



## Early View

Original research article

# Lung cancer mortality in Europe and the United States between 2000 and 2017: an observational analysis

Chinmay Jani, Dominic C Marshall, Harpreet Singh, Richard Goodall, Joseph Shalhoub, Omar Al Omari, Justin D Salciccioli, Carey C Thomson

Please cite this article as: Jani C, Marshall DC, Singh H, *et al.* Lung cancer mortality in Europe and the United States between 2000 and 2017: an observational analysis. *ERJ Open Res* 2021; in press (<https://doi.org/10.1183/23120541.00311-2021>).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Lung cancer mortality in Europe and the United States between 2000 and 2017: an observational analysis

**Authors:** Chinmay Jani MBBS<sup>1,2</sup>, Dominic C Marshall MBBS<sup>3</sup>, Harpreet Singh MBBS<sup>4</sup>, Richard Goodall MBChB<sup>5</sup>, Joseph Shalhoub MBBS<sup>5,6</sup>, Omar Al Omari<sup>1,2</sup>, Justin D Saliccioli MBBS<sup>2,7</sup>, Carey C Thomson MD<sup>1,2,8</sup>

**Affiliations:**

1. Department of Medicine, Mount Auburn Hospital/Beth Israel Lahey Health, Cambridge, MA, USA
2. Harvard Medical School, Boston, MA, USA
3. National Heart and Lung Institute, Imperial College London, UK
4. Department of Pulmonary and Critical Care, Medical College of Wisconsin, Milwaukee, WI, USA
5. Department of Surgery and Cancer, Imperial College of London, London, UK
6. Imperial Vascular Unit, Imperial College Healthcare NHS Trust, London, UK
7. Division of Pulmonary and Critical Care, Brigham and Women's Hospital, Boston, MA, USA
8. Division of Pulmonary and Critical Care, Mount Auburn Hospital, Cambridge, MA, USA

**Correspondence:**

Justin Saliccioli, MD  
Brigham and Women Hospital  
75 Francis St,  
Boston, MA 02115  
United States  
617-301-0761  
Justin.saliccioli@gmail.com

**Conflicts of interest:**

The authors do not have any conflicts of interest or any disclosures.

**Disclosures of funding:** This research received no specific grant from any funding agency in public, commercial or not-for-profit sectors.

**Prior abstract presentations:**

1. Trends in lung cancer mortality between 2001 and 2017: An observational study in USA and EU. 2<sup>nd</sup> June 2020. Presented at ASCO (American Society of Clinical Oncology)
2. Persistent sex-difference in lung cancer mortality between 2001 and 2017 in the US and EU, 17<sup>th</sup> September 2020. Presented at ESMO (European Society of Medical Oncology)

**Summary:**

Lung cancer mortality trends have steadily decreased for males between 2000 and 2017 in Europe and the United States, whereas increasing mortality trends have been observed for females. Investigation into the gender-mortality gap is called for.

**Abbreviations:**

ASDR - Age Standardized Death Rates

CDC - Centers for Disease Control and Prevention

CI – Confidence Interval

CR - Cancer Registries

EAPC - Estimated Annual Percentage Change

HR – Hazard Ratio

ICD - International Classification of Diseases

IQR - Inter-Quartile Range

LDCT – Low-Dose Computed Tomography

LOWESS – Locally Weighted Scatterplot Smoothing

LUSI – Lung Cancer Screening Intervention

NLST- The National Lung Screening Trial

SEER - Surveillance, Epidemiology, and End Results Program

US – United States

WHO – World Health Organization

## **Abstract**

### *Background*

The lung is the most common site for cancer and has the highest worldwide cancer-related mortality. Our study reports and compares trends in lung cancer mortality in the United States (US) and 26 European countries.

### *Study design and methods*

Lung cancer mortality data were extracted for males and females for each of the years 2000-2017 from the World Health Organization (WHO) Mortality and the Centers for Disease Control and Prevention (CDC) WONDER databases. Lung cancer mortality trends were compared using Joinpoint regression analysis, and male-to-female mortality ratios were calculated.

### *Results*

Down-trending lung cancer mortality rates were observed in males in all countries except Cyprus and Portugal between 2000 and 2017. In females, increasing mortality rates were observed in 22 of the 27 countries analyzed. Latvia had the highest estimated annual percentage change (EAPC) in male mortality (-9.6%) between 2013-2015. In the US, EAPCs were -5.1% for males and -4.2% for females between 2014-2017. All countries had an overall decrease in the ratio of male-to-female lung cancer mortality. The most recent observation of median male-to-female mortality was 2.26 (IQR 1.92 – 4.05). The countries with the greatest current sex disparity in lung cancer mortality were Lithuania (5.51) and Latvia (5.00).

### *Conclusion*

Between 2000 and 2017, lung cancer mortality rates were decreasing for males in Europe and the US, whereas increasing lung cancer mortality rates were generally observed in females. There is a persistent but decreasing sex-mortality gap, with men having persistently greater lung cancer mortality but with rates decreasing faster than women.

**Keywords:** Lung Cancer, Mortality, Europe, UK, US, Joinpoint

## **Introduction**

Lung cancer is the leading cause of cancer death in males and the third most diagnosed and second leading cause of cancer death in females worldwide. In the United States (US), lung cancer is the most common cancer and the leading cause of cancer deaths in males and females<sup>1,2</sup>. The World Health Organization (WHO) estimated that, in 2018, there were 2.09 million cases of lung cancer and 1.76 million lung cancer-related deaths annually worldwide<sup>3</sup>. Overall, there has been a worldwide decline in the incidence of lung cancer<sup>4,5</sup>. However, multiple European studies have reported incongruous falls in lung cancer incidence in males versus females<sup>4,5</sup>. Up to date comparisons of the recent trends in lung cancer mortality across the EU, the UK and the US are lacking.

The principal aim of this study was to compare the trends in mortality from lung cancer across the US and European Union countries over recent decades, using data obtained from the Centers for Disease Control and Prevention Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER) and the WHO Mortality Databases. A secondary aim was to compare the differential trends amongst males and females within each analyzed country to identify sex disparities in temporal lung cancer mortality trends. We have previously used similar methods to describe trends in mortality from cardiovascular<sup>6</sup> and respiratory diseases<sup>7,8</sup>.

## **Methods**

### *Data sources*

Data were obtained from two publicly available online databases: CDC WONDER for the US, and the WHO Mortality Database for the 27 European Union countries (inclusive of the United Kingdom).

Lung cancer mortality data were identified and extracted from the WHO database from 2000 to 2017 using the International Classification of Diseases (ICD) system code C34 ('Malignant neoplasm of bronchus and lung') and its sub-codes. The WHO evaluates the quality of the data to ensure comparability and reliability without adjustment for underreporting<sup>9</sup>. Luxembourg and Malta were excluded based on the data quality and multiple missing data points for more than three consecutive years. Twenty-five member states of the European Union (EU), the UK, and the US were selected to produce a defined group for analysis<sup>10</sup>. WHO Mortality lacks data for the USA after the year 2007. Therefore, the CDC Wonder database was used for the USA.

Lung cancer mortality data for individuals in the US were extracted from the CDC WONDER database in collaboration with the National Center for Health Statistics and the Vital Statistics Cooperative Program <sup>11</sup>. CDC WONDER is a comprehensive online public health information system developed and owned by the CDC and its collaborating partners to serve public health practice and research <sup>12,13</sup>. The mortality database is updated annually from deaths registered by national civil registration systems. Data is collected according to ICD tenth revision, a process that has been used previously with adequate validity and the provision of robust data <sup>6,8</sup>.

Crude mortality rates were dichotomized by sex and reported by year. We computed age-standardized death rates (ASDRs) per 100,000 population using the World Standard Population for Europe and the US Standard Population for the US. The ASDR was defined as mortality weighted to the distribution of mortality per 5-year age group, according to the appropriate standard population <sup>14</sup>. This removes the effects of historical events on age structure and controls for differences in age structure in populations. The estimated level of coverage for deaths with a recorded cause for death is calculated by actual reporting divided by the estimated mortality rate. Population and birth recording in all countries exceed 90%, as per the WHO standard for inclusion in the database <sup>9</sup>. Institutional review board approval was not necessary as the data collected is available in the data-repositories mentioned above in a de-identified format.

### *Statistical analyses*

Joinpoint regression analysis with annualized data (between 2000 and 2017, where available) was used to assess changes in linear slope for mortality trends over time. In brief, Joinpoint analysis assesses the overall trends in mortality, initially with no Joinpoints, and tests for significant changes in the model with the sequential addition of Joinpoints where there is a significant change in the slope of the line. Joinpoint software (Command Line Version 4.5.0.1) is provided by the US National Cancer Institute Surveillance Research Program <sup>15</sup>. The model computes an estimated annual percentage change (EAPC) for each trend by fitting a regression line to the natural logarithm of the rates. Mortality data were missing in a small subset of countries in the WHO Mortality Database for one or more calendar years. Joinpoint software requires continuous data throughout the observation period to be suitable for analysis. Therefore, we imputed using the last observation carried forward for countries with missing data for the purpose of Joinpoint analysis only. If a country had more than three consecutive years of missing data during the observation period, this was excluded from the analysis to avoid excess imputation. There were no other modifications to the data. Changes

in ASDR over the observation period are calculated as crude absolute differences between first and last data points for the earliest and most recent years available.

### *Post hoc analysis*

From our primary analysis, we observed convergent trends in male and female mortality during the observation period across all countries. Given the magnitude and changing trends for males and females, a *post hoc* analysis was performed to assess the changing magnitude of this male-to-female mortality difference. We computed male-to-female mortality ratios and used locally weighted scatterplot smoothing (LOWESS) plots fit to the ratios of male-to-female mortality using SAS v9.4 (SAS, Cary, NC). We plotted the results of this analysis for visual inspection. As this was a *post hoc* analysis, we treated this as exploratory and descriptive, with no further tests of the data performed.

## **Results**

Data from a total of 27 countries were analyzed (25 EU nations (inclusive of the UK) and the US). 6 countries had complete data for each of the years 2000-2017, 12 had data from 2000-2016, 7 countries had data from 2000-2015 and 2 countries had data from 2000-2014, accounting for a total of 898 data elements available for analysis. For the purpose of Joinpoint analysis alone, 14 (1.6%) data points were imputed for missing data points, as described above.

### *Current lung cancer mortality*

**Table 1** and **Figure 1** show the most recent calendar year mortality data. In 2017, Hungary had the highest observed lung cancer ASDR of all analyzed countries for both males and females, 64.51/100,000 and 31.04/100,000, respectively. In 2017, the lowest lung cancer mortality rate was observed in Sweden for males (17.31/100,000) and Lithuania for females (7.58/100,000). ASDRs for the US in 2017 for males and females were 44.30/100,000 and 30.60/100,000, respectively.

### *Changes in lung cancer mortality between 2000 and 2017*

**Table 1** and **Figures 1 and 2** show lung cancer mortality rates at the beginning and the end of the study period. The overall trend for lung cancer mortality for males across Europe and the US was decreasing steadily over time. Mortality rates in males decreased in the majority of the included countries, with the only exceptions being Bulgaria (+3.45%), Portugal (+1.60%), and Romania (+0.03%). The largest decreases in male mortality in European countries were observed in the Czech Republic (-27.34%) and Hungary (-20.30%). The US

showed a decrease of 32.40% in male mortality between 2000 and 2017. In contrast to males, the majority of the analyzed countries had an increase in lung cancer mortality rates among females. Only in Ireland (-0.36%) and the US (-10.70%) decreased lung cancer mortality rates were observed for females. All remaining countries had increasing lung cancer mortality rates for females, with the highest increases observed in Hungary (+7.80%) and the Netherlands (+7.10%).

#### *Joinpoint regression for changes in lung cancer mortality trends in males*

**Table 2** and **Figure 2** show the results of the Joinpoint regression analysis for lung cancer mortality rates in males from 2000 to 2017. Significant trend changes were observed. The most rapid decreases in lung cancer mortality rates were identified in Latvia between 2013-2015 (EAPC -9.6%), followed by Belgium between 2010 and 2016 (EAPC -4.2%), Austria between 2013-2017 (EAPC -3.5%), Italy between 2012-2015 (EAPC -3.3%) and Greece between 2014-2016 (EAPC -3.2%). Male mortality declined consistently across the study period, with only 1 Joinpoint in Czech Republic, Denmark, Estonia, Finland, Hungary, Ireland, Lithuania, Slovakia, Slovenia, the UK, and the Netherlands. Bulgaria, Romania, Spain, and Sweden also showed increased mortality in the initial years of the investigation, followed by a subsequent downward trend. Greece showed a notable trend with 3 Joinpoints; there was a steady decline until 2011 (EAPC -0.4%), followed by increasing mortality between 2011 and 2014 (EAPC 2.8%), and the second period of decline after 2014 (EAPC -3.2%). Spain and Germany also demonstrated more variable trends with 3 Joinpoints over the time period studied, and both with significant reductions in lung cancer mortality over the periods covered by the most recent trends (Spain between 2011-2015, EAPC -2.3%; Germany between 2013-2016, EAPC -2.5%). The United States had variable trends in lung cancer mortality for males, with 4 Joinpoints identified and a steady decline in mortality since 2000, followed by a more rapid decline recently (EAPC -5.1%, 2014-2017).

#### *Joinpoint regression for changes in lung cancer mortality trends in females*

**Table 2** and **Figure 2** show the results of a Joinpoint regression analysis for lung cancer mortality rates in females between 2000 to 2017 for each included country. For females, 21 of the 26 European nations reported increasing rates in lung cancer mortality, with the exceptions being Belgium, Denmark, Ireland, Sweden, and the UK. Sweden, Ireland, and Denmark showed declining mortality rates from 2005 to 2006, the UK from 2008, whereas Belgium did not show a decreasing mortality trend until 2011. The highest EAPC (+4.4%, 2000-2015) is noted in Spain. The greatest recent decline in mortality was in Denmark, with an EAPC of -0.9% (2005-2015). The US had 4 Joinpoints for females, in a pattern similar to that observed



for males. The US had an increase in mortality from the year 2000 to 2004 (+0.2%), followed by a steady decline. Like males, female mortality rates have also declined recently (-4.2%, 2014-2017).

#### *Post hoc analysis of the male-to-female ratio of lung cancer mortality*

**Table 4** and **Figure 3** show sex-ratio trends for lung cancer. Lung cancer mortality rates were higher in males than females in all countries for each year of comparison. Over the observation period, all countries had an overall decrease in the ratio of male-to-female mortality: in 2000, the median male-to-female mortality ratio was 5.35 (IQR 3.65 – 6.06), whereas, for the most recent year, the median male-to-female mortality ratio was 2.26 (IQR 1.92 – 4.05). The countries with the greatest current disparity in lung cancer mortality by sex were Lithuania (male-to-female mortality ratio 5.51), Latvia (5.00), and Bulgaria (4.40). The countries with the smallest differences in mortality between sex were Sweden (male-to-female mortality ratio 1.10), Denmark (1.13), and the UK (1.39). The median percentage change for all countries was -44.45% (IQR -50.44% – -30.56%). The countries with the greatest percentage change in male-female lung cancer mortality ratios were Spain (-55.19%), Belgium (-55.18%), and Cyprus (-53.64%). The countries with the smallest percentage change in male-female lung cancer mortality ratios were Bulgaria (-21.65%), the US (-22.05%), and Portugal (-25.46%).

## **Discussion**

### *Principal findings*

In this observational study of lung cancer mortality in Europe and the United States, male lung cancer mortality steadily declined in the majority of countries. However, for females, there were increasing lung cancer mortality trends in the majority of countries. The US was a notable exception to this observation, with decreasing lung cancer mortality rates observed in females over the 17-year study period. There remains a persistent sex-mortality gap from lung cancer, with male mortality rates remaining consistently higher than those for females. However, the magnitude of these differences in male-female lung cancer mortality ratios is decreasing over time, resulting from both general decreases in male lung cancer mortality rates and increases in female lung cancer mortality rates.

The primary aim of this investigation was to investigate the changes in trends in lung cancer mortality between males and females over the past two decades and provide up-to-date estimates of the burden of lung cancer mortality across EU countries and the US. To our knowledge, this is the first paper to compare the trends in lung cancer mortality rates across

the EU and the US using data obtained from both the CDC WONDER and WHO mortality databases.

### Possible contributors to the observed trends

A number of population-level and public health efforts within cancer control programs have been implemented in attempts to improve both the prevention of and mortality from lung cancer in the US and EU countries. Being aware that the present data is observational, discussion as to the contributors to the observed trends in mortality should be cautious, however likely contributors to the reducing rates of lung cancer mortality include the development and implementation of cancer registries across the US and EU countries, changes in smoking behaviors, the advent of newer treatment modalities and the development of screening programs.

Cancer Registries (CRs) provide a means to identify high-risk patient cohorts and, therein, define patients to be targeted for resource allocation to enable both prevention strategies and early diagnosis and treatment. Currently, there are 55 cancer registries in the US, covering 94% of the population, the first of which was the Surveillance, Epidemiology, and End Results (SEER) Program (established in 1973) <sup>16</sup>. CRs have been an essential adjunct to the implementation of high-quality lung cancer screening programs <sup>17</sup>, and their use has previously been suggested to reduce population-level mortality, which may be contributory to the observed earlier improvements in lung cancer mortality in the US compared to the majority of European nations <sup>17</sup>. CRs - which also enable identification of geographical differences in treatment outcomes - have progressed consistently since 1990 and have increased to nearly 200 in Europe <sup>18</sup>, covering approximately 60% of the European population. However, significant disparities of population coverage by CRs exist across EU countries, especially in south-eastern Europe <sup>18</sup>. Countries like Hungary (1999), Croatia (2001), and Poland (1999), who are still having high mortalities, incorporated cancer registries late as compared to other countries like Denmark (1982), Sweden (1958) with low mortality rates. We also saw that the Baltic countries like Lithuania (1993), Latvia (2000) also started having registries later. Newer treatment modalities, including immunomodulators, have become a feature of lung cancer therapy since 2014 and have resulted in improvements in mortality, with further data pertaining to the impact of these novel therapies awaited <sup>19</sup>.

The tobacco epidemic has remained closely associated with the incidence and mortality of lung cancer and has been a focus of considerable attention and intervention. Population-level efforts to reduce smoking prevalence are also evidenced to contribute to reductions in lung cancer mortality <sup>20</sup>, and peaks in lung cancer mortality have mirrored the smoking epidemic <sup>20</sup>.

European countries have started implementing policies for outdoor smoking as well, although still majority of these laws fail to implement smoke-free outdoor areas. Few countries adopted these policies earlier <sup>21</sup>. Countries having higher mortality rates like Hungary (ASDR of 64.5 for males and 31 for females): Croatia (54.8 for males, 30,6 for females), Poland (53 for males, 18.9 for females), Greece (50 for males, 11.8 for females) and Romania (47.5 for males, 11.7 for females) still do not have policies for a ban on outdoor smoking <sup>22</sup>. Whereas currently, Sweden is one of the only countries in Europe with a complete ban on outdoor smoking that had very low mortality (17.3 for males, 7,6 for females) <sup>22</sup>. Countries with a high Human Development Index with early initiatives to reduce smoking prevalence have shown a steady reduction in lung cancer <sup>23</sup>. Interestingly, these same countries have also observed a disparity in smoking cessation by sex<sup>20</sup>, which may contribute to the differential lung cancer mortality trends observed amongst men and women in the present analysis.

More recently, lung cancer screening has contributed to improvements in the diagnosis of early-stage lung cancer <sup>24</sup>. Large population screening trials in the US and Europe have highlighted the benefits of lung cancer screening on mortality rates and have also demonstrated important sex disparities. The National Lung Screening Trial (NLST) carried out in the USA compared low-dose computed tomography (LDCT) scanning versus chest radiography in high-risk individuals, reporting a 20% reduction in lung cancer mortality for LDCT-screened participants, leading to a grade B recommendation from the US Preventive Services Task Force in 2013 indicating high certainty that there will be moderate net benefit <sup>25</sup>. At the same time, the Nelson trial in Europe also showed that the cumulative rate ratio for death from lung cancer at ten years was 0.76 (95% CI, 0.61 to 0.94; P=0.01) in the screening group <sup>26</sup>. German Lung Cancer Screening Intervention (LUSI) results were also in the same line with HR of 0.74 (95% CI: 0.46-1.19; p = 0.21) <sup>27</sup>. The evidence supporting the benefits of screening upon lung cancer outcomes has led the European Round Table to recommend all National Health care policymakers implement lung cancer screening in Europe. We will be able to study its effects on the general population in the coming decade <sup>28</sup>.

Also, Socioeconomic disparities are associated with a more delayed diagnosis which plays a significant role in the outcomes of lung cancer. It is also linked with decreased chances of receiving treatment <sup>29</sup>. When comparing health care costs per person for lung cancer between different European countries in 2009, it is found that countries like Hungary (4 €) and Poland (5 €) are spending less as compared to the European Union average (8 €) or Sweden (8 €) <sup>30</sup>. When comparing the US and western Europe between 1982-2010, the cost of lung cancer care exceeded that in Europe by 406 billion. Despite that, the US still had a high ASDR. Analysis showed that higher cost spending in cancer care could avert deaths in breast,

prostate, and colorectal but rather showed excess deaths for lung cancer<sup>31</sup>. This suggests that higher spending alone cannot decrease mortality. There needs to be a multifactorial approach.

### The gender gaps

We also observed that the overall male to female ratio is steadily decreasing in all the countries throughout the observation period. Various plausible explanations exist, including the smoking pandemic<sup>32</sup>. In most countries, female smoking has lagged behind male smoking, and so have the resulting mortality peaks due to earlier cultural prohibition<sup>20</sup>. This has caused smoking rates in older women to continue to rise for most countries in Europe, with its corresponding impact on lung cancer mortality<sup>33, 34</sup>. In the US, the smoking incidence has decreased in both males and females. The decline is comparatively slower in females, which can be correlated to a late decline in female mortality trend compared to males in our study<sup>32</sup>. It is also found that women might be more susceptible to cigarette carcinogens in cigarettes<sup>35, 36</sup>. The gastrin-releasing peptide receptor gene found on the X chromosome has been linked with bronchial cells proliferation when activated. This Gene has been activated more and earlier in females when exposed to carcinogens due to smoking<sup>37</sup>.

A recent study reported the unique finding that females were 36% less likely to discuss lung cancer screening with the health care provider than males<sup>38</sup>. Various trials have shown encouraging results to promote lung cancer screening in females. The NLST reported minor evidence of differential benefit in females with lower RRs for small cell and squamous cell carcinoma in females on early detection<sup>39</sup>. At the same time, sub-group analysis of the NELSON trial of Europe identified screening to be more effective at decreasing mortality in high-risk females (HR 0.39 – 0.61) than in males (HR 0.59 – 0.91) over ten years<sup>26</sup>. The German Lung Cancer Screening Intervention (LUSI) study reported up to 69% reduction in lung cancer mortality among females (HR 0.31 [95% CI 0.10 – 0.96]), as compared to 6% in males (HR 0.94 [95% CI 0.54 – 1.61])<sup>27</sup>. The PLCO trial involving 77,911 females demonstrated a protective effect of hormone replacement therapy against lung cancer development and mortality<sup>40</sup>. Efforts are now needed to increase the awareness amongst females.

### The Baltics

As seen in Figures 2 and 3, Lithuania, Latvia, and Estonia had fluctuations in the trends. Various plausible explanations exist. Baltic states have unique environmental exposure due to the Chernobyl effect. These countries have a population directly exposed to said

perturbator, with documented effects <sup>41</sup>, which may predispose them to other types of cancer (i.e., Thyroid) rather than lung <sup>42</sup>. The analyses on the matter are beyond the scope of the paper; it still represents a caveat when interpreting the results <sup>35 42</sup>. Similar to the Baltics, Portugal and Cyprus also showed an increasing trend. An analysis from 2009 showed that Portugal was still entering the third stage of the smoking epidemic <sup>43</sup>. Also, other cancers like colorectal, breast, and prostate are more prevalent in Portugal than lung cancer <sup>44</sup>. Therefore, a strategic approach might be needed in similarly managing lung cancer mortality as other cancers. Similarly, in the Baltic countries, more awareness exists for thyroid cancer screening than other cancers <sup>41</sup>. A unified approach to all cancers is needed for these countries.

### Strengths and limitations

The strengths of this investigation include the use of annual mortality data collected from national surveillance statistics from the WHO and the CDC. These data have made it possible to assess population-level trends over an extended observation period, allowing comparisons in trends rather than absolute annual mortality rates. Despite this study's strengths, there are a number of limitations that should be considered when interpreting the results. The US ASDRs were based on the US Standard Population, whereas the World Standard Population was utilized for the ASDR calculation for European nations. Therefore, these results cannot be directly compared. However, one notable strength of using longitudinal data is commenting on overall trends within individual countries after standardization and reporting these differences between health systems. Second, we did not attempt to assess the prevalence of morbidity associated with lung cancer as our primary aim was to better understand changes in mortality trends; there may be substantial differences in the prevalence of lung cancer between countries that we cannot elucidate in this current report. Third, we combined subtypes of lung cancer in our findings as mortality data is not recorded separately for each pathological subtype. It is also found that the number of deaths from lung cancer nationally in the US was lower than that reported by death certificate data <sup>32</sup>. Finally, as with any observational study, causal statements regarding the observed trends cannot be made. The discussion is provided to assist future researchers, policymakers, and public health experts in focusing their efforts.

## **Conclusion**

This report reveals decreasing trends in lung cancer mortality in Europe and the US for men between 2000 and 2017. For women, many European countries demonstrate a gradually rising trend in lung cancer mortality over the same time period. There is a persistent but decreasing sex-mortality gap across Europe and the US. Future efforts should be targeted to aligning policy and public health interventions to further guide implementation strategies for cancer registries, smoking cessation programs and large-scale lung cancer screening with gender equity in mind.

**Acknowledgements:** None

**Author contributions:** Each of the authors significantly contributed to this manuscript. Dr Jani, Dr Saliccioli, Dr Singh and Dr Thomson made significant contributions to the concept and design of this paper. Dr Saliccioli, Dr Marshall, and Dr Jani were significantly involved in the statistical analysis. Dr Jani, Dr Marshall, Dr Singh, Dr Goodall, Dr Shalhoub, Dr Al Omari, Dr Saliccioli and Dr Thomson were greatly involved in drafting manuscript. Dr Shalhoub, Dr Saliccioli and Dr Thomson were involved in critical revision of the manuscript and contributed vital intellectual content. Chinmay Jani (corresponding author, guarantor) takes responsibility for the content of the manuscript, including the data and analysis.

## References

1. United States cancer statistics: data visualizations. Retrieved September. 2018;27.
2. Xu J, Kochanek KD, Murphy SL, Arias E. Mortality in the United States, 2012: US Department of Health and Human Services, Centers for Disease Control and ...; 2014.
3. World Health Organization. Fact Sheets. Geneva: World Health Organization; 2020. [Available from: <https://www.who.int/news-room/fact-sheets/detail/cancer>.
4. Zhang Y, Ren JS, Huang HY, Shi JF, Li N, Zhang Y, et al. International trends in lung cancer incidence from 1973 to 2007. *Cancer Med*. 2018;7(4):1479-89.
5. Mousavi SM, Schmid S, Cerny T, Fruh M. Lung cancer and smoking trends in the young in Switzerland: a study based on data of the National Institute for Cancer Epidemiology and Registration and of the Swiss Health Surveys. *Swiss Med Wkly*. 2018;148:w14708.
6. Hartley A, Marshall DC, Saliccioli JD, Sikkil MB, Maruthappu M, Shalhoub J. Trends in Mortality From Ischemic Heart Disease and Cerebrovascular Disease in Europe: 1980 to 2009. *Circulation*. 2016;133(20):1916-26.
7. Saliccioli JD, Marshall DC, Shalhoub J, Maruthappu M, De Carlo G, Chung KF. Respiratory disease mortality in the United Kingdom compared with EU15+ countries in 1985-2015: observational study. *BMJ*. 2018;363:k4680.
8. Marshall DC, Saliccioli JD, Shea BS, Akuthota P. Trends in mortality from idiopathic pulmonary fibrosis in the European Union: an observational study of the WHO mortality database from 2001–2013. *European Respiratory Journal*. 2018;51(1):1701603.
9. World Health Organization. 2014. Census and Civil Registration Coverage Data by Country. <http://apps.who.int/gho/data/node.main.121?lang=en>WHO.%202014.%20WHO. Access date May 03, 2020. [
10. European Commission. 2020. EU member states.
11. Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death" "1999-2018 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999-2018, as" "compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed" "at <http://wonder.cdc.gov/ucd-icd10.html> on May 6, 2020 10:49:22 AM.



12. Friede A, Reid JA, Ory HW. CDC WONDER: a comprehensive on-line public health information system of the Centers for Disease Control and Prevention. *Am J Public Health*. 1993;83(9):1289-94.
13. Friede A, Rosen DH, Reid JA. CDC WONDER: a cooperative processing architecture for public health. *J Am Med Inform Assoc*. 1994;1(4):303-12.
14. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. <https://www.who.int/healthinfo/paper31.pdf>.
15. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19(3):335-51.
16. White MC, Babcock F, Hayes NS, Mariotto AB, Wong FL, Kohler BA, et al. The history and use of cancer registry data by public health cancer control programs in the United States. *Cancer*. 2017;123 Suppl 24:4969-76.
17. Parkin DM. The role of cancer registries in cancer control. *Int J Clin Oncol*. 2008;13(2):102-11.
18. Forsea AM. Cancer registries in Europe-going forward is the only option. *Ecancermedicalscience*. 2016;10:641.
19. Forde PM, Chaft JE, Pardoll DM. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *N Engl J Med*. 2018;379(9):e14.
20. Thun M, Peto R, Boreham J, Lopez AD. Stages of the cigarette epidemic on entering its second century. *Tobacco control*. 2012;21(2):96-101.
21. Martinez C, Guydish J, Robinson G, Martinez-Sanchez JM, Fernandez E. Assessment of the smoke-free outdoor regulation in the WHO European Region. *Prev Med*. 2014;64:37-40.
22. Smokefree Map. Smoke free partnership foundation. (<https://www.smokefreepartnership.eu/smokefree-map>).
23. CI5plus. Cancer Incidence in Five Continents time trends. Lyon: International Agency for Research on Cancer; 2020.
24. Kowall B, Jockel KH, Stang A. [Lung cancer screening: current trends]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2018;61(12):1551-8.

25. Aberle D, Adams A, Berg C, Black W, Clapp J, Fagerstrom R, et al. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening New England Journal of Medicine 365 (5): 395-409 DOI 10.1056. NEJMoa1102873. 2011.
26. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382(6):503-13.
27. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. Int J Cancer. 2020;146(6):1503-13.
28. Field JK, deKoning H, Oudkerk M, Anwar S, Mulshine J, Pastorino U, et al. Implementation of lung cancer screening in Europe: challenges and potential solutions: summary of a multidisciplinary roundtable discussion. ESMO Open. 2019;4(5):e000577.
29. Ebner PJ, Ding L, Kim AW, Atay SM, Yao MJ, Toubat O, et al. The Effect of Socioeconomic Status on Treatment and Mortality in Non-Small Cell Lung Cancer Patients. Ann Thorac Surg. 2020;109(1):225-32.
30. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol. 2013;14(12):1165-74.
31. Soneji S, Yang J. New analysis reexamines the value of cancer care in the United States compared to Western Europe. Health Aff (Millwood). 2015;34(3):390-7.
32. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med. 2020;383(7):640-9.
33. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. Jama. 2014;311(2):183-92.
34. Torre LA, Siegel RL, Ward EM, Jemal A. International variation in lung cancer mortality rates and trends among women. Cancer Epidemiol Biomarkers Prev. 2014;23(6):1025-36.
35. Fontham ET, Correa P, Reynolds P, Wu-Williams A, Buffler PA, Greenberg RS, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. JAMA. 1994;271(22):1752-9.

36. Wang TJ, Zhou BS, Shi JP. Lung cancer in nonsmoking Chinese women: a case-control study. *Lung Cancer*. 1996;14 Suppl 1:S93-8.
37. Shriver SP, Bourdeau HA, Gubish CT, Tirpak DL, Davis AL, Luketich JD, et al. Sex-specific expression of gastrin-releasing peptide receptor: relationship to smoking history and risk of lung cancer. *J Natl Cancer Inst*. 2000;92(1):24-33.
38. Warner ET, Lathan CS. Race and sex differences in patient provider communication and awareness of lung cancer screening in the health information National Trends Survey, 2013-2017. *Prev Med*. 2019;124:84-90.
39. Pinsky PF, Church TR, Izmirlian G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer*. 2013;119(22):3976-83.
40. Abdel-Rahman O. Lung cancer incidence and mortality in relationship to hormone replacement therapy use among women participating in the PLCO trial: a post hoc analysis. *Int J Clin Oncol*. 2020;25(5):885-91.
41. Rahu K, Hakulinen T, Smailyte G, Stengrevics A, Auvinen A, Inskip PD, et al. Site-specific cancer risk in the Baltic cohort of Chernobyl cleanup workers, 1986-2007. *Eur J Cancer*. 2013;49(13):2926-33.
42. Samet JM, de Gonzalez AB, Dauer LT, Hatch M, Kostis O, Mettler FA, Jr., et al. Gilbert W. Beebe Symposium on 30 Years after the Chernobyl Accident: Current and Future Studies on Radiation Health Effects. *Radiat Res*. 2018;189(1):5-18.
43. Alves L, Bastos J, Lunet N. Trends in lung cancer mortality in Portugal (1955-2005). *Rev Port Pneumol*. 2009;15(4):575-87.
44. *Globocon 2020 Statistics for Portugal*. World Health Organization. <https://gco.iarc.fr/today/data/factsheets/populations/620-portugal-fact-sheets.pdf>.

## **Table Legends:**

**Table 1:** Lung cancer age-standardized death rates for males and females, and male-to-female ratios. \*The US data is standardized based on the US population. CDC WONDER database is used for data collection in the US. (Luxembourg and Malta were excluded due to data quality.)

**Table 2:** Joinpoint analysis for lung cancer mortality for males in 25 European Union countries, the UK and the US, for Years 2000 to 2017, where data available. \*The US data is standardized based on the US population. CDC WONDER database is used for data collection in the US. CI, confidence interval; EAPC, estimated annual percentage change.

**Table 3:** Joinpoint analysis for lung cancer mortality for females in 25 European Union countries, the UK and the US, for Years 2000 to 2017, where data available. \*The US data is standardized based on the US population. CDC WONDER database is used for data collection in the US. CI, confidence interval; EAPC, estimated annual percentage change.

**Table 4:** Post hoc analysis of the male-to-female ratio of lung cancer Mortality.

Figure Legends:

### Age Standardized Death Rate

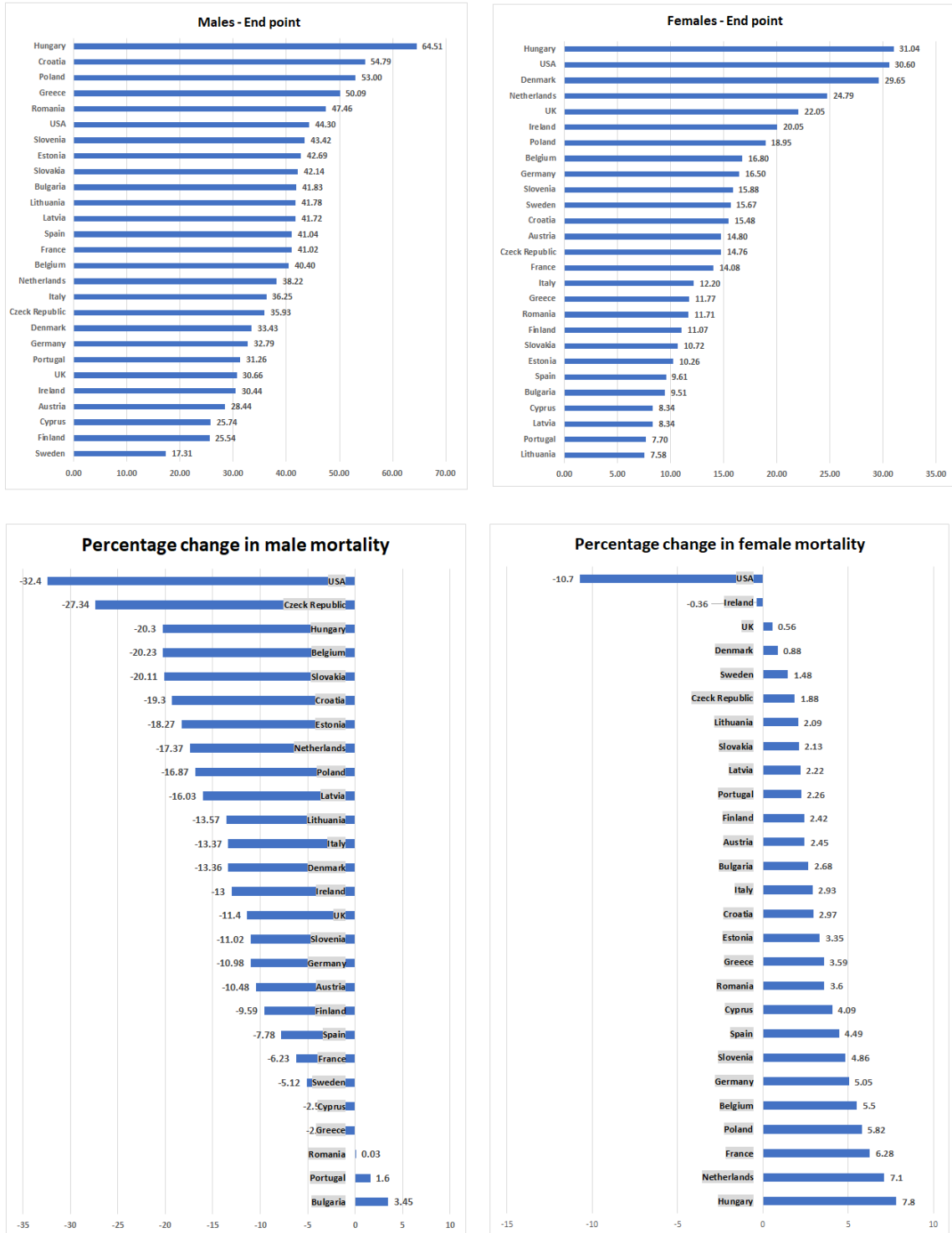
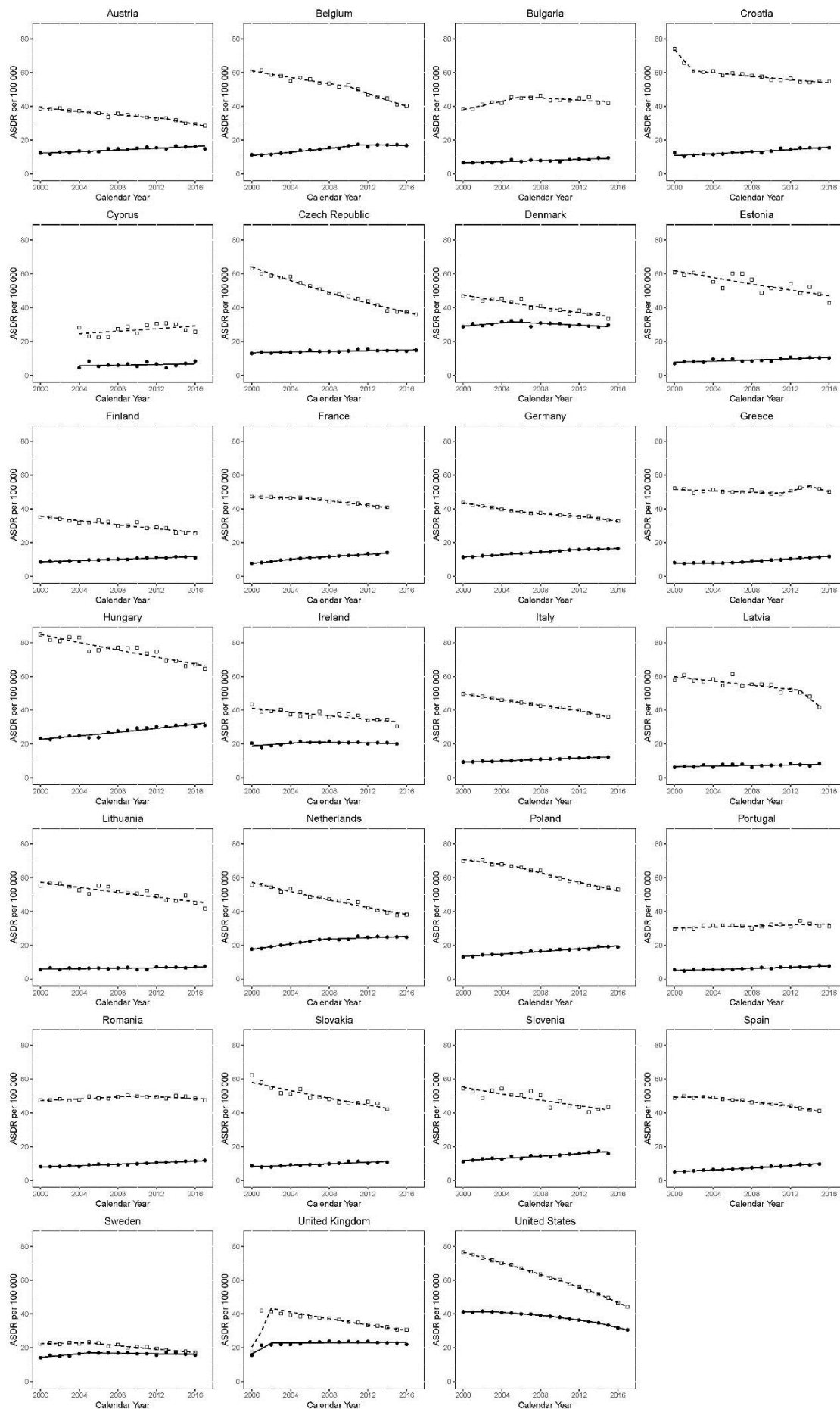
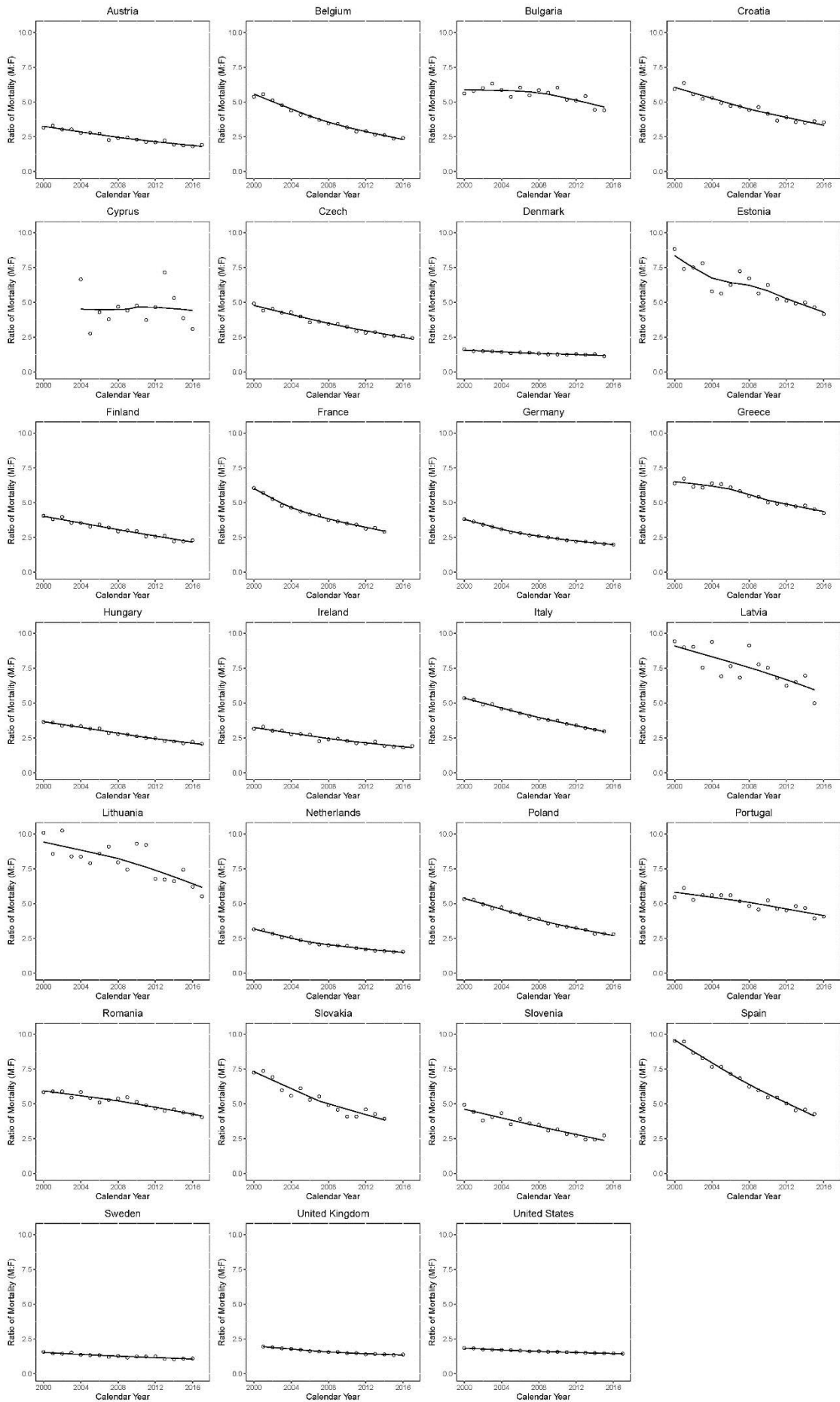


Figure 1: Lung cancer age-standardized death rates for males and females.



**Figure 2:** Trends in age-standardized death rates per 100,000 for lung cancer. Squares indicate male mortality, whereas circles indicate females.



**Figure 3:** Trends in the ratio of male-to-female mortality for lung cancer between 2001 and 2017.



**Table 1: Age Standardized Death Rate in males and females.**

Country	Start Point			End Point			Overall percentage change in mortality	
	Year of diagnosis	Age Adjusted Rate in Males	Age Adjusted Rate in Females	Year of diagnosis	Age Adjusted Rate in Males	Age Adjusted Rate in Females	Males	Females
<b>Austria</b>	2000	38.92	12.35	2017	28.44	14.80	-10.48	2.45
<b>Belgium</b>	2000	60.63	11.30	2016	40.40	16.80	-20.23	5.50
<b>Bulgaria</b>	2000	38.38	6.83	2015	41.83	9.51	3.45	2.68
<b>Croatia</b>	2000	74.09	12.51	2016	54.79	15.48	-19.30	2.97
<b>Cyprus</b>	2004	28.28	4.25	2016	25.74	8.34	-2.54	4.09
<b>Czech Republic</b>	2000	63.27	12.88	2017	35.93	14.76	-27.34	1.88
<b>Denmark</b>	2000	46.79	28.77	2015	33.43	29.65	-13.36	0.88
<b>Estonia</b>	2000	60.96	6.91	2016	42.69	10.26	-18.27	3.35
<b>Finland</b>	2000	35.13	8.65	2016	25.54	11.07	-9.59	2.42
<b>France</b>	2000	47.25	7.80	2014	41.02	14.08	-6.23	6.28
<b>Germany</b>	2000	43.77	11.45	2016	32.79	16.50	-10.98	5.05
<b>Greece</b>	2000	52.28	8.18	2016	50.09	11.77	-2.19	3.59
<b>Hungary</b>	2000	84.81	23.24	2017	64.51	31.04	-20.30	7.80
<b>Ireland</b>	2000	43.44	20.41	2015	30.44	20.05	-13.00	-0.36
<b>Italy</b>	2000	49.62	9.27	2015	36.25	12.20	-13.37	2.93
<b>Latvia</b>	2000	57.75	6.12	2015	41.72	8.34	-16.03	2.22
<b>Lithuania</b>	2000	55.35	5.49	2017	41.78	7.58	-13.57	2.09
<b>Netherlands</b>	2000	55.59	17.69	2016	38.22	24.79	-17.37	7.10
<b>Poland</b>	2000	69.87	13.13	2016	53.00	18.95	-16.87	5.82

<b>Portugal</b>	2000	29.66	5.44	2016	31.26	7.70	1.60	2.26
<b>Romania</b>	2000	47.43	8.11	2017	47.46	11.71	0.03	3.60
<b>Slovakia</b>	2000	62.25	8.59	2014	42.14	10.72	-20.11	2.13
<b>Slovenia</b>	2000	54.44	11.02	2015	43.42	15.88	-11.02	4.86
<b>Spain</b>	2000	48.82	5.12	2015	41.04	9.61	-7.78	4.49
<b>Sweden</b>	2000	22.43	14.19	2016	17.31	15.67	-5.12	1.48
<b>UK</b>	2001	42.06	21.49	2016	30.66	22.05	-11.40	0.56
<b>USA*</b>	2000	76.70	41.30	2017	44.30	30.60	-32.40	-10.70

**\*USA data is standardized based on US population. CDC WONDER database is used for data collection in the USA. (Luxembourg and Malta were excluded due to data quality.)**





<b>Poland</b>	<b>2000-2015</b>	<b>-1</b>	<b>-1.9</b>	<b>-0.1</b>	<b>2005-2016</b>	<b>-2.3</b>	<b>-2.5</b>	<b>-2</b>								
<b>Portugal</b>	<b>2000-2016</b>	<b>0.5</b>	<b>0.1</b>	<b>0.8</b>												
<b>Romania</b>	<b>2000-2010</b>	<b>0.6</b>	<b>0.2</b>	<b>0.9</b>	<b>2010-2017</b>	<b>-0.5</b>	<b>-1.1</b>	<b>0.1</b>								
<b>Slovakia</b>	<b>2000-2014</b>	<b>-2.2</b>	<b>-2.6</b>	<b>-1.7</b>												
<b>Slovenia</b>	<b>2000-2015</b>	<b>-1.8</b>	<b>-2.4</b>	<b>-1.2</b>												
<b>Spain</b>	<b>2000-2003</b>	<b>0.2</b>	<b>-1.3</b>	<b>1.7</b>	<b>2003-2011</b>	<b>-1.2</b>	<b>-1.6</b>	<b>-0.8</b>	<b>2011-2015</b>	<b>-2.3</b>	<b>-3.2</b>	<b>-1.4</b>				
<b>Sweden</b>	<b>2000-2005</b>	<b>0.5</b>	<b>-1.5</b>	<b>2.6</b>	<b>2005-2016</b>	<b>-2.5</b>	<b>-3.1</b>	<b>-1.9</b>								
<b>UK</b>	<b>2001-2009</b>	<b>-1.7</b>	<b>-2</b>	<b>-1.4</b>	<b>2009-2016</b>	<b>-2.5</b>	<b>-2.9</b>	<b>-2.2</b>								

\*USA data is standardized based on US population. CDC WONDER database is used for data collection in the USA.









<b>Slovakia</b>	2000-2014	2.4	1.7	3.1												
<b>Slovenia</b>	2000-2015	2.5	2	3.1												
<b>Spain</b>	2000-2015	4.4	4.1	4.7												
<b>Sweden</b>	2000-2005	3.5	1.2	5.9	2005-2016	-0.5	-1.2	0.2								
<b>UK</b>	2001-2008	1.7	1.1	2.3	2008-2016	-0.7	-1.2	-0.2								

**\*USA data is standardized based on the US population. CDC WONDER database is used for data collection in the USA.**

**Table 4: Post hoc analysis of the male-to-female ratio of lung cancer Mortality.**

Country	Start Point		End Point	
	Year of diagnosis	Sex ratio	Year of diagnosis	Sex ratio
Spain	2000	9.53	2015	4.27
Estonia	2000	8.82	2016	4.16
Lithuania	2000	10.07	2017	5.51
Latvia	2000	9.44	2015	5.00
Cyprus	2004	6.65	2016	3.08
Slovakia	2000	7.25	2014	3.93
France	2000	6.06	2014	2.91
Belgium	2000	5.37	2016	2.41
Poland	2000	5.32	2016	2.80
Czech Republic	2000	4.91	2017	2.43
Croatia	2000	5.92	2016	3.54
Italy	2000	5.35	2015	2.97
Slovenia	2000	4.94	2015	2.74
Greece	2000	6.39	2016	4.26
Germany	2000	3.82	2016	1.99
Romania	2000	5.85	2017	4.05
Finland	2000	4.06	2016	2.31
Netherlands	2000	3.14	2016	1.54
Hungary	2000	3.65	2017	2.08
Portugal	2000	5.45	2016	4.06
Austria	2000	3.15	2017	1.92

<b>Bulgaria</b>	2000	5.62	2015	4.40
<b>Ireland</b>	2000	2.13	2015	1.52
<b>UK</b>	2001	1.96	2016	1.39
<b>Denmark</b>	2000	1.63	2015	1.13
<b>Sweden</b>	2000	1.58	2016	1.10
<b>USA*</b>	2000	1.86	2017	1.45

**\*USA data is standardized based on the US population. CDC WONDER database is used for data collection in the USA.**