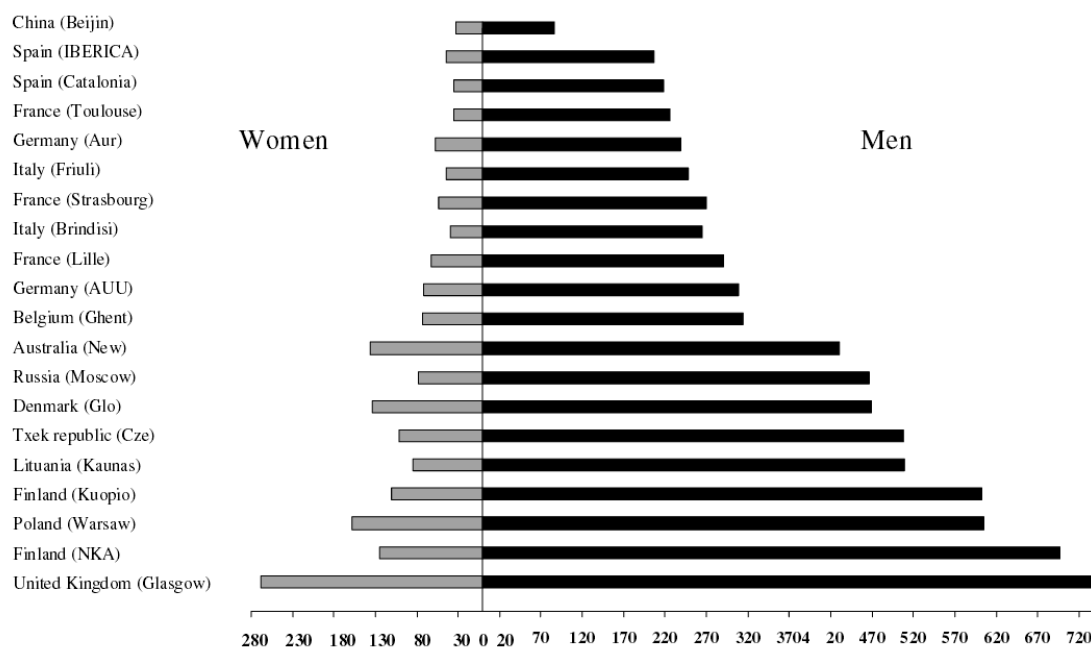


Figure 3. Age-standardized cumulative annual event rate by sex including fatal and non-fatal *definite*, fatal *possible* and fatal *insufficient data* myocardial infarction cases in a selection of regions participating in the WHO-MONICA study (aggregated data from 1984 to 1995) and in the seven regions of the IBERICA Study, Spain (aggregated data from 1997 to 1998). Based on reference number 4

The large variability in MI event rates within a low MI incidence area indicate that whatever the environmental risk (and protective) factors and their interaction with genetic characteristics vary at many levels, which provides interesting opportunities for investigating which factors may play a role in protecting population from coronary heart diseases. In particular, the effect of high levels of cholesterol may not have the same 25-year cardiovascular risk implications in Mediterranean countries of southern Europe as in the United States and central or northern Europe [19]. There are data indicating that cholesterol levels may have been high for as long as 25 years in Spain without producing the expected increase in the number of coronary events [20]. The modulation of cholesterol levels may be sensitive to

other diet factors such as antioxidants, and to life-style characteristics such as physical activity which are frequent in Spain, and may counteract the effect of the high prevalence of cardiovascular risk factors [10].

Population 28-day case fatality was higher not only than that described in MI clinical trials (due to non-inclusion of patients who die before reaching hospital in the latter), but also than that of hospitalized MI patients [15]. Furthermore, our registry showed that 28-day case-fatality increased approximately by 25% when the 65–74 years decade was considered. Out-of-hospital deaths constitute more than two thirds of the 28-day overall case-fatality.

In our study, the age range was 25–74 years although the usual range in many studies is 35–64 years [21]. At least seven MONICA centers widened their registries to cover this range [5, 22, 23]. Comparability with other registries is, however, ensured by appropriate standardization of age groups 35–64 years.

Study characteristics

One limitation, shared by all MI registries, arises when a MI patient fails to contact at least one of the sources of information periodically checked [10]. This is unlikely to occur [7]. Other limitations of this type of registries regard missing silent MI cases and failure to identify MI misdiagnosed as other pathologies. The frequency of the former has been estimated to be around 30% of all MI occurred in the Framingham cohort [24]. The latter was assessed in an analysis of 395 death certificates investigated in one of the participant areas [25]. It was concluded that investigating death certificates with 410–414 ICD 9th revision codes provided a specific criterion which failed to identify only 0.3% of definite and 3% of possible cases as compared with an extended revision of death certificates with other codes (i.e. diabetes mellitus, heart failure, hypertensive heart disease, hypertension and arrhythmia). In our study ECG was not coded with Minnesota code owing to the complexity of obtaining satisfactory standardization: thus, specially trained non-cardiologist physicians assessed ECGs.

Results have been presented in two groups of MI categories: fatal and non-fatal *definite* and fatal *possible*, and these categories plus dead patients with *insufficient data*. Figures obtained by the latter represent the most adverse situation if all *insufficient data* cases were in fact MI patients [25]. Only 3–6% of such episodes are given a diagnosis other than MI when evaluated at necropsy [14]. On the other hand, the low number of autopsies (19.0% of all fatal cases) led to a greater proportion of *possible* MI cases. Fatal cases classified as *insufficient data* in the MONICA project represented 22.9% of the whole [4], a figure similar to ours (23.6%). The MONICA *possible* category in the present study was counted when assigned to fatal cases only. The 242 cases of non-fatal *possible* events in our study correspond to a clinical diagnosis of non-Q-wave MI or unstable angina cases in whom incomplete or non-specific cardiac enzyme curves were found along with a *probable* or *ischaemic* ECG. These patients were in consequence not included in the analysis. There is a high variability in the proportion of patients with non-Q wave MI in clinical series which is likely to be related to the fuzzy limit between non-Q wave MI and unstable angina. Neither these, nor other MONICA non-fatal *possible* cases were included in rate calculation since the vast majority of the latter usually correspond to unstable or other forms of angina patients and their inclusion would produce a difficult-to-interpret overestimation of rates. In fact, the inclusion of this category yields increases in rates that vary greatly among areas [7, 26]. Other more sensitive categorization strategies derived from WHO-MONICA algorithm [27] yield higher rates but it is likely that specificity then drops owing to inclusion of a number of unstable angina patients as MI.

Another important characteristic of the study is that we used the classical definition of MI according to the MONICA algorithm [16] since the new MI definition was not published at the time the study was carried out [28].

Conclusion

Our results confirm that cumulative incidence and mortality rates from MI in Spain are among the lowest in the industrialized world, although there is a substantial variability in event rates among regions in Spain: regions with the highest rates have approximately 50% higher rates than the regions with the lowest rates.

Key messages

- The myocardial infarction rates in Spain are among the lowest of the industrialized world,
- there is a substantial variability in event rates among regions,
- the variability among Spanish regions is lower than that found in international comparisons.

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Appendix 1

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