Trends in mortality related to pulmonary embolism in the European Region, 2000–15: analysis of vital registration data from the WHO Mortality Database

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Summary

Background European estimates of the burden imposed by pulmonary embolism are not available to this date. We aimed to assess pulmonary embolism-related mortality and time trends in the WHO European Region.

Methods We analysed vital registration data from the WHO Mortality Database (2000–15) covering subregions of the WHO European Region: Eastern Europe, Northern Europe, Southern Europe, Western Europe, and Central Asia. Deaths were considered pulmonary embolism-related if International Classification of Disease-10 code for acute pulmonary embolism (I26) or any code for deep or superficial vein thrombosis was listed as the primary cause of death. We used locally estimated scatterplot smoothing weighted by size of the Member State population to calculate proportionate mortality and time trends in age-standardised mortality.

Findings In the 3-year period between 2013 and 2015, an average of 38 929 pulmonary embolism-related deaths occurred annually in the 41 Member States with available data and a population of 650 950 921; among individuals aged 15–55 years, pulmonary embolism accounted for 8–13 per 1000 deaths in women and 2–7 per 1000 deaths in men. Between 2000 and 2015, age-standardised annual pulmonary embolism-related mortality rates decreased linearly from 12·8 (95% CI 11·4–14·2) to 6·5 (5·3–7·7) deaths per 100 000 population without substantial sex-specific differences.

Interpretation The observed decreasing trends in pulmonary embolism-related mortality might reflect improved management of the disease, in line with case fatality data from cohort studies. Additional, or alternative, explanations might include the absence of a uniform case definition and changes in coding practices and performing autopsy. Pulmonary embolism still imposes a relevant medical and societal burden. Continuing efforts are warranted to improve awareness and implement effective preventive and therapeutic measures.

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Introduction

Pulmonary embolism occurs in 39–115 individuals per 100 000 population.[1] Several countries have reported that its incidence has increased considerably in the past two decades.[2] This trend might be due to increasing numbers of patients surviving severe comorbidities, such as cancer, with higher risk of developing venous thromboembolism, and to the availability of more accurate diagnostic imaging tests and a lower threshold for suspicion of the disease.[3–5] Globally, awareness of pulmonary embolism as a cause of death remains low.[6] Of note, acute pulmonary embolism was not accounted for as a specific and plausible underlying cause of death contributing to global cause-specific mortality in the comprehensive analyses of the Global Burden of Disease Study initiative.[1,7,8]

Acute pulmonary embolism can be rapidly fatal in the case of cardiorespiratory decompensation.[9] In the past 20 years, a progressive decrease of in-hospital case fatality ratio, defined as the proportion of people dying from acute pulmonary embolism among all patients with a diagnosis of acute pulmonary embolism, was reported in several countries, as well as a similar decrease in the number of early all-cause deaths among patients diagnosed with acute pulmonary embolism.[2,10–14] Whether this favourable trend results from advances in management or whether it reflects more frequent diagnosis of smaller, low-risk pulmonary embolism remains unclear.[4] To evaluate the effects of contemporary management strategies, it is necessary to find out if decreasing case fatality ratios are accompanied by a reduction in age-standardised pulmonary embolism-related mortality rate, defined as the proportion of individuals who die from pulmonary embolism in the general population per year, which is not affected by trends in diagnosis of low-risk pulmonary embolism.[1]

Understanding mortality trends not only helps in the assessment of the effects of novel drugs, regimens, and guideline recommendations,[15,16] but might also contribute to establishing future priorities for prevention and allocation of health-care resources. In contrast to

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Research in context

Evidence before this study

We searched PubMed, Web of Science, and Google Scholar for epidemiological studies and reviews published in any language from Jan 1, 1995, to June 31, 2019, using the search terms "mortality", "deaths", "fatality", "pulmonary embolism", "venous thromboembolism", "epidemiology", "systematic review", and "incidence". Available epidemiological data related to the global burden of thrombosis have been summarised in systematic and narrative reviews published by the World Thrombosis Day Steering Committee. Furthermore, we consulted the publications of the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study initiative and the corresponding online material to retrieve information on global mortality related to pulmonary embolism or venous thromboembolism.

Estimates of and time trends in pulmonary embolism-related mortality in Europe are not available to this date. This gap in knowledge is in sharp contrast with three studies of pulmonary embolism-related mortality in the USA, which were done by use of the information reported in the Multiple Cause of Death database or in the Nationwide Inpatient Sample database. Moreover, differences in estimated mortality rates of around ten times were reported in 2007 between surveillance data from individual European countries and modelling-based methods. Pulmonary embolism has not been considered as a sufficiently specific and plausible underlying cause of death in the GBD Study and, therefore, has not been included in its comprehensive analysis of around 300 diseases or injuries. Acute pulmonary embolism can, by itself, be the primary cause of death in patients in whom no comorbidities or risk factors are identified. Furthermore, it represents a potentially preventable cause of death, which might occur in otherwise healthy patients (eg, during pregnancy or treatment with oral contraceptives) or might complicate elective surgical procedures that are characterised by negligible fatality.

Added value of this study

To the best of our knowledge, our study, based on medically certified vital registration data from the WHO Mortality Database, provides the first comprehensive analysis of the disease burden from pulmonary embolism and time trends within the WHO European Region, covering a large part of Eurasia, a total population of more than 650 million, and a time period of 16 years. Our results reveal an age-standardised pulmonary embolism-related mortality close to 7 per 100 000 population per year. This mortality rate is much less than the estimate of up to 120 per 100 000 per year that was obtained from previous epidemiological models.

Since 2000, age-standardised mortality related to pulmonary embolism has been decreasing steadily in both sexes across all European subregions except for Central Asia, possibly reflecting advances in prophylaxis and treatment. Nevertheless, pulmonary embolism remains an important contributor to total mortality, especially among women aged 15–55 years.

Implications of all the available evidence

Our data contribute to a substantial correction of past mortality estimates, strengthening the basis for cause of death estimation of venous thromboembolic disorders.

Considerable progress occurred for many subregions of the WHO European Region, with a decline in age-standardised pulmonary embolism-related mortality rates. Despite this trend, pulmonary embolism remains an important cause of death, particularly for young women. Moreover, because pulmonary embolism-related mortality increases exponentially with age, the overall medical, societal, and economic burden related to the increasing number of pulmonary embolism diagnoses and deaths could continue to grow. Therefore, efforts to implement large-scale preventive programmes and to apply the available risk-stratification schemes in clinical practice must be maintained to continue this positive trend.

See **Online** for appendix

other major acute cardiovascular syndromes, estimates of the burden imposed by pulmonary embolism and time trends in pulmonary embolism-related mortality in Europe are only available for very few individual countries or are outdated,[1,17] and existing estimates largely rely on epidemiological models or on studies combining surveillance data and modelling methods.[1,18]

We aimed to document the disease burden and time trends in pulmonary embolism-related mortality in the WHO European Region by analysing the vital registration data from the WHO Mortality Database.

Methods

Data source

The WHO European Region includes 53 Member States. Based on the classification by the UN Statistics Division, the subregions of the WHO European Region were defined and analysed as Eastern Europe, Northern Europe, Southern Europe, Western Europe, and Central Asia (appendix p 13).[19]

We did an analysis of vital registration data from the WHO Mortality Database (2000–15). The WHO Mortality Database incorporates Member State-level data grouped by age and sex for the primary causes of death. These data are based on medically certified reports submitted annually to WHO by Member States, which require legal certification of death as standard International Classification of Disease (ICD) codes, and therefore rely on national vital registration systems.[20] The information transmitted by each Member State is validated according to standard procedures, including plausibility check, agreement with certain distributions and previous years, and validation against the ICD codes.[20] WHO Mortality Database data have been used previously for analysis of time trends in cerebrovascular, cardiovascular, and respiratory causes of death[19,21–24] and in the Global Burden of Disease Study.[7,8]

In this analysis, we focused on pulmonary embolism-related mortality and contribution to total mortality calculated in the WHO European Region for the most recent period available in the WHO Mortality Database (2013–15) and on time trends across age groups, sexes, and subregions from 2000 to 2015.

Definition of pulmonary embolism-related death

Deaths were considered related to pulmonary embolism if either the ICD 10th Revision (ICD-10) code specific for acute pulmonary embolism with or without acute cor pulmonale (I26) was listed as the primary cause of death, defined as "the disease or event that started the chain of events that led to death", or any code referring to otherwise non-fatal manifestations of venous thromboembolism, or with the potential of evolving to acute pulmonary embolism was listed as the primary cause of death; these included deep vein thrombosis or phlebitis and thrombophlebitis (appendix p 12).[14] This approach is supported by previous studies, which showed that thrombophlebitis, or deep vein thrombosis, was listed as the primary cause of death in a significant proportion of patients with venous thromboembolism,[25–28] or accepted pulmonary embolism as a secondary diagnosis if the principal diagnosis was respiratory failure or deep vein thrombosis.[29] In an analysis of the Nationwide Inpatient Sample in the USA,[29] the authors reported that up to 14·3% of patients who experienced fatal pulmonary embolism had deep vein thrombosis listed as the first cause of death, followed by pulmonary embolism itself.

We did a sensitivity analysis accounting for the ICD-10 code specific for acute pulmonary embolism (I26) only. Codes referring to other venous thrombotic events at sites not directly linked to pulmonary embolism (eg, cerebral or splanchnic vein thrombosis) were not considered.

Data extraction

We extracted the number of pulmonary embolism-related deaths, total deaths, and population size from the WHO Mortality Database (latest update December, 2018) for the period from 2000 (or the first available year) to 2015 (or the last available year if it preceded 2015). We chose this particular period based on three considerations: (1) homogeneous diagnostic criteria, standardised anticoagulant treatment regimens, and evidence-based management guidelines only became widely available in Europe after 2000; (2) drastic changes were made to the definition of pulmonary embolism in the transition from ICD-9, which had been used in most Member States until the end of the 1990s, to ICD-10;[30] and (3) the years after 2015 still had a high proportion of missing values due to delays in the submission of national data. Information on secondary causes of death, ethnic origin, and socioeconomic status are not available in the WHO Mortality Database.

We followed the Guidelines for Accurate and Transparent Health Estimates Reporting standards.[31] This study did not need ethics or institutional review board approval.

Statistical analysis

We calculated crude annual average pulmonary embolism-related mortality rates for 2013–15 and for individual years between 2000 and 2015 by dividing the number of pulmonary embolism-related deaths by the total corresponding population. We calculated annual mortality rates per 100 000 population and the corresponding 95% CI (exact Poisson). To permit geographical and temporal comparisons, we provided age-standardised pulmonary embolism-related mortality rates with corresponding 95% CIs (Fay's method)[32] accounting for differences in the age distribution of populations among Member States and their changes over time. The standardisation of all the aggregate rates was based on the updated standard European population released in 2013 by the European Commission for the EU-27 and the European Free Trade Association countries.[33] Because age groups were reported differently across Member States, we created homogeneous 5-year age groups up to 85 years. We considered zero counts as true zeroes in calculations.

For the analysis of pulmonary embolism-related mortality (2013–15, annual average), missing population data for single years were calculated from the slope obtained for the other two available years. To obtain the age-specific pulmonary embolism-related mortality for the entire WHO European Region, we calculated unweighted and weighted (random effects model) pooled mortality rates. We used smoothed lines generated by locally estimated scatterplot smoothing to depict the proportion of deaths attributed to pulmonary embolism (proportionate mortality), reported as the number of pulmonary embolism-related deaths per 1000 deaths.

To analyse time trends in pulmonary embolism-related mortality from 2000 to 2015, we did not apply any imputation technique for Member States with missing data. Each Member State contributed to the analysis only for the years with complete data; we did sensitivity analyses accounting for different thresholds of missing data and excluding Member States accordingly. We reported pooled mortality rates, weighted by the population size of each Member State, and corresponding 95% CI using a locally estimated scatterplot smoothing procedure. We used joinpoint regression (JoinPoint version 4.6.0.0) to identify changes in trends and timepoints with significant inflections on the basis of a series of hypothesis tests. We ran sensitivity analyses with different assumptions concerning error variance and calculated the average annual percentage change with corresponding 95% CIs. We used a standard

	Population	Number of pulmonary embolism-related deaths per year	Crude annual pulmonary embolism-related mortality rate (95% CI)	Crude annual pulmonary embolism-related mortality rate by age group																		Age-standardised annual pulmonary embolism-related mortality rate (95% CI)
				0–4 years of age	5–9 years of age	10–14 years of age	15–19 years of age	20–24 years of age	25–29 years of age	30–34 years of age	35–39 years of age	40–44 years of age	45–49 years of age	50–54 years of age	55–59 years of age	60–64 years of age	65–69 years of age	70–74 years of age	75–79 years of age	80–84 years of age	≥85 years of age	
Bulgaria	7 244 527	1738	24·0 (22·9–25·1)	0	0	0	0·3	0·7	1·1	1·1	1·9	5·4	8·3	12·8	22·4	31·7	45·8	61·8	110	144·4	222·0	24·7 (23·6–26·0)
Czech Republic	10 526 148	1355	12·9 (12·2–13·6)	0·1	0	0	0·1	0·4	0·4	0·7	1·6	2·5	4·5	5·8	8·9	15·7	22·4	34·9	60·4	99·8	185·0	15·1 (14·3–16·0)
Slovakia	5 416 017	497	9·2 (8·4–10)	0	0	0	0·2	0·3	0·6	0·6	0·8	2·3	4·6	4·7	7·8	15·7	20·2	34·4	51·5	84·8	138·1	12·9 (11·7–14·1)
Lithuania	2 931 655	343	11·7 (10·5–13·0)	0	0	0	0	0·1	1·0	1·7	2·6	2·8	5·5	7·7	9·9	17·0	24·1	29·1	42·4	72·6	99·8	11·9 (10·7–13·3)
Luxembourg	556 428	42	7·6 (5·6–10·2)	0	0	0	0	0	0	0·7	0·7	0·7	6·0	0	6·6	8·1	14·3	12·6	30·9	83·4	137·2	9·6 (6·9–13·1)
Germany	81 104 951	8313	10·2 (10–10·5)	0	0	0	0·2	0·4	0·6	0·8	1·2	2·0	2·8	4·4	6·6	9·2	13·1	19·5	33·2	60·8	120·8	9·4 (9·2–9·6)
UK	64 604 147	5348	8·3 (8·1–8·5)	0	0	0	0·1	0·3	0·4	0·8	1·5	2·3	3·4	4·2	6·4	9·3	14·5	22·3	34·0	55·8	99·8	9·0 (8·8–9·3)
Bosnia and Herzegovina	3 827 343	233	6·1 (5·3–6·9)	0	0	0	0·4	0·4	1·2	0·4	0·4	0·8	2·5	2·0	4·9	6·2	18·7	17·8	27·5	70·5	107·1	8·7 (7·5–10·1)
Serbia	7 130 434	562	7·9 (7·2–8·6)	0	0	0	0	0	0·2	0·3	1·1	1·0	2·6	4·8	6·4	8·6	14·3	22·7	40·7	60	70·7	8·4 (7·7–9·2)
Slovenia	2 061 271	151	7·3 (6·2–8·5)	0	0	0	0	0·3	0	0·2	0	0·5	2·1	1·8	3·3	4·8	5·6	14·1	36·8	65·3	117·8	7·9 (6·7–9·3)
Poland	38 006 458	2341	6·2 (5·9–6·4)	0	0	0	0	0·2	0·3	0·5	1·2	1·6	2·6	4·1	5·8	9·3	13·5	20	28·9	45·5	67·4	7·4 (7·1–7·7)
Belgium	11 223 851	793	7·1 (6·6–7·6)	0	0	0	0·1	0·3	0·3	1·0	0·6	1·5	2·9	2·8	4·7	6·7	10·1	15·7	23·4	42·5	100·9	7·2 (6·7–7·7)
Armenia	3 013 469	115	3·8 (3·2–4·6)	0	0	0	0	0·3	0·1	1·1	1·0	0·6	1·1	1·5	2·8	5·7	8·1	14·7	30·2	35·7	114·5	7·1 (5·7–8·6)
Estonia	1 315 717	90	6·8 (5·5–8·3)	0	0	0	0	0·8	0	0·3	1·4	1·4	1·2	4·1	7·1	8·9	10	15·2	27·6	49·2	68·4	7·0 (5·6–8·6)
Kazakhstan	17 289 504	632	3·7 (3·4–3·9)	0·1	0	0	0·1	0·3	0·5	1·3	2·0	2·6	4·3	7·0	11·0	14·7	18·3	20·8	22·5	21·0	22·6	6·9 (6·3–7·5)
Turkey	77 151 669	2101	2·7 (2·6–2·8)	0	0	0	0·1	0·1	0·2	0·3	0·5	0·9	1·1	2·0	3·1	5·5	8·6	15·9	28·8	48·3	94·5	6·9 (6·6–7·2)
Hungary	9 867 530	591	6·0 (5·5–6·5)	0	0	0	0·1	0·2	0·3	0·6	0·5	1·4	2·3	3·6	4·4	6·6	9·0	14·2	25·5	47·8	80·5	6·7 (6·2–7·3)
Portugal	10 405 483	715	6·9 (6·4–7·4)	0	0·1	0	0·1	0·5	0·5	0·9	1·5	1·3	2·5	3·1	4·0	5·5	8·9	12·9	21·4	40·5	91·1	6·6 (6·1–7·1)
Ireland	4 593 125	182	4·0 (3·4–4·6)	0	0	0	0·4	0·5	0·5	0·6	0·6	1·1	2·2	1·5	4·0	5·1	11·1	17·2	22·7	39·0	64·9	6·0 (5·2–7·0)
Greece	10 856 667	719	6·6 (6·1–7·1)	0	0	0	0·1	0·3	0·1	0·3	1·1	0·7	1·7	2·3	2·9	5·2	6·7	10	19·0	38·0	95·4	5·9 (5·5–6·4)
Romania	19 908 281	1027	5·2 (4·8–5·5)	0	0	0	0	0·1	0·3	0·4	0·8	1·4	2·6	3·9	5·5	7·6	10·9	16·8	23·7	30·3	48·2	5·8 (5·5–6·2)
Austria	8 550 227	476	5·6 (5·1–6·1)	0	0	0·1	0·1	0·1	0·1	0·6	0·4	1·0	1·5	2·6	3·3	5·2	7·2	11·8	20	36·0	82·1	5·7 (5·2–6·3)
Switzerland	8 089 348	410	5·1 (4·6–5·6)	0	0	0	0	0·1	0·4	0·2	0·4	0·6	1·2	1·8	2·1	3·7	5·4	8·5	15·4	37·4	96·9	5·4 (4·9–5·9)
Finland	5 450 242	287	5·3 (4·7–5·9)	0	0	0	0	0·4	0·2	0·4	0·9	0·9	2·5	3·2	3·4	6·1	8·5	11·7	21·9	31·0	58·4	5·3 (4·7–6·0)
France	63 955 634	3544	5·5 (5·4–5·7)	0	0	0	0·1	0·2	0·3	0·3	0·5	1·1	1·4	1·9	2·9	4·6	6·7	9·5	16·4	31·8	86·2	5·3 (5·1–5·5)
Malta	427 575	19	4·5 (2·9–6·9)	0	0	0	0	0	2·2	0	1·0	1·1	1·2	2·4	0	2·4	6·8	19·2	18·8	45·1	55·3	5·3 (3·2–8·4)
Sweden	9 664 200	479	5·0 (4·5–5·4)	0	0	0	0	0·2	0·2	0·3	0·5	0·7	1·5	2·0	3·3	4·7	6·6	11·1	17·2	34·3	66·3	5·0 (4·6–5·5)
Spain	46 486 170	2243	4·8 (4·6–5·0)	0	0	0	0·1	0·2	0·2	0·3	0·6	1·0	1·4	2·2	2·6	3·8	5·1	8·7	15·4	28·4	72·8	4·7 (4·5–4·9)
Latvia	1 994 652	93	4·6 (3·8–5·7)	0	0	0	0	0	0	0·7	1·3	2·9	2·2	3·6	7·1	7·6	7·9	12·6	17·7	21·7	26·2	4·6 (3·7–5·7)
Kyrgyzstan	5 837 646	107	1·8 (1·5–2·2)	0	0	0	0·1	0·4	0·8	1·0	1·7	2·0	3·5	3·5	6·3	8·2	14·3	14·1	15·2	11·9	11·9	4·5 (3·5–5·7)
Israel	8 218 425	202	2·5 (2·1–2·8)	0	0	0	0·1	0	0·1	0·2	0·2	0·3	0·4	0·6	1·8	2·2	2·7	8·1	14·0	32·9	81·2	4·3 (3·8–5·0)
Croatia	4 232 561	168	4·0 (3·4–4·6)	0	0	0	0	0	0·3	0·2	0·5	0·8	1·8	2·6	2·8	4·2	6·6	10·5	14·0	29·1	47·4	4·2 (3·6–4·9)
Moldova	3 556 364	111	3·1 (2·6–3·8)	0	0	0·2	0	0	0·4	0·3	1·4	1·4	3·0	3·9	8·0	10·8	11·1	14·3	10·3	14·7	5·4	4·1 (3·4–5·1)
Denmark	5 642 284	206	3·7 (3·2–4·2)	0	0	0	0·1	0·1	0·4	0·5	0·3	1·2	1·0	2·6	3·4	3·8	6·9	7·4	12·0	28·1	49·5	4·0 (3·5–4·6)
Norway	5 135 834	158	3·1 (2·6–3·6)	0	0	0	0·1	0·4	0·6	0·4	0·3	0·7	1·2	1·6	2·0	2·4	3·5	5·8	11·9	24·8	55·0	3·6 (3·0–4·2)
Iceland	327 321	8	2·3 (1·1–4·4)	0	0	0	0	0	0	0	0	0	1·4	1·4	0	4·0	0	9·9	13·1	16·0	58·2	3·3 (1·4–6·8)
Netherlands	16 869 800	450	2·7 (2·4–2·9)	0	0	0	0·1	0·2	0·5	0·4	0·7	1·1	1·5	1·7	2·3	2·8	4·4	5·1	10·6	16·6	35·1	3·0 (2·7–3·3)
Cyprus	852 738	18	2·1 (1·3–3·2)	0	0	0	0	0	0	0	0	1·2	0·5	0·5	3·3	2·8	8·0	10·6	4·2	12·7	34·3	2·9 (1·7–4·6)
Georgia	3 977 000	89	2·2 (1·8–2·7)	0	0	0	0	0·1	0	0·3	0·5	1·1	1·0	1·8	2·7	2·8	6·1	8·1	10·4	18·3	22·9	2·9 (2·3–3·6)
Italy	60 584 569	1946	3·2 (3·1–3·4)	0	0	0	0·1	0	0·1	0·2	0·3	0·4	0·6	0·8	0·8	1·4	2·5	4·3	8·3	18·9	49·2	2·7 (2·6–2·8)
North Macedonia	2 063 658	25	1·2 (0·8–1·8)	0	0	0	0	0	0	0	0	0·7	1·4	0·7	0·7	0·9	2·3	4·3	16·7	6·9	22·2	2·0 (1·2–3·3)
Women	332 080 153	22 514	6·8 (6·7–6·9)	0	0	0	0·1	0·3	0·3	0·5	0·8	1·2	1·9	2·4	3·4	5·4	8·5	14·0	24·7	43·5	89·2	6·5 (6·2–6·6)
Men	318 870 768	16 415	5·1 (5·1–5·2)	0	0	0	0·1	0·2	0·3	0·5	0·9	1·5	2·4	3·8	5·9	8·5	11·5	16·5	24·8	39·7	74·2	6·9 (6·8–7·3)
Entire population	650 950 921	38 929	6·0 (5·9–6·0)	0	0	0	0·1	0·2	0·3	0·5	0·8	1·4	2·1	3·1	4·6	6·9	10	15·1	24·7	42·0	84·6	6·8 (6·5–6·9)
Women (weighted)	..	..	6·0 (5·0–7·0)	0	0	0	0·1 (0–0·1)	0·2 (0·1–0·3)	0·2 (0·1–0·3)	0·4 (0·3–0·6)	0·7 (0·5–0·9)	1·0 (0·8–1·3)	1·8 (1·5–2·2)	2·2 (1·8–2·7)	3·4 (2·7–4·1)	5·0 (4·0–6·0)	8·0 (6·5–9·7)	13·1 (10·8–15·7)	23·5 (19·5–27·9)	41·0 (34·7–47·7)	75·4 (65·1–86·5)	6·0 (5·2–6·9)
Men (weighted)	..	..	4·6 (3·8–5·5)	0	0	0	0 (0–0·1)	0·1 (0·1–0·1)	0·3 (0·2–0·4)	0·4 (0·3–0·6)	0·8 (0·6–1·0)	1·3 (1·0–1·7)	2·4 (1·8–3·0)	3·5 (2·8–4·4)	5·4 (4·2–6·7)	7·9 (6·2–9·8)	11·4 (9·0–14·1)	16·4 (13·2–20)	22·7 (18·3–27·5)	37·1 (30·8–44·0)	67·7 (58·5–77·6)	6·5 (5·5–7·5)
Entire population (weighted)	..	..	5·3 (4·4–6·2)	0	0	0	0·1 (0–0·1)	0·2 (0·1–0·2)	0·3 (0·2–0·4)	0·5 (0·4–0·6)	0·8 (0·6–0·9)	1·3 (1·0–1·6)	2·1 (1·7–2·6)	2·8 (2·3–3·4)	4·4 (3·5–5·4)	6·5 (5·2–7·9)	9·6 (7·8–11·6)	14·5 (11·9–17·3)	23·4 (19·4–27·7)	39·3 (33·3–45·8)	72·4 (62·9–82·6)	6·3 (5·4–7·2)

significance threshold of 5% for p values, which depicts the probability of observing more extreme data under the null hypothesis assumption of a smaller number of joinpoints for each hypothesis test.[34] R version 3.5.1 (with the tidyverse, epitools, and metaphor packages) was used for data analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

41 of the 53 Member States of the WHO European Region had available data for the period 2013–15; Albania, Andorra, Azerbaijan, Belarus, Monaco, Montenegro, Russia, San Marino, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan did not have available data.

Between 2013 and 2015, the population of the 41 Member States amounted to an average of 650 950 921 individuals. The annual average number of pulmonary embolism-related deaths in the 3-year period was 38 929, corresponding to a crude annual mortality rate of 6·0 deaths per 100 000 population (95% CI 5·9–6·0; figure 1). The age-standardised annual pulmonary embolism-related mortality rate was 6·8 deaths per 100 000 population (6·5–6·9; figure 1). A visual summary of geographical differences is provided in the appendix (p 3).

Annually, an average of 22 514 pulmonary embolism-related deaths occurred among 332 080 153 women and 16 415 among 318 870 768 men between 2013 and 2015, corresponding to crude annual mortality rates of 6·8 per 100 000 population (95% CI 6·7– 6·9) in women and 5·1 deaths per 100 000 population (5·1 –5·2) in men. The observed age-standardised annual pulmonary embolism-related mortality rates were 6·5 deaths per 100 000 women (6·2–6·6) and 6·9 per 100 000 men (6·8–7·3; figure 1). Pulmonary embolism-related mortality increased with age, with a seemingly exponential distribution (figure 2).

Figure 1: **Annual pulmonary embolism-related mortality rates in the WHO European Region, 2013–15.**

Displayed is the average population and average number of annual pulmonary embolism-related deaths in each country between 2013 and 2015. Countries are shown in order of observed age-standardised annual pulmonary embolism-related mortality rate. The colours represent the value of the observed age-standardised annual pulmonary embolism-related mortality rates, ranging from green (lowest) to red (highest). Annual pulmonary embolism-related mortality rates are calculated based on the average number of pulmonary embolism-related deaths per 100 000 population between 2013 and 2015. Member States not shown in this figure had no available data for any of the 3 years. Age-specific, sex-specific, and sex-specific age-standardised mortality rates pooled using a random effects model and weighted by Member State population size are provided with the corresponding 95% CIs.

Women had higher pulmonary embolism-related mortality rates than men at 15–29 years of age and after 80 years of age, whereas mortality was higher in men at 40–79 years of age (appendix p 5).

In the entire population, pulmonary embolism was reported as the primary cause of death in 7·5 cases per 1000 deaths (95% CI 7·4–7·6) in women versus 5·4 cases per 1000 deaths (5·4–5·5) in men (proportionate mortality) between 2013 and 2015. This difference was most prominent between 15 and 55 years of age (figure 3). In this age group, pulmonary embolism-related deaths accounted for 8–13 cases per 1000 deaths in women and 2–7 cases per 1000 deaths in men (figure 3). Both the overall sex difference and the age-specific peaks were less evident in Eastern Europe (figure 3). Total and pulmonary embolism-related deaths, classified by sex for each individual country, are shown in the appendix (pp 14–17).

In the WHO European Region, the observed age-standardised annual pulmonary embolism-related mortality rate decreased from 12·7 deaths per 100 000 population in 2000 to 6·5 deaths per 100 000 population in 2015 (figure 4). The age-standardised annual pulmonary embolism-related mortality rate by locally estimated scatterplot smoothing decreased from 12·8 deaths per 100 000 population (95% CI 11·4–14·2) in 2000 to 6·5 deaths per 100 000 population (5·3–7·7) in 2015 (figure 4). Crude annual pulmonary embolism-related mortality rate decreased from 9·4 deaths per 100 000 population in 2000 to 5·8 deaths per 100 000 population in 2015.

Joinpoint regression analysis (appendix p 6) revealed a linear decrease in age-standardised pulmonary embolism-related mortality from 2000 to 2015 (annual change –0·48 deaths per 100 000 population [95% CI –0·52 to –0·43]), which was consistent between sexes. The locally estimated scatter plot smoothed curve for time trends (figure 3; appendix p 7) confirmed the linearity of this trend. At sensitivity analysis, the exclusion of Member States without complete data for each year during the investigated period did not lead to appreciable differences from the aforementioned estimates (appendix p 9). The time trend analysis by subregion showed that this reduction was consistent across all subregions, except for Central Asia, which had an increasing trend from 2000 to 2015 (figure 5). The men-to-women ratio of age-standardised pulmonary embolism-related mortality was close to unity in all subregions; however, in Eastern Europe, men had higher pulmonary embolism-related mortality rates, with the men-to-women ratio decreasing from to 1·35 to 1·20 between 2000 and 2015 (figure 5). Time trend analysis by observation period and sex for individual Member States is shown in the appendix (pp 18–22).

Trends in the proportion of pulmonary embolism-related deaths per 1000 total deaths (proportionate mortality) showed that the increased pulmonary

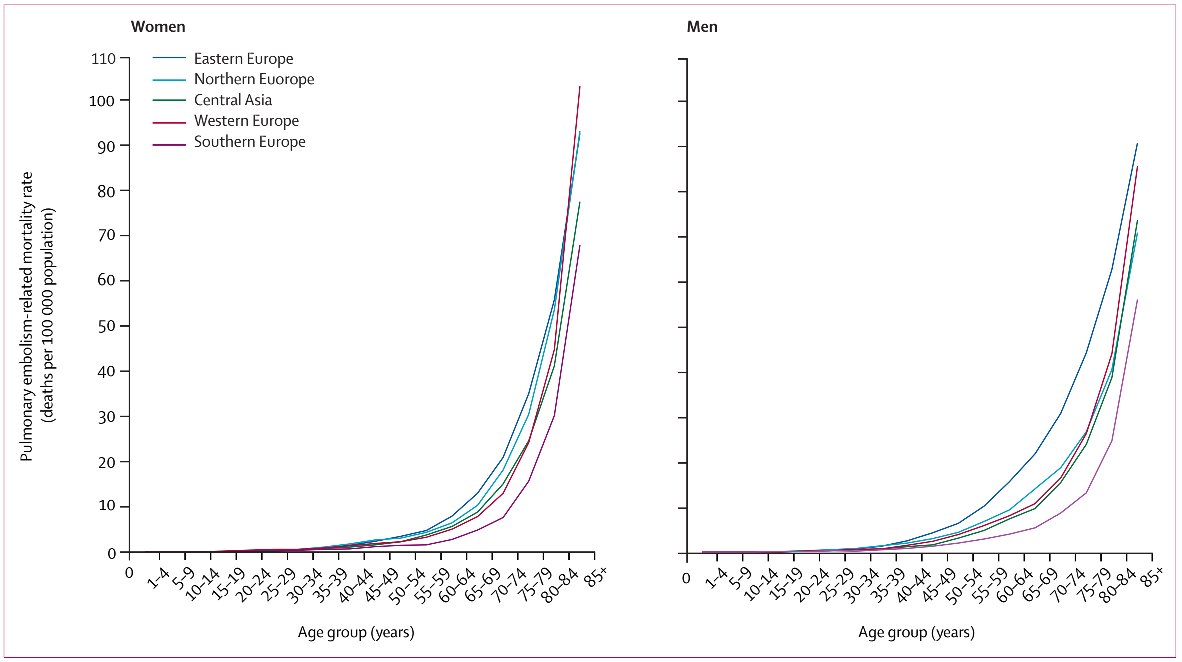

Figure 2: **Pulmonary embolism-related mortality rates in subregions of the WHO European Region by age group and sex, 2013–15.**
Average annual pulmonary embolism-related deaths per 100 000 population in 41 Member States with available data between 2013 and 2015. Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Moldova, Romania, and Slovakia; Northern Europe: Iceland, Denmark, Estonia, Finland, Ireland, Latvia, Lithuania, Norway, Sweden, and the UK; Southern Europe: Bosnia and Herzegovina, Croatia, Greece, Italy, Malta, Portugal, Serbia, Slovenia, Spain, and North Macedonia; Western Europe: Austria, Belgium, France, Germany, Luxembourg, Netherlands, and Switzerland; Central Asia: Armenia, Cyprus, Georgia, Israel, Kazakhstan, Kyrgyzstan, and Turkey.

embolism-related burden in women aged 15–55 years persisted throughout the entire observation period (appendix p 10). Trends were consistent across all subregions (appendix p 11), keeping in mind the aforementioned interregional variations.

Around 75% of all pulmonary embolism-related deaths were primarily coded with the ICD-10 code I26 for pulmonary embolism (86 554 pulmonary embolism-related deaths of 115 272 total deaths over 3 years), whereas I80 (phlebitis and thrombophlebitis) was listed as the primary or underlying cause of death in 23% of the reported deaths (23 864 of 115 272 total deaths), leaving 2% (2854 of 115 272 total deaths) of deaths explained by other codes (appendix p 12). 29 293 deaths were attributed to pulmonary embolism in 2013–15, when only I26 was used as the primary code. With this definition, the crude annual pulmonary embolism-related mortality rate was 4·5 deaths per 100 000 population in the WHO European Region; the overall age-standardised annual mortality rate was 5·1 deaths per 100 000 population, with 4·9 deaths per 100 000 women versus 5·3 per 100 000 men. Pulmonary embolism-related deaths corresponded to 5·6 per 1000 total deaths in women and 4·2 per 1000 total deaths in men (proportionate mortality) with similar age distribution to that of the primary analysis (appendix p 25). The characteristics of the time trends in age-standardised pulmonary embolism-related mortality and contribution to total mortality did not show relevant differences compared with the primary analysis (appendix pp 26–37).

Discussion

In contrast with existing data on around 300 other diseases or injuries causing premature death,[1,7] European estimates of pulmonary embolism-related mortality are not available to this date.[1] To the best of our knowledge, our study, based on medically certified vital registration data from the WHO Mortality Database, provides the first comprehensive analysis of the disease burden within the WHO European Region, covering a total population of more than 650 million and a period of 16 years. We showed that acute pulmonary embolism is responsible for around 7 deaths per 100 000 population, with considerable differences between individual Member States and subregions. Since 2000, age-standardised pulmonary embolism-related mortality has been decreasing steadily in both sexes and across all European subregions, but not in Central Asia. Despite this trend, pulmonary embolism remains a substantial contributor to total mortality, especially among women aged 15–55 years. Moreover, pulmonary embolism-related mortality increases exponentially with age. As societies age worldwide, the overall medical,[2] societal,[35] and economic[36] burden related to the increasing number of acute pulmonary embolism diagnoses and deaths will continue to grow. Therefore, efforts towards implementation of large-scale preventive programmes, applying the available risk-stratification schemes in clinical practice and studying their effect on mortality, must be maintained to continue this positive trend.

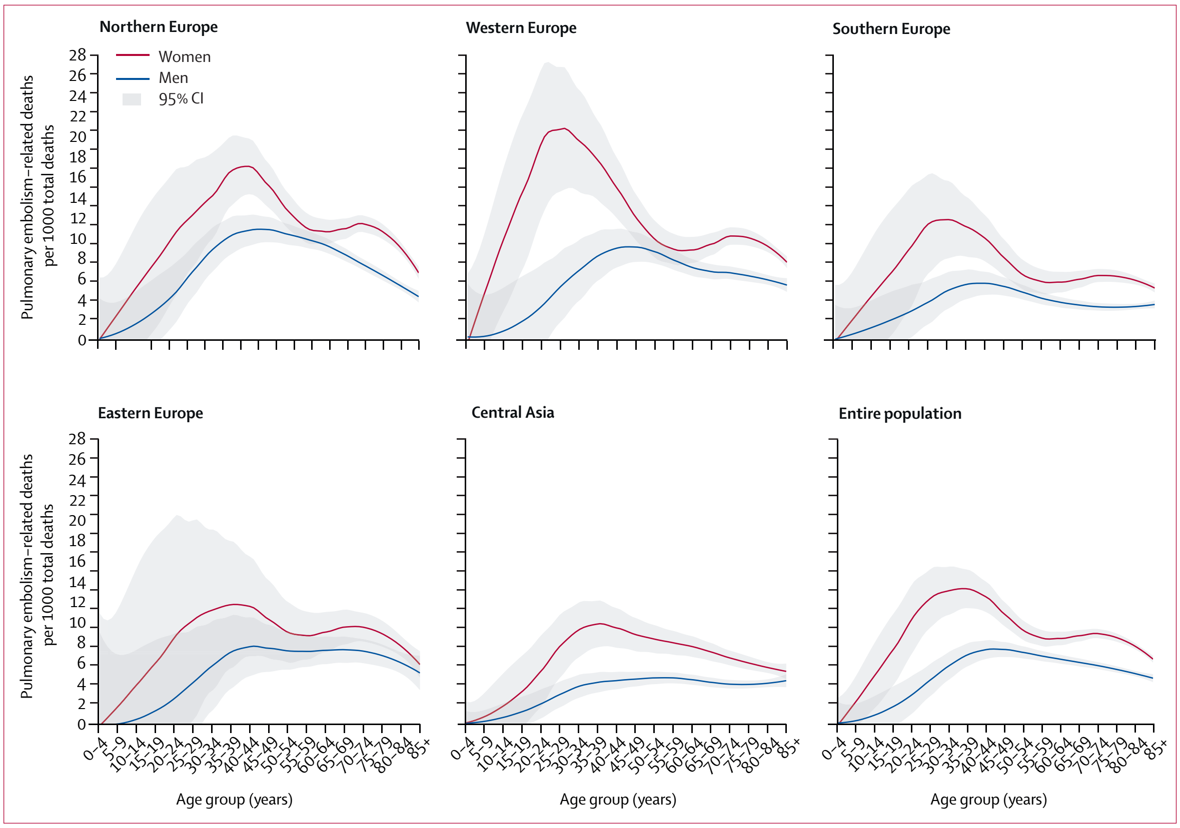

Figure 3: **Average annual number of pulmonary embolism-related deaths per 1000 total deaths, 2013–15.**
Locally estimated scatterplot smoothed lines for men (blue lines) and women (red lines) and 95% CIs (grey) showing the average annual number of pulmonary embolism-related deaths per 1000 total deaths (proportionate mortality) in 41 Member States with available data between 2013 and 2015. Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Moldova, Romania, and Slovakia; Northern Europe: Iceland, Denmark, Estonia, Finland, Ireland, Latvia, Lithuania, Norway, Sweden, and the UK; Southern Europe: Bosnia and Herzegovina, Croatia, Greece, Italy, Malta, Portugal, Serbia, Slovenia, Spain, and North Macedonia; Western Europe: Austria, Belgium, France, Germany, Luxembourg, Netherlands, and Switzerland; Central Asia: Armenia, Cyprus, Georgia, Israel, Kazakhstan, Kyrgyzstan, and Turkey.

The age-standardised annual pulmonary embolism-related mortality rate that we observed is lower than estimates from studies that combined modelling methods and vital registration data; these calculations suggested annual mortality rates of up to 32 deaths per 100 000 population.[1,17] A model focusing on six European countries even yielded rates as high as 120 pulmonary embolism-related deaths per 100 000 population, presuming misdiagnosed and unrecognised fatal events on the basis of historical low projections of in-hospital thromboprophylaxis.[18] In contrast, studies based on vital registration data and done primarily outside Europe are more in line with our results.[25–27,29,37,38] Earlier analyses also reported annual mortality rates not exceeding 10 deaths per 100 000 population if pulmonary embolism was listed as the first cause of death. In any case, our results highlight pulmonary embolism as a substantial cause of death in the European population, with disease-related mortality rates quite similar to those of respiratory infections (6–8 per 100 000 population) or obstructive pulmonary disease (11–15 per 100 000 population).[24] Given our results, it is surprising that pulmonary embolism was not included as an underlying cause of death in the Global Burden of Disease Study,[39] the largest effort to quantify and provide yearly updates of the magnitude, distribution, and trends in disease-specific mortality.[1,7] In those analyses, pulmonary embolism was listed as a garbage code.[7,8] This coding was proposed to redistribute conditions that, in the investigators' opinion, were not underlying causes but rather intermediate or final causes of death. However, acute pulmonary embolism can by itself be an underlying and plausible cause of death in patients in whom no comorbidities or risk factors are identified. Furthermore, acute pulmonary embolism might occur under physiological states (for example, during pregnancy) or complicate elective surgical procedures that are characterised by negligible fatality.

We observed a continuous decrease in pulmonary embolism-related mortality from 2000 to 2015, which is consistent with the decreasing trend reported by some,[26,27,37,38] but not all,[29,40] publications from mostly non-European countries in the 1990s and early 2000s. Possible explanations include improved venous thromboembolism

	Age-standardised annual pulmonary embolism-related mortality rates, number of deaths per 100 000 population																AAPC (95% CI)
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	
Bulgaria						24·8	22·8	26·9	27·8	24·5	25·0	25·5	28·7	25·9	23·5		0·3 (–1·6 to 2·3)
Czech Republic	28·7	29·3	28·4	31·3	27·2	27·1	27·9	25·5	27·9	29·7	27·1	19·9	18·8	15·9	14·1	15·4	–5·0 (–6·7 to –3·2)
Slovakia	32·8	29·1	33·0	32·8	32·8	28·3	28·2	27·0	26·2	24·2	21·1		10·4	13·9	11·8		–7·6 (–10·4 to –4·8)
Lithuania	11·1	10·8	12·0	11·5	11·1	12·9	15·5	13·9	10·7	12·7	10·5	10·5	11·5	13·3	10·8	11·7	–0·1 (–1·5 to –1·4)
Luxembourg	12·2	9·1	14·6	26·5	17·5	18·4	18·5	16·6	19·3	20·5	20·1	18·3	14·5	11·3	9·0	8·8	–4·1 (–9·5 to –1·7)
Germany	16·2	15·8	14·3	14·8	14·4	14·5	13·4	13·2	12·9	12·4	11·6	10·5	9·9	10·1	9·1	9·1	–3·9 (–4·6 to –3·2)
UK		16·3	15·9	16·3	15·1	14·3	14·2	13·3	13·2	13·0	13·0	9·5	9·4	9·3	8·9	8·9	–4·7 (–5·6 to –3·8)
Bosnia and Herzegovina												7·6			8·7		NA
Serbia	8·2	7·0	6·9	6·2	7·2	8·5	8·4	7·2	7·3	7·4	7·7	7·3	7·8	8·6	8·0	8·7	0·9 (–0·0 to –1·9)
Slovenia	7·6	11·7	8·6	6·9	8·5	10·8	13·4	9·6	7·7	9·5	8·9	8·8	9·6	8·5	7·4	7·8	–1·2 (–3·3 to 1·0)
Poland	11·1	11·3	11·7	11·7	12·6	12·4	11·5	10·5	10	10·4	9·1	8·8	8·6	7·9	7·1	7·1	–3·0 (–3·8 to –2·3)
Belgium	13·1	13·6	13·8	13·7	12·6	11·5	10·1	10·5	8·9	9·0	9·2	7·7	7·7	7·6	7·0	7·1	–4·3 (–6·9 to –1·7)
Armenia									9·5				11·3	5·4	8·8	6·8	–4·4 (–19·8 to 14·0)
Estonia	6·2	7·6	6·4	9·6	8·6	8·4	7·8	7·6	10·2	9·0	7·0	7·0	8·1	5·8	7·2	7·9	–0·3 (–2·2 to 1·6)
Kazakhstan														7·7	6·9	6·1	–11·0 (–18·3 to –3·0)
Turkey										5·0	5·1	5·8	5·8	6·9	8·0	5·8	5·9 (–1·2 to 13·4)
Hungary	19·8	25·0	22·2	17·1	13·6	8·6	7·9	8·0	7·8	9·0	8·3	7·1	7·7	7·4	6·8	6·0	–7·4 (–11·2 to –3·4)
Portugal			10·6	11·5				8·8	8·4	8·3	7·3	6·1	5·5	6·1	6·8	6·8	–4·7 (–6·4 to –3·0)
Ireland								7·5	7·7	7·2		7·0	6·9	6·2			–2·9 (–4·9 to –0·9)
Greece															6·3	5·6	NA
Romania	5·4	5·5	5·4	5·2	4·9	4·6	5·2	5·0	4·8	5·1	5·1	5·3	5·2	5·5	5·7	6·2	0·6 (–0·3 to 1·6)
Austria			11·1	10·6	9·4	10·7	9·5	8·8	7·1	7·1	7·0	6·0	5·8	5·6	5·4	6·1	–5·8 (–6·9 to –4·6)
Switzerland	8·5	8·1	8·1	7·9	6·4	6·5	5·7	5·2	5·5	5·8	5·3	5·3	5·7	5·3			–3·7 (–5·2 to –2·1)
Finland	7·9	8·1	8·8	7·9	8·9	8·0	7·7	8·2	6·6	6·5	6·7	6·4	6·1	5·9	5·2		–2·7 (–4·3 to –1·0)
France	13·3	13·2	13·2	13·1	11·8	11·0	10·3	9·8	9·1	8·7	8·2	6·1	5·8	5·4	5·0		–7·4 (–8·8 to –5·9)
Malta	10·6	11·5	7·3	7·1	5·1	6·4	6·6	5·9	8·7	3·9	4·7	5·2	6·4	6·9	3·6	5·4	–4·2 (–6·8 to –1·5)
Sweden	10·9	9·8	10·3	9·3	6·1	6·2	5·9	5·9	5·6	5·8	4·7	5·5	5·8	5·2	5·0	4·8	–5·4 (–7·7 to –3·2)
Spain	8·7	8·5	8·5	8·4	7·3	7·6	6·7	7·0	6·7	6·3	5·3	5·1	4·9	4·7	4·6	4·8	–4·3 (–6·6 to –1·8)
Latvia	4·4	3·2	3·8	3·6	3·7	3·3	4·7	4·0	4·3	4·1	6·2	4·8	4·3	4·7	4·6	4·6	2·0 (0·3 to 3·7)
Kyrgyzstan	6·0	6·3	5·4	6·1	4·2	3·7	4·1	4·9	4·5	3·0	4·0	3·2	3·4	3·9	5·0	4·5	–1·6 (–5·4 to 2·3)
Israel	5·4	4·8	6·6	5·5	5·2	5·5	5·3	5·8	5·1	4·9	4·3	4·1	4·2	4·3	4·8	3·9	–2·3 (–3·4 to –1·2)
Croatia	23·6	18·5	19·8	20·1	18·5	15·4	14·8	15·7	11·3	6·9	5·0	5·7	4·6	4·0	4·1	4·6	–10·5 (–16·3 to –4·3)
Moldova	2·1	2·8	2·9	2·6	3·5	4·1	3·7	4·2	4·0	3·5	2·8	3·4	3·4	3·2	3·9	5·3	5·9 (0·7 to 11·3)
Denmark	7·7	7·1	7·4	8·2	8·6	6·6	6·3	5·6	5·0	5·4	4·6	4·9	4·7	4·1	3·9	4·1	–4·0 (–7·4 to –0·4)
Norway	5·0	5·4	6·1	6·1	6·9	4·2	4·4	4·3	4·3	4·0	4·2	3·8	4·0	3·4	3·6	3·8	–3·7 (–5·2 to –2·2)
Iceland	10·7	10·3	13·0	7·0	5·7	4·3	3·7	9·7	7·1	5·0	3·6	3·7	4·2	3·6	2·5	3·9	–8·2 (–11·4 to –4·9)
Netherlands	6·2	5·5	5·6	5·6	5·5	5·1	5·0	4·6	4·3	4·3	3·9	3·5	3·8	3·1	2·8	3·0	–4·9 (–5·5 to –4·2)
Cyprus					2·6	3·2	3·7	2·0	2·8	2·9	2·6	2·7	2·5	2·3	2·5	3·9	0·4 (–3·3 to 4·1)
Georgia	0·9	1·1			4·5	2·6	4·2	2·5		2·9	1·0	3·0	2·5	2·5	1·0	5·4	2·8 (–4·6 to 10·7)
North Macedonia							2·4	2·7	2·2	1·9	2·8	2·8	2·7	2·0			0·3 (–5·5 to 6·4)
Italy				5·2	4·6	4·6	4·5	4·3	3·0	3·1	2·8	3·0	3·0	2·7	2·6	2·8	–5·8 (–7·4 to –4·3)
Montenegro	3·9	4·9	5·1	5·3	5·0	3·4	5·8	2·7	4·7	2·8							–3·1 (–9·5 to 3·6)
Uzbekistan					2·1	0·9											NA
Women	12·2	12·7	12·4	11·5	10·5	10·2	9·9	9·4	9·1	8·6	8·1	7·1	6·9	6·8	6·4	6·3	–4·9 (–5·3 to –4·5)
Men	13·1	13·5	13·0	11·9	11·0	10·9	10·3	10·2	9·5	9·1	8·5	7·4	7·2	7·1	6·8	6·6	–5·0 (–5·4 to –4·6)
Entire population	12·7	13·2	12·8	11·8	10·8	10·6	10·2	9·9	9·4	9·0	8·4	7·3	7·2	7·0	6·7	6·5	–5·0 (–5·4 to –4·6)
Women (LOESS)	12·3 (11·0–13·66	11·9 (11·0–12·8)	11·4 (10·7–12·1)	11·0 (10·3–11·6)	10·5 (9·8–11·2)	10·0 (9·3–10·7)	9·6 (8·9–10·3)	9·2 (8·5–9·9)	8·7 (8·1–9·4)	8·2 (7·6–8·9)	7·7 (7·1–8·4)	7·3 (6·6–7·9)	6·9 (6·3–7·5)	6·6 (6·0–7·2)	6·4 (5·7–7·2)	6·3 (5·2–7·4)	
Men (LOESS)	13·4 (11·8–14·9)	12·8 (11·8–13·9)	12·3 (11·5–13·1)	11·8 (11·1–12·6)	11·3 (10·5–12·1)	10·8 (10·0–11·6)	10·4 (9·6–11·2)	10·0 (9·1–10·8)	9·4 (8·7–10·2)	8·9 (8·1–9·6)	8·3 (7·5–9·0)	7·7 (6·9–8·5)	7·3 (6·6–8·0)	7·0 (6·3–7·7)	6·8 (5·9–7·7)	6·7 (5·4–8·0)	
Entire population (LOESS)	12·8 (11·4–14·2)	12·4 (11·4–13·3)	11·9 (11·2–12·6)	11·4 (10·8–12·1)	11·0 (10·3–11·7)	10·5 (9·7–11·2)	10·0 (9·3–10·7)	9·6 (8·9–10·4)	9·1 (8·4–9·8)	8·6 (7·9–9·3)	8·0 (7·3–8·7)	7·5 (6·8–8·2)	7·2 (6·5–7·8)	6·9 (6·2–7·5)	6·7 (5·9–7·4)	6·5 (5·3–7·7)	

***Figure 4:* Time trends in age-standardised pulmonary embolism-related mortality rates**

Observed age-standardised annual mortality rates are reported for individual States and for the entire population. Age-standardised annual mortality rates are also estimated by LOESS for the entire population, where specified, and are shown with corresponding 95% CIs. Countries are shown in order of observed age-standardised annual pulmonary embolism-related mortality rate between 2013 and 2015. The colours represent the value of the observed age-standardised annual pulmonary embolism-related mortality rates, ranging from green (lowest) to red (highest). Cells are empty if no data were available. AAPC=average annual percentage change. LOESS=Locally estimated scatterplot smoothing. NA=Not applicable.

prevention strategies in hospitalised patients,[41,42] decreased case fatality due to improved treatment, and changes in entering vital registration data. With regard to prevention, the National Health System in England observed a reduction in incidence of pulmonary embolism and pulmonary embolism-related in-hospital mortality nationally, possibly related to better risk assessment and appropriate thromboprophylaxis at their hospitals.[42] However, an opposite trend of steadily increasing incidence of pulmonary embolism has been reported in several other countries.[2] Advances in pulmonary embolism management might better explain the decreasing trends in mortality in the European Region, consistent with case fatality data from a 2019 nationwide cohort study[11] and with previous findings summarised in a narrative review of the literature.[2] Among other potential reasons, the acute management of pulmonary embolism might have benefited from the introduction of low-molecular-weight heparins, the improvement in monitoring of vitamin K antagonist therapy, treatment given according to the evolving concept of risk stratification, and more effective patient referral to high-volume centres.[43] Changes over time in the classification of pulmonary embolism as a cause of death cannot be ruled out, including a decrease in the assignment to so-called garbage codes in the past four decades.[8] Changes in the practice of selecting specific codes as underlying causes of death might affect time trends in mortality.[44,45]

Despite the overall decreasing trend, high pulmonary embolism-related mortality persists in Eastern Europe, especially among men. This observation is not different from what has been described for cerebrovascular disease and coronary heart disease,[19,46–48] as well as for deaths attributed to cardiovascular risk factors, including tobacco use, physical inactivity, dietary risks, high body-mass index, hypercholesterolemia, and arterial hypertension.[48] In this study, pulmonary embolism emerged as a substantial cause of death in younger women. This observation is in line with reports in other populations[27,49,50] and might reflect the hormone and pregnancy-associated risk of pulmonary embolism in women aged 15–55 years. This age-related peak in the proportionate mortality was consistent from 2000 to 2015. Of note, not all major advances in pulmonary embolism treatment apply to pregnancy because pregnant women have been excluded from the large phase 3 trials and, unitl 2008, from diagnostic studies.[51,52]

In an analysis of vital registration data, the possibility of underestimating mortality related to pulmonary embolism cannot be excluded because the database only included cases coded with pulmonary embolism or deep vein thrombosis as the underlying cause of death.[2] Of note, both the incidence and the fatality estimates might be twice as high if secondary codes are also considered.[2] Nonetheless, the diagnosis might have been missed, especially if death occurred suddenly or outside the hospital because autopsies are infrequently done in that setting. However, this might apply mainly to deaths in individuals older than 60 years, in whom the proportion of autopsies is lowest,[53,54] and, therefore, the attribution of death to pulmonary embolism is more problematic and dependent on clinical history.[55–57] Furthermore, deaths in patients with severe comorbidities might not have been attributed to pulmonary embolism according to the ICD principle that demands the underlying condition to be entered. This issue would possibly not have been solved even if routine autopsy had been done because the post-mortem detection of pulmonary emboli does not automatically imply that was the underlying cause of death.[58] However, the accuracy of death certificate completion might also be suboptimal for other acute

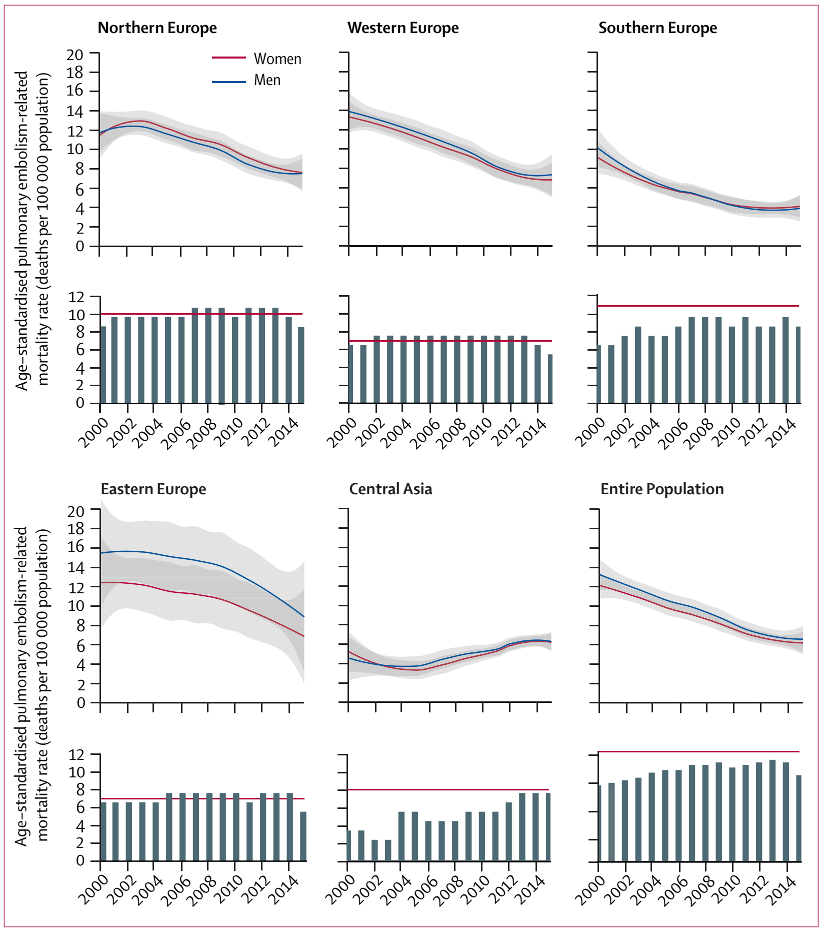

Figure 5: **Time trends in age-standardised pulmonary embolism-related mortality rates, 2000–15**
Locally estimated scatterplot smoothed lines for men (blue lines) and women (red lines) and 95% CIs (grey) for the annual age-standardised pulmonary embolism-related mortality rate in 41 European Member States with available data from 2000 to 2015. The number of Member States with available data each year, classified by subregion, is shown below each panel. The plotted weights and distribution of age-standardised pulmonary embolism-related mortality rates in each Member State from 2000 to 2015, which contributed to the locally estimated scatterplot smoothed estimates, are shown in the appendix (p 7). Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Moldova, Romania, and Slovakia; Northern Europe: Iceland, Denmark, Estonia, Finland, Ireland, Latvia, Lithuania, Norway, Sweden, and the UK; Southern Europe: Bosnia and Herzegovina, Croatia, Greece, Italy, Malta, Portugal, Serbia, Slovenia, Spain, and North Macedonia; Western Europe: Austria, Belgium, France, Germany, Luxembourg, Netherlands, and Switzerland; Central Asia: Armenia, Cyprus, Georgia, Israel, Kazakhstan, Kyrgyzstan, and Turkey.

cardiovascular events.[59] The difficulties in attributing deaths to pulmonary embolism reflect the absence of a validated case definition based on broadly accepted criteria. Definitions previously used in the pulmonary embolism literature ranged from "autopsy-confirmed pulmonary embolism" to "sudden death after venous thromboembolism in the absence of a more probable cause of death".[58] Acute pulmonary embolism represents a potentially preventable cause of in-hospital death; therefore, some physicians might be reluctant to list it as the primary cause of death. Because the WHO Mortality Database does not contain information on the secondary causes of death, ethnic origin, and socioeconomic status for specific conditions in the general population, we could not do additional analyses that focused on patient subgroups. Moreover, the Database does not provide data on the number of diagnosed cases, which are necessary for estimation of case fatality trends. Relevant geographical differences might exist not only for the quality of care, including the implementation of validated diagnostic algorithms for pulmonary embolism and acute management, but also regarding the quality and completeness of vital registration data submitted to WHO.[20,60,61] Of note, we verified that the data in the WHO Mortality Database correspond to national vital registration data used in individual studies.[27,37] These elements are to be considered when comparing mortality rates across Member States and subregions.

In conclusion, our comprehensive analysis of the vital registration data of Member States from the WHO European Region shows that pulmonary embolism still causes a large number of deaths and contributes considerably to total mortality, particularly among women aged 15–55 years. The age-standardised pulmonary embolism-related mortality has been continuously declining in most Member States since the beginning of the 21st century. Pulmonary embolism represents a global problem, which requires continuous efforts to improve awareness and implement effective preventive and risk-adapted therapeutic measures.

Contributors

SB conceived the study. SB, SHM, and LV designed the study and wrote the manuscript. SHM and LV did the statistical analysis. All authors interpreted the results. SHM, LV, FAK, TM, SM, WA, ATC, BJH, and SVK critically reviewed the manuscript. All authors gave final approval to the submitted manuscript.

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