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Original article

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Interstitial lung disease incidence and mortality in the United Kingdom and the European Union: an observational study, 2001-2017

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Abstract

Objective

To compare the trends in age-standardised incidence and mortality from interstitial lung diseases (ILD) in the United Kingdom (UK) and the European Union (EU).

Design

Observational study using data obtained from the Global Burden of Disease Study.

Setting and Participants

Residents of the UK and of the twenty-seven EU countries.

Main outcome measures

ILD age-standardised incidence rates per 100,000 (ASIR), age-standardised death rates per 100,000 (ASDR), and mortality-to-incidence ratio (MIRs) are presented for males and females separately for each country, for the years 2001-2017. Trends were analysed using Joinpoint regression analysis.

Results

For men, in 2017, the median incidence of ILD was 7.22 (IQR 5.57–8.96) per 100,000 population. For women, in 2017, the median incidence of ILD was 4.34 (IQR 3.36–6.29) per 100,000 population. For men, in 2017, the median ASDR attributed to ILD was 2.04 (IQR 1.13–2.71) per 100,000 population. For women, the median ASDR in 2017 for ILD was 1.02 (0.68–1.37) per 100,000 population. There was an overall increase in ASDR during the observation period with a median change of +20.42% (IQR 5.44–31.40) for men and an increase of +15.44% (IQR -1.01–31.52) for women. Despite increases in mortality over the entire observation period, there were decreasing mortality trends in the majority of countries at the end of the observation period (75% for men and 86% for women).

Conclusion

Over the past two decades, there have been increases in the incidence and mortality of interstitial lung diseases in Europe. The most recent trends, however, demonstrate decreases in mortality from ILD in the majority of European countries for both men and

women. These data support the ongoing improvements in the diagnosis and management of ILD.

Take home message:

For Interstitial Lung Diseases, recent improvements in diagnostics and management as well as the introduction of therapeutic agents has resulted in significant decreases in mortality in the majority of European countries.

Plain language summary:

Interstitial lung diseases are rare but are associated with significant morbidity and mortality. The management of ILDs is challenging and there are limited therapies available to slow their progression which have recently been introduced into practice. Although the incidence and mortality from ILDs has increased over the past two decades, there have been significant reductions in mortality rates since the introduction of new therapeutic agents.

Introduction

Interstitial lung disease (ILD) is a group of heterogeneous diseases with a common feature of damage to lung parenchyma and alveoli, and is characterised by inflammation and fibrosis(1). ILDs have been associated with systemic inflammatory diseases such as rheumatoid arthritis and sarcoidosis, and may also be associated with environmental or occupational exposures. In the majority of ILD, however, a specific etiologic factor is never identified. The last two decades have also seen changes in therapies for ILD, particularly for idiopathic pulmonary fibrosis (IPF) where some therapies demonstrated harm (2) and two novel agents antifibrotic agents have been licensed (3–5).

Estimates of incidence and mortality attributed to ILD have increased in recent years but remain limited, in part due to the multiple etiologic factors and difficulty in diagnosis, as well as geographical differences in diagnostic criteria and thresholds (6). Previous reports on ILD incidence in Europe include registries and questionnaires (7–9). One recent review assessed incidence of fibrosing-type in IPF and ILDs globally and found that there is a paucity of data on the incidence of this heterogenous group of diseases, with substantial variation between health systems (10). We have previously reported on mortality from IPF across the European Union (EU), reporting substantial variation in mortality between countries (11) and this analysis used the World Health Organization (WHO) mortality database composed of mandatory reporting of cause of death. However, there was no similar widespread registry data for disease incidence and as such, an up to date analysis of ILD incidence and mortality across the United Kingdom (UK) and EU is warranted.

The objective of this study was to describe current incidence and mortality rates, as well as overall trends in ILD in the EU and UK using the Global Burden of Disease (GBD) study results. These data are collated by the GBD Collaborators and made available publicly for our analysis. Given the increasing recognition of ILDs as an important cause of morbidity and mortality, and their increasing case identification, our hypothesis was that there would be increasing trends in both incidence and mortality from ILDs across the UK and EU. We

analysed trends in ILD incidence and mortality between 2001 and 2017 using Joinpoint regression analysis.

Methods

Data source

The data for this observational analysis of ILD was obtained from the GBD database, which collates mortality and disability data (deaths, death rates, years of life lost due to premature mortality, prevalence and incidence) for a collection of global health concerns. The exact GBD methodology has been published previously (12) and we have used the GBD source previously in reports relating to abdominal aortic aneurysm (13) and peripheral arterial disease (14). Briefly, the GBD uses systematic reviews, survey data, disease registries, hospital administrative data, claims, inpatient and outpatient data, and case notifications as data sources to estimate disease incidence. Disease classifications are based on the International Classification of Disease (ICD) coding system (9th and 10^{th} revisions). The data is collated by the GBD collaborators and made available publicly for analysis.

Cases were defined as a combined output of interstitial lung disease including pulmonary sarcoidosis using the ICD-10 codes J84 and D86, respectively. Previous reports on interstitial lung diseases have included sarcoidosis in this definition and has been reported by the GBD investigators (15,16). Incidence data was sourced from literature review, claims data (for the United States, not required in our study) and hospital inpatient records. Using these data as input, incidence estimates were computed using a standard strategy with parameters described previously (17).

Mortality data is collected primarily from seven sources (vital registration, verbal autopsy, cancer registry, police records, sibling history, surveillance, and survey/census). The produced information is available to the public and can be extracted via the GBD Results Tool (http://ghdx.healthdata.org/gbd-results-tool). We used this tool to extract age-standardised incidence and mortality rates for ILD for EU countries and the UK between 2001 and 2017. Mortality was also reported as a combined value for ILD and pulmonary

sarcoidosis. Due to the manner in which data are stored in the GBD study, we are unable to separate sarcoidosis from other aetiologies of ILD for the purposes of this analysis. Input for estimates were sourced from vital registration and surveillance data from the cause of death database. These data were filtered using the following exclusion criteria: values implausible high or low, significant conflict with established age or temporal patterns, significant conflict with other sources of data for the same or similar regions. Input data was used to compute mortality estimates using the standard GBD modelling described in detail by the GBD collaborators (17).

Handling of the GBD data

Age-standardised incidence rates (ASIRs) and age-standardised death rates (ASDRs) for ILD stratified by sex and age-standardized per 100,000 population were extracted from the GBD results tool for each of the years between 2001 and 2017, inclusive, for the UK and EU countries. Extracting age-standardised rates improves inter-country comparability, because differences in the age-structure of different populations are accounted for. For all age-standardised rates, the GBD study computes a standard population using a non-weighted average across a percentage of the population of all countries in each five-year age bracket (years 2010-2035) from the United Nations Population Division's World Population Prospects (2012 revision).

Absolute and relative changes in ASIRs and ASDRs over the observation period (i.e. differences between the rates in 2001 and 2017) were calculated for each sex in each country. ASDRs were quantified as a proportion of ASIRs by dividing ASDR by the ASIR to calculate a mortality-to-incidence ratio (MIR) for each year (2001 – 2017, inclusive) for each sex in each country. Mortality-to-incidence ratio has previously been shown to correlate well with cancer management outcomes, and their use can help us to understand how the impact and management of ILD has varied temporally with sex and location. The MIR represents the case-fatality rate, and is calculated by dividing the mortality count to incidence per annum for a specific population. This allows for comparisons between different geographical

locations to be standardized to local incidence rates and is useful to understand survival and burden of disease, as it provides an estimate of regional case-fatality. A low MIR would mean there is a lower mortality of the condition in relation to incidence and a higher MIR would equate to higher morality of the condition in relation to the incidence in that population. The MIR has been used in multiple previous investigations related to cancer mortality data (18) and we have previously used this metric to assess survival in other populations (13,14).

The GBD quantifies the availability and completeness of the mortality data by each location-year to indicate the reliability of cause of death data. Each country is graded on a 5-star scale. For the countries analysed in the present analysis, with the exceptions of Cyprus and Slovakia (2-stars and 3-stars, respectively), 15 EU countries scored 4-stars (Belgium, Bulgaria, Croatia, Czech Republic, Denmark, France, Germany, Greece, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovenia and Spain), representing greater than 65% completeness of mortality data. The UK and the 10 remaining EU countries have 5-star data, demonstrating greater than 85% completeness of the data (Austria, Estonia, Finland, Hungary, Ireland, Italy, Latvia, Lithuania, Malta and Sweden). In addition to the above analysis for 28 European Union member states, we performed a secondary post-hoc analysis of the 5-star countries and provide these figures in the Supplemental Materials.

Statistical analysis

Joinpoint regression analysis was used to assess trends in the disease burden of ILD. The Joinpoint software (Joinpoint Command Line Version 4.5.0.1) was provided by the United States National Cancer Institute Surveillance Research Program (19). This software tracks trends in data over time (for the present analysis, ASIRs, ASDRs), then fits the simplest model possible to the data by connecting several different line segments on a logarithmic scale. These segments are known as ‘Joinpoints’, with the simplest model (i.e. 0 Joinpoints) being a straight line. As more Joinpoints are added, each is tested for significance using a Monte Carlo permutation method. The software also gives estimated annual percent changes (EAPC) for each line segment (with corresponding 95% confidence intervals). Each

EAPC is tested to establish if a difference from the null hypothesis of no change exists. Consequently, the final model consists of multiple Joinpoints, each representing a statistically significant (*p* value <0.05) change in trend (increase or decrease), with each trend described by the EAPC and the associated confidence intervals. The EAPC allows assessment of trend changes at a constant percent per year.

Results

A total of 28 countries were included in this investigation which included the United Kingdom as well as the 27 European Union member states, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden.

Current estimates of ILD incidence

A summary of current estimates of ILD incidence is shown in Figure 1 (left). For men in 2017, the median incidence of ILD was 7.22 (interquartile range [IQR] 5.57 – 8.96) per 100,000 population. The countries with the highest ASIRs of ILD per 100,000 population in 2017 include Romania (11.14), UK (10.92), Slovakia (10.58), and Slovenia (9.93). The countries with the lowest ASIRs per 100,000 population in 2017 include Greece (3.30), Italy (4.18), Luxembourg (5.15), and Belgium (5.33). For women in 2017, the median incidence of ILD was 4.34 (IQR 3.36 – 6.29) per 100,000 population. The countries with the highest ASIRs in 2017 included Slovakia (8.25), Romania (7.52), Czech Republic (7.10), and Slovenia (6.83). The countries with the lowest ASIRs in 2017 for women include Greece (2.26), Italy (2.53), Belgium (2.96), and France (3.08).

Current estimates of ILD mortality

A summary of the current estimates of ILD mortality is shown in Figure 1 (right). Overall, the median ASDR attributed to ILD was 2.04 (IQR 1.13 – 2.71) and 1.02 (0.68 – 1.37) per 100,000 population, for men and women respectively . The countries with the highest

ASDRs in 2017 for men included UK (5.27), Ireland (5.18), Cyprus (4.52), and Malta (4.14). The countries with the lowest ASDRs for men in 2017 included Croatia (0.44), Bulgaria (0.47), Lithuania (0.64), and Latvia (0.86). The countries with the highest ASDRs for women in 2017 included UK (2.89), Ireland (2.73), Malta (2.51), and Spain (2.25). The countries with the lowest ASDRs for women in 2017 included Bulgaria (0.18), Croatia (0.26), Lithuania (0.26), and Latvia (0.33).

Current estimates of ILD mortality-to-incidence ratios

The median MIR was 0.38 (IQR 0.13 – 0.47) and 0.31 (IQR 0.10 – 0.42) for men and women respectively. The countries with the highest MIRs in 2017 for men were Ireland (0.68), Cyprus (0.67), Spain (0.50), and Malta (0.49). The countries with the lowest MIRs in 2017 were Bulgaria (0.06), Croatia (0.07), Slovakia (0.09), and Latvia (0.10). The countries with the highest MIRs in 2017 for women were Ireland (0.65), Spain (0.51), Cyprus (0.50), and Malta (0.50). The countries with the lowest MIRs in 2017 included Bulgaria (0.03), Latvia (0.05), Lithuania (0.06), and Croatia (0.06).

Changes in ILD incidence between 2001 and 2017

For men, there was an overall increase in the incidence of ILD with a median change of +7.14% (IQR 2.23 – 12.29) (Figure 3). The incidence of ILD was increasing across all countries except for Romania (-12.95%), Latvia (-4.94%), Bulgaria (-1.48%), and Cyprus (-1.30%) which all had overall decreases in the incidence of ILD for men. The countries with the greatest increases in ASIRs for men included Greece (+35.51%), Netherlands (+22.03%), UK (21.27%), and Ireland (+20.79%). A summary of the changes in incidence rates for men is shown in Table 1. For women, there was an overall increase in the incidence of ILD with median change of 7.66% (IQR 3.29 – 10.70). There was an increase in ILD incidence for women in all countries except for Romania (-20.76%) and Cyprus (-9.11%). All other countries had increases in ASIRs, with the greatest increases observed in

Greece (+38.36%), UK (+25.39%), Luxembourg (+17.28%), and Netherlands (+14.64%). A summary of the changes in incidence rates for women is shown in Table 2.

Changes in ILD mortality between 2001 and 2017

For men, there was an overall increase in ASDR during the observation period with a median change of +20.42% (IQR 5.44 – 31.40) (Figure 4). The ASDRs for ILD were increasing in all countries except Bulgaria (-32.38%), Estonia (-18.63%), Latvia (-16.72%), Romania (-16.57%), and Croatia (-7.09%). All other countries observed an increase in ASDRs for men, with the greatest increases in Greece (+108.1%), Czech Republic (+78.02%), UK (+43.49%), and Ireland (+43.19%). A summary of the changes in male mortality from ILD is shown in Table 1. For women, there was an overall increase in ASDR during the observation period with a median increase of +15.44% (IQR -1.01 – 31.52). There were overall decreases in ILD mortality in women in Romania (-45.66%), Latvia (-20.48%), Bulgaria (-17.57%), Cyprus (-8.21%), Croatia (-5.40%), France (-2.47%), Denmark (-1.17%), and Poland (-0.84%). All other countries had increasing mortality in women, with the greatest increases observed in Greece (+132.61%), UK (+54.56%), Czech Republic (+53.40%), and Luxembourg (+49.43%). A summary of the changes in female mortality from ILD is shown in Table 2.

Changes in ILD mortality-to-incidence ratios between 2001 and 2017

The MIR for men increased over the observation period with a median change of +9.76% (IQR 1.10–18.43). There were decreasing MIRs in Bulgaria (-31.37%), Estonia (-20.08%), Latvia (-12.39%), Croatia (-11.12%), Romania (-4.15%), and Italy (-2.32%). The countries with the greatest percentage increase in MIRs were Czech Republic (+56.29%), Greece (+53.56%), Slovenia (+24.72%), and Slovakia (+24.04%). For women, there was an overall MIR increase (+7.46%;IQR -4.22–19.33). The countries with the greatest decreases in MIR for women were Romania (-31.42%), Bulgaria (-23.82%), Latvia (-21.63%), and Croatia (-

11.62%). The countries with the greatest increases in MIR for women were Greece (+68.12%), Czech Republic (+40.55%), Slovakia (+37.28%), and Luxembourg (+27.42%).

Joinpoint trends for ILD incidence

The results of Joinpoint regression analysis for incidence are shown in Figure 3 (and Supplemental Tables 1 and 2). For men, the greatest decreases in EAPCs were observed in Latvia between 2005 and 2009 (EAPC -1.5; 95% confidence interval [CI] -1.7--1.3) and Romania (EAPC -1.3; 95% CI -1.4--1.3). In men, the greatest increases in EAPCs were observed in Greece between 2006 – 2010 (EAPC +2.0; 95% CI 1.9-2.1), between 2010 and 2013 (EAPC +2.4; 95% CI 2.2-2.6), and between 2013 and 2017 (EAPC +3.0; 95% CI 3.0-3.1). For women, decreasing EAPCs were observed in Romania between 2001 and 2003 (EAPC -1.6; 95% CI -1.6--1.6) and in Cyprus between 2014 and 2017 (EAPC -1.6; 95% CI -1.8--1.4). The greatest increases in EAPCs for women were in Greece between 2006 and 2014 (EAPC +2.6; 95% CI 2.5-2.6), and between 2014 and 2017 (EAPC +2.8; 95% CI 2.6-3.0).

Joinpoint trends for ILD mortality

The results of Joinpoint regression analysis for mortality are shown in Figure 4 (and Supplemental Tables 3 and 4). For men, trends in ASIRs varied between countries and the greatest negative EAPCs were observed in Bulgaria between 2001 and 2006 (EAPC -6.7; 95% CI -7.3--6.2), in Slovakia between 2015 and 2017 (EAPC -5.1; 95% CI -8.1--2.1), and in Hungary (EAPC -4.5; 95% CI -6.6--2.4). For women, the greatest decreasing EAPCs were in Greece between 2015 and 2017 (EAPC -7.8; 95% CI -13.8--1.3) and in Hungary (EAPC -7.3; 95% CI -9.5--5.1). For women, the greatest increases in EAPCs were in Greece between 2001 and 2004 (EAPC +6.4; 95% CI 2.9-10.0) and between 2004 and 2012 (EAPC +9.6; 95% CI 8.6-10.6). Despite overall increases in EAPC for mortality over the entire observation period, there were decreasing mortality trends in the majority of countries at the

end of the observation period (21 / 28, 75% for men and 24 / 28, 86% for women; Supplemental Tables 3 and 4).

Joinpoint trends for ILD mortality-to-incidence ratios

The results of Joinpoint regression for MIRs for men and women shown in Supplemental Figure 1 and summarised in Supplemental Tables 5 and 6. For men, the greatest decreases in EAPCs were in Greece between 2015 and 2017 (EAPC -8.7; 95% CI -14.2--2.8) and in Bulgaria (EAPC -6.7; 95% CI -7.2--6.1). The greatest increases in MIR EAPCs for men were in Greece between 2005 and 2011 (EAPC +8.4; 95% CI 6.9-10.0) and in Slovenia (EAPC +7.2; 95% CI 3.1-11.4). For women, the greatest decreases in MIR were observed between 2015 and 2017 in Greece (EAPC -10.3; 95% CI -15.6--4.6), Croatia (EAPC -7.6; 95% CI -14.6--0.1), and in Hungary (EAPC -7.4; 95% CI -9.7--5.0). The greatest increases in EAPCs for women were observed in Greece between 2001 and 2012 (EAPC +7.0; 95% CI 6.6-7.4) and in Hungary (EAPC +6.2; 95% CI 4.9-7.6). Despite overall increasing MIR over the entire observation period, there were decreasing MIR trends in the majority of countries at the end of the observation period (23 / 28, 82% for both men and women; Supplemental Tables 5 and 6).

Discussion

Principal findings

In this observational study of interstitial lung disease across the EU and UK between 2001 and 2017, we have shown an overall increasing incidence of ILD across most countries for both men and women. In most countries, men have greater incidence and mortality compared to women, a difference which persists throughout the observation period. Further, despite overall increases in mortality between 2001 and 2017, there have been decreases in mortality for men and women in the majority of countries at the end of the observation period. The ratio of mortality-to-incidence of ILD is flattening or decreasing in most countries, also with negative trends in MIR for men and women in the majority of countries in Europe.

The principal aim of this investigation was to obtain current estimates of the burden of ILD across Europe. Specifically, we sought to understand the changes in incidence and mortality over the past two decades as this time period has seen much development in the classification, diagnosis and management of various interstitial lung diseases. Providing a comprehensive look at incidence and mortality from ILD across Europe this report will serve as a useful benchmark for current burden of ILD and for monitoring future progress in management of this heterogenous group of chronic lung diseases.

Comparison with prior studies

The majority of reports to date have attempted to provide estimates of incidence and mortality in ILDs utilizing primary physician surveys, large health system databases, or surveys of respiratory physicians. These previous reports have focused on single health systems and are unable to make strong comparisons in incidence and mortality between countries or health systems. For instance, Kornum and colleagues performed an analysis of a national health database in Denmark and reported adjusted incidence rates of ILD of approximately 2.91 per 100,000 population (20) while another study from the same country reported annual incidence of 4.1 per 100,000 population cohort (21). These estimates are similar to incidence as estimated in other health systems including Greece which had a reported incidence of 4.63 per 100,000 population (22) and significantly higher than the incidence reported recently in France at 1.94 per 100,000 population (23). These data highlight significant differences in estimates of incidence of ILDs between health systems and no prior study has attempted to make direct comparisons between countries as we have done in the current report.

Previously, our research group assessed mortality from IPF across Europe (11). We demonstrated that across most of the EU, the mortality from IPF was increasing between 2001 and 2014. This report was limited, however, in that we were unable to estimate incidence rates and it was not possible to understand whether increases in mortality from IPF were related to increased awareness and identification of IPF, or whether mortality was

increasing independent of incidence. One previous report has also shown increasing incidence and prevalence of IPF in the United Kingdom over a similar period (24). As a result, we planned the current study to better estimate both incidence and mortality from ILD (inclusive of IPF) and to estimate the changes in mortality relative to changing incidence over a similar observation period. Here our data suggest that over the past two decades, there have been marginal increases in the overall incidence of ILD and greater increases in mortality during the time period.

Despite this, we observe significant decreasing trends in ILD mortality and in mortality-to-incidence ratios in multiple countries during the most recent 5 years of observation. Specifically, we observed statistically significant negative trends in mortality for 21(75%) countries for men, and in 24(86%) for women for trends ending in 2017. Further, using MIR to understand recent management of this chronic lung disease, we demonstrated that for men there were significant decreasing trends in MIR in 23(82%) of countries and for women in 23(82%) of countries for women. Although our study assessed ILD broadly, this finding is important as there have been advances in the treatment of IPF, with the introduction of anti-fibrotic agents in the EU from as early as 2012 (3,4). The approval of anti-fibrotic agents was a significant event in the treatment of IPF as, for the first time, therapeutic agents were available to slow the progression of lung fibrosis and reduce mortality. Although our data are observational in nature and we are unable to make causal statements, IPF constitutes a significant portion of ILD diagnoses with estimates of nearly 20% of all ILDs related to IPF (2) and the result of our study suggest that decreases in mortality from ILD after the introduction of anti-fibrotic agents in multiple health systems. Future investigations should, therefore, aim to clarify whether the observed decreases in mortality from ILD are, in fact, driven by improved management of IPF during this period. Furthermore, while no one particular feature has been identified as the causal in the development of interstitial lung disease including sarcoidosis, there are multiple potential explanations for the between-country differences observed in our study. Previous reports of sarcoidosis, for example, have highlighted geographic differences in sarcoidosis and

potentially associated with geographic features including higher latitudes and sunlight exposure, exposure to coastal or rural areas, as well as agricultural employment or exposure to environmental antigens. Other ILDs may have other associated risk factors: hypersensitivty pneumonitis, for example, may have greater burden in areas with high agricultural employment or IPF, which has been associated with greater exposure to environmental particulate (eg. PM2.5), as well as strong associations lifestyle factors such as tobacco smoke and with other comorbid conditions such as gastroesophageal reflux disease. Our study was not designed to assess each of these potential contributors and although it is unlikely that any one of these additional variables is the single explanatory factor for the observed differences, we have highlighted these additional potential variables as future work may help to elucidate the individual relationships for ILD morbidity and mortality across Europe.

Strengths and weaknesses of the study

The major strengths of this report are the total number of countries observed and the total duration of the observation period for analysis. We used standardized estimates of incidence and mortality which allows us to make comparisons between countries by removing the influence of country-specific demographics on these variables. Most previous reports have focused on the epidemiology of ILD within a single health system or with shorter observation periods. Furthermore, we have also utilized MIR as a marker of performance in management of ILD.

Despite these strengths, there are several limitations which must be considered when interpreting the results of this observational study. First, the data attained are applicable solely for the purpose of identification and comparison of ILD between the EU countries and the UK and, as such, causal relationships cannot be drawn. We acknowledge that confounding variables beyond the scope of discussion will have differential effects by country on the data presented from this observational study: using sex-specific, age-standardised mortality and incidence rates attempts to account for some confounding of

demography. Next, our data represent the broad category of ILDs which are heterogenous in clinical features and diagnosis, with variations in management and prognosis. Individuals with sarcoidosis, for example, may carry the diagnosis through lymph node biopsy but lack pulmonary involvement until late stages (ie. stage IV) of the disease. Due to the manner in which GBD reports their data, we are unable to ascertain specific features of trends relating to specific causes of ILD such as IPF and by including sarcoidosis we may potentially underestimate the true mortality burden from other ILDs. Future work should attempt to characterize trends in individual ILD aetiologies. As outlined above, there is variation in the reporting of data quality between European countries which may also influence the results of this study. We attempted to address this limitation by performing a sub-group analysis with data restricted to those countries with 5-star rating in order to improve comparability (Supplemental Material).

Conclusion

Over the past two decades, there have been increases in the incidence and mortality of interstitial lung diseases in Europe. Recent trends, however, demonstrate decreases in mortality from from ILD in the majority of European countries for both men and women. These data support the ongoing improvements in the diagnosis and management of ILD.

Transparency statement

The authors confirm that the manuscript is an honest, accurate and transparent report on the trends in interstitial lung disease mortality and incidence, with no important data deliberately withheld.

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None

Disclosures

None

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Figure Legends

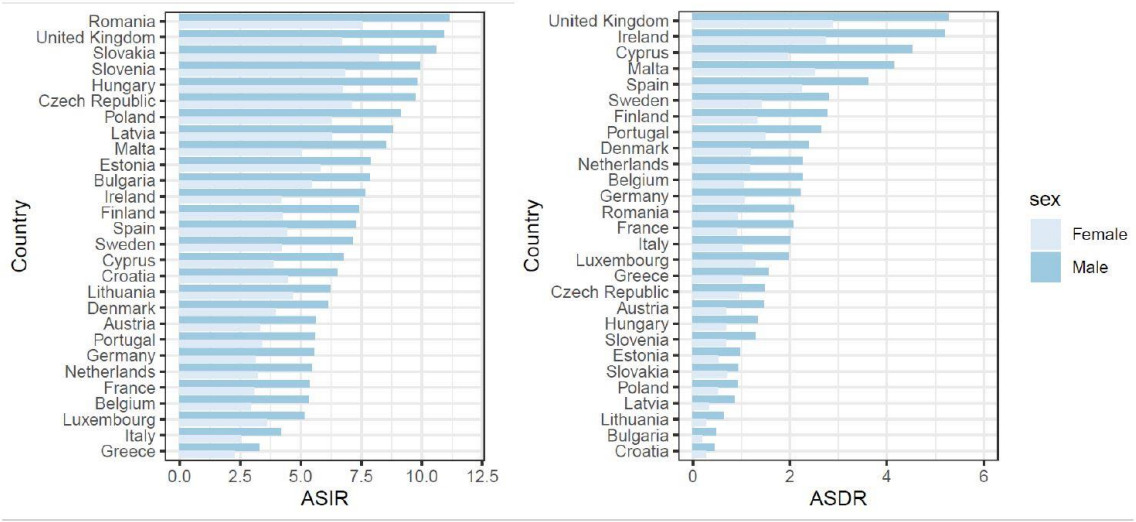


Figure 1: 2017 age-standardised incidence rates (left, A) and age-standardised mortality rates (right, B) per 100,000 population for Interstitial Lung Diseases for males and females in Europe.

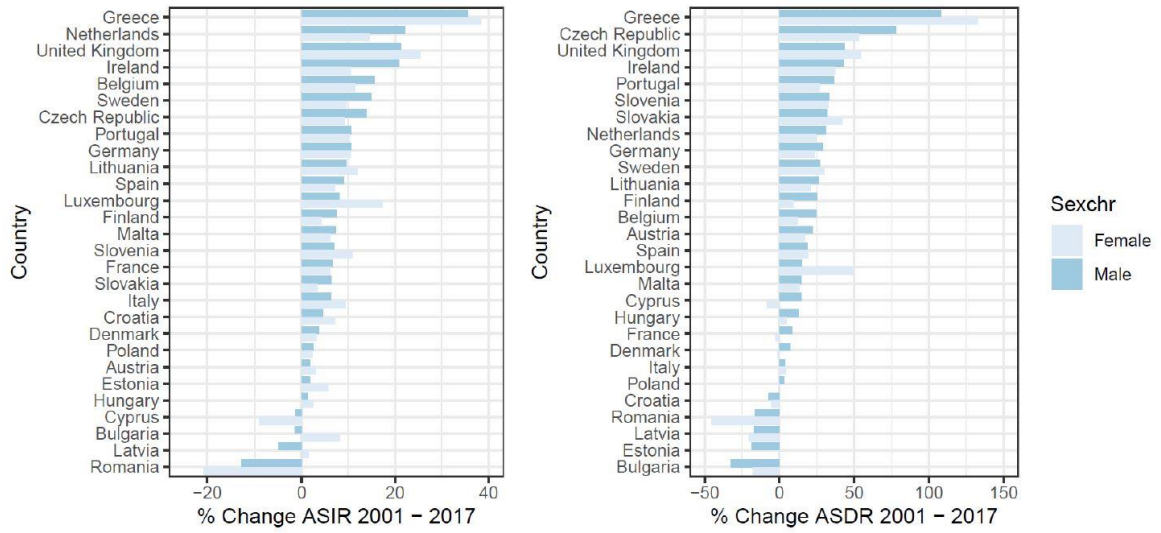
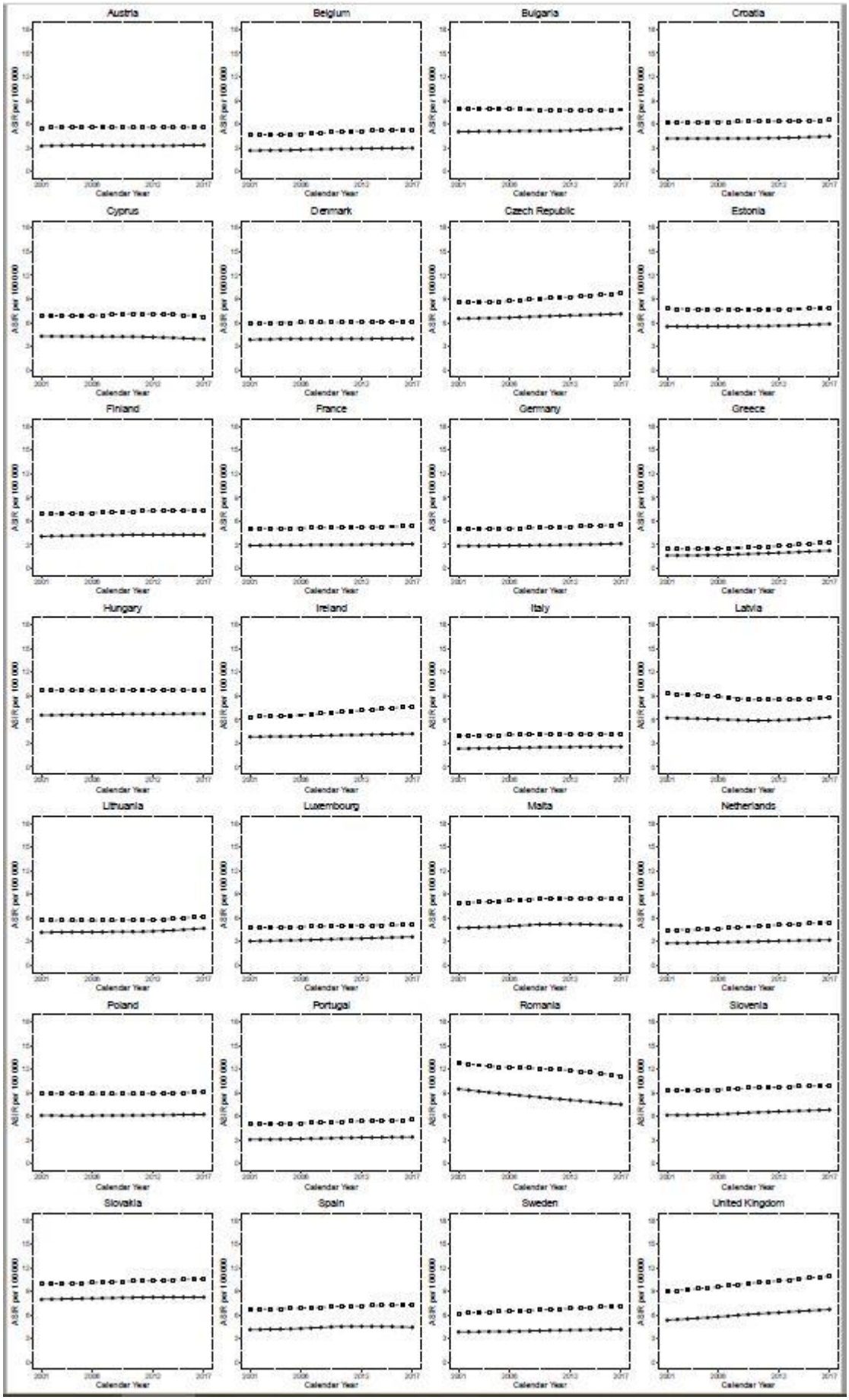


Figure 2: Changes in age-standardised incidence rates (left, A) and age-standardised mortality rates (right, B) for Interstitial Lung Diseases for males and females in Europe.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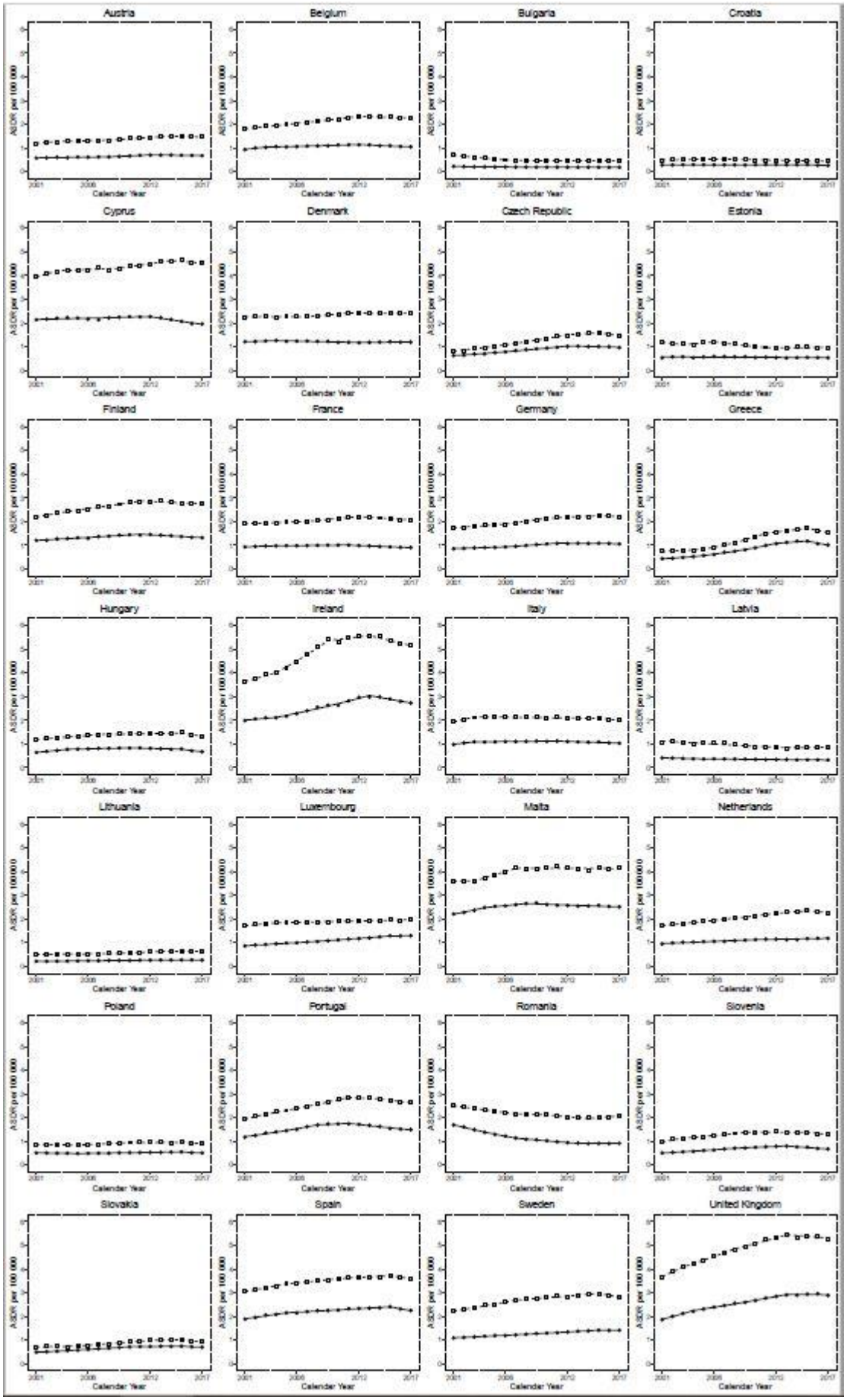
Latvia
Lithuania
Luxembourg
Malta
Netherlands
Poland
Portugal
Romania
Slovenia
Slovakia
Spain
Sweden
United Kingdom
ASIR per 100 000
Calendar Year

Figure 3: Trends in age-standardised incidence rates per 100,000 for Interstitial Lung Diseases across Europe. White circles represent male and solid squares represent female.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Luxembourg
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Poland
Portugal
Romania
Slovenia
Slovakia
Spain
Sweden
United Kingdom
ASDR per 100 000
Calendar Year

Figure 4: Trends in age-standardised mortality rates per 100,000 for Interstitial Lung Diseases across Europe. White circles represent male and solid squares represent female.

Table Legends

Table 1: Male age-standardised incidence rates and age-standardised mortality rates per 100,000 population between 2001 and 2017, as well as percentage change over the observation period.

Table 2: Female age-standardised incidence rates and age-standardised mortality rates per 100,000 population between 2001 and 2017, as well as percentage change over the observation period.

Table 1

	Incidence (ASIR per 100 000)			Mortality (ASDR per 100 000)		
Country	**Start**	**End**	**Change (%)**	**Start**	**End**	**Change (%)**
Austria	5.51	5.61	0.1(1.88)	1.19	1.46	0.27(22.27)
Belgium	4.61	5.33	0.72(15.56)	1.81	2.26	0.45(25.02)
Bulgaria	7.97	7.85	-0.12(-1.48)	0.7	0.47	-0.23(-32.38)
Croatia	6.22	6.51	0.28(4.54)	0.48	0.44	-0.03(-7.08)
Cyprus	6.86	6.77	-0.09(-1.3)	3.94	4.52	0.58(14.64)
Czech Republic	8.55	9.74	1.19(13.89)	0.83	1.47	0.64(78)
Denmark	5.93	6.15	0.22(3.72)	2.24	2.4	0.16(7.09)
Estonia	7.74	7.88	0.14(1.81)	1.18	0.96	-0.22(-18.63)
Finland	6.88	7.4	0.52(7.53)	2.2	2.76	0.56(25.52)
France	5.04	5.37	0.33(6.59)	1.91	2.07	0.16(8.35)
Germany	5.03	5.57	0.53(10.62)	1.72	2.22	0.5(28.74)
Greece	2.43	3.3	0.86(35.51)	0.75	1.55	0.81(108.1)
Hungary	9.7	9.82	0.12(1.22)	1.19	1.34	0.15(12.69)
Ireland	6.35	7.66	1.32(20.79)	3.62	5.18	1.56(43.19)
Italy	3.93	4.18	0.25(6.26)	1.94	2.01	0.07(3.79)
Latvia	9.27	8.81	-0.46(-4.94)	1.04	0.86	-0.17(-16.72)
Lithuania	5.67	6.21	0.54(9.44)	0.51	0.64	0.13(26.01)
Luxembourg	4.76	5.15	0.38(8)	1.71	1.97	0.26(15.17)
Malta	7.93	8.51	0.58(7.3)	3.61	4.14	0.53(14.81)
Netherlands	4.46	5.44	0.98(22.03)	1.73	2.26	0.53(30.9)
Poland	8.88	9.11	0.23(2.58)	0.88	0.91	0.03(3.15)
Portugal	5.03	5.57	0.54(10.69)	1.95	2.65	0.71(36.28)
Romania	12.8	11.14	-1.66(-12.95)	2.5	2.08	-0.41(-16.56)
Slovakia	9.95	10.58	0.63(6.34)	0.7	0.93	0.22(31.9)
Slovenia	9.28	9.93	0.65(6.98)	0.97	1.29	0.32(33.42)
Spain	6.69	7.29	0.6(9.01)	3.05	3.61	0.57(18.56)
Sweden	6.22	7.14	0.92(14.84)	2.21	2.81	0.6(27.2)
United Kingdom	9	10.91	1.91(21.27)	3.67	5.27	1.6(43.49)

Table 2

	Incidence (ASIR per 100 000)			Mortality (ASDR per 100 000)		
Country	**Start**	**End**	**Change (%)**	**Start**	**End**	**Change (%)**
Austria	3.24	3.33	0.09(2.91)	0.58	0.68	0.1(17.49)
Belgium	2.65	2.96	0.3(11.47)	0.93	1.05	0.12(12.32)
Bulgaria	5.04	5.45	0.41(8.2)	0.22	0.18	-0.04(-17.57)
Croatia	4.16	4.45	0.29(7.04)	0.28	0.26	-0.01(-5.4)
Cyprus	4.28	3.89	-0.39(-9.11)	2.13	1.96	-0.18(-8.21)
Czech Republic	6.51	7.1	0.6(9.14)	0.63	0.96	0.33(53.4)
Denmark	3.84	3.96	0.12(3.13)	1.21	1.19	-0.01(-1.17)
Estonia	5.51	5.82	0.31(5.65)	0.53	0.53	0(0.41)
Finland	4.07	4.24	0.17(4.24)	1.21	1.32	0.11(9.37)
France	2.91	3.08	0.18(6.04)	0.93	0.91	-0.02(-2.48)
Germany	2.84	3.14	0.3(10.44)	0.86	1.06	0.2(23.44)
Greece	1.63	2.26	0.63(38.36)	0.44	1.02	0.58(132.61)
Hungary	6.56	6.73	0.17(2.56)	0.64	0.68	0.03(4.79)
Ireland	3.81	4.2	0.4(10.49)	1.99	2.73	0.74(37.38)
Italy	2.32	2.53	0.22(9.28)	0.98	1.03	0.05(4.63)
Latvia	6.22	6.31	0.09(1.47)	0.41	0.33	-0.08(-20.48)
Lithuania	4.19	4.69	0.5(11.83)	0.22	0.26	0.05(20.83)
Luxembourg	3.08	3.61	0.53(17.28)	0.87	1.29	0.43(49.43)
Malta	4.76	5.05	0.29(6.1)	2.21	2.51	0.3(13.39)
Netherlands	2.8	3.21	0.41(14.64)	0.95	1.18	0.23(24.63)
Poland	6.12	6.26	0.14(2.26)	0.52	0.52	0(-0.84)
Portugal	3.08	3.39	0.31(10.23)	1.18	1.5	0.32(26.84)
Romania	9.49	7.52	-1.97(-20.76)	1.7	0.92	-0.77(-45.66)
Slovakia	7.98	8.25	0.28(3.46)	0.49	0.7	0.21(42.03)
Slovenia	6.17	6.84	0.67(10.92)	0.51	0.68	0.17(32.87)
Spain	4.15	4.44	0.3(7.13)	1.89	2.25	0.36(19.32)
Sweden	3.85	4.22	0.37(9.51)	1.09	1.41	0.33(30.17)
United Kingdom	5.35	6.7	1.36(25.39)	1.87	2.89	1.02(54.56)

Supplemental Materials

Supplemental Figure Legends

Supplemental Figure 1: Trends in mortality-to-incidence ratios for Interstitial Lung Diseases across Europe. White circles represent male and solid squares represent female.

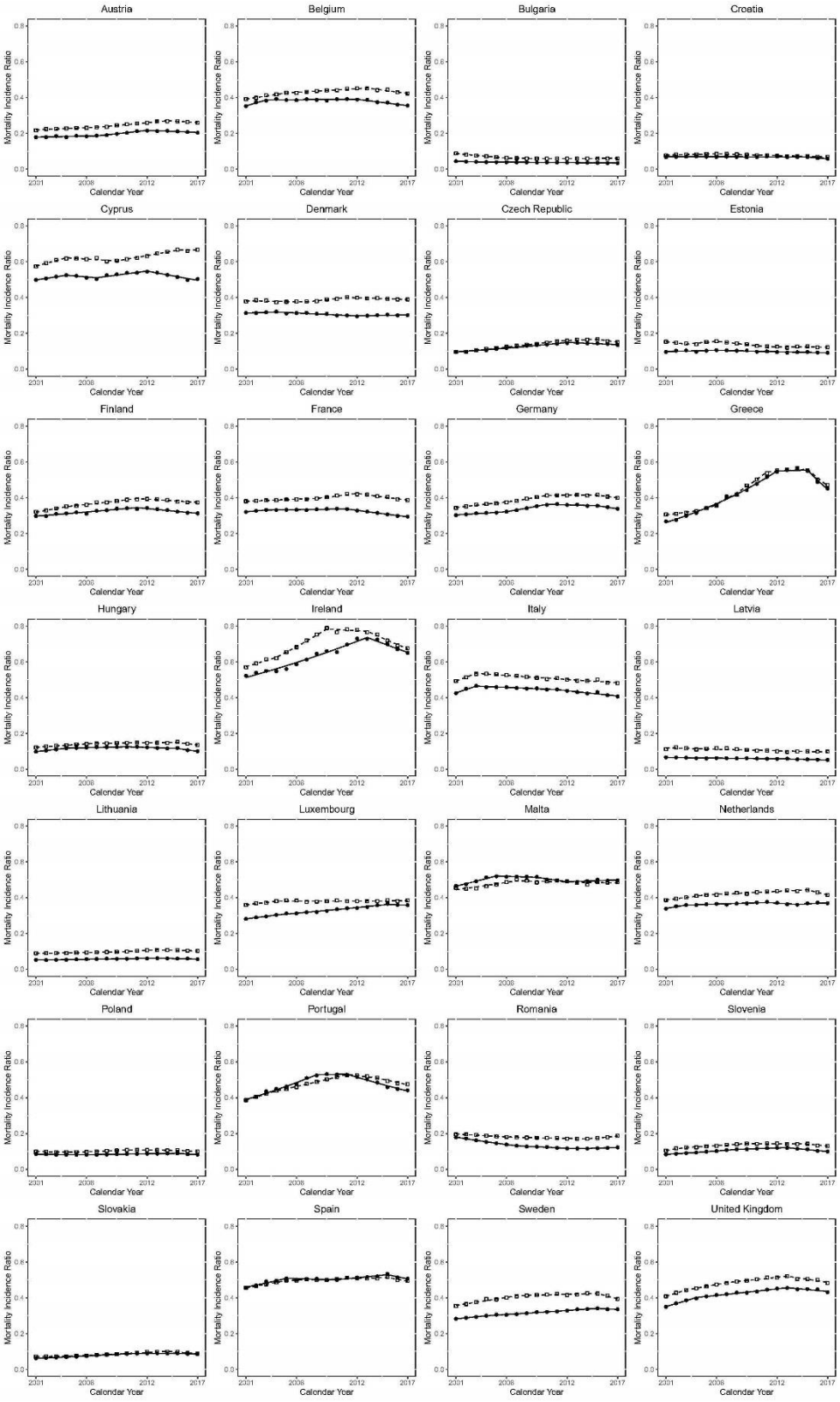
Supplemental Figure 2: Trends in incidence for Interstitial Lung Diseases for European countries with high (5-star) data quality rating. White circles represent male and solid squares represent female.

Supplemental Figure 3: Trends in mortality for Interstitial Lung Diseases for European countries with high (5-star) data quality rating. White circles represent male and solid squares represent female.

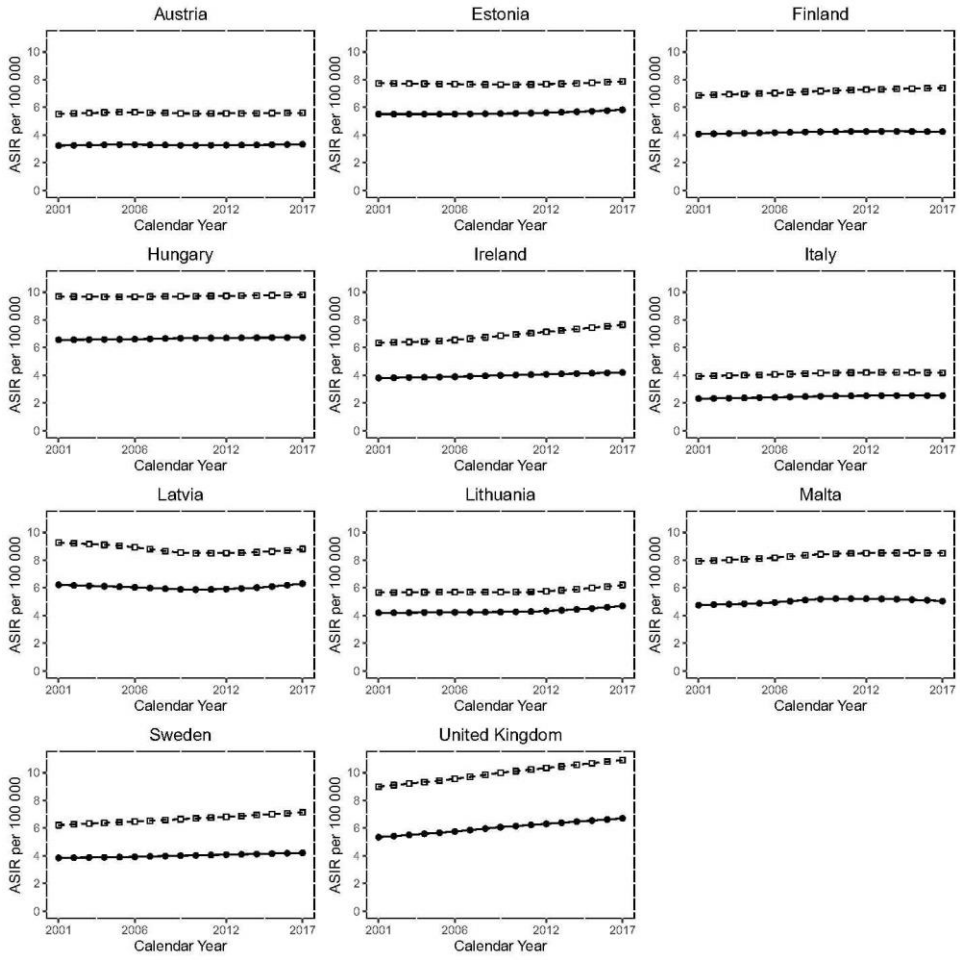
Supplemental Figure 4: Trends in DALYs for Interstitial Lung Diseases for European countries with high (5-star) data quality rating. White circles represent male and solid squares represent female.

Supplemental Figure 5: Trends in MIR for Interstitial Lung Diseases for European countries with high (5-star) data quality rating. White circles represent male and solid squares represent female.

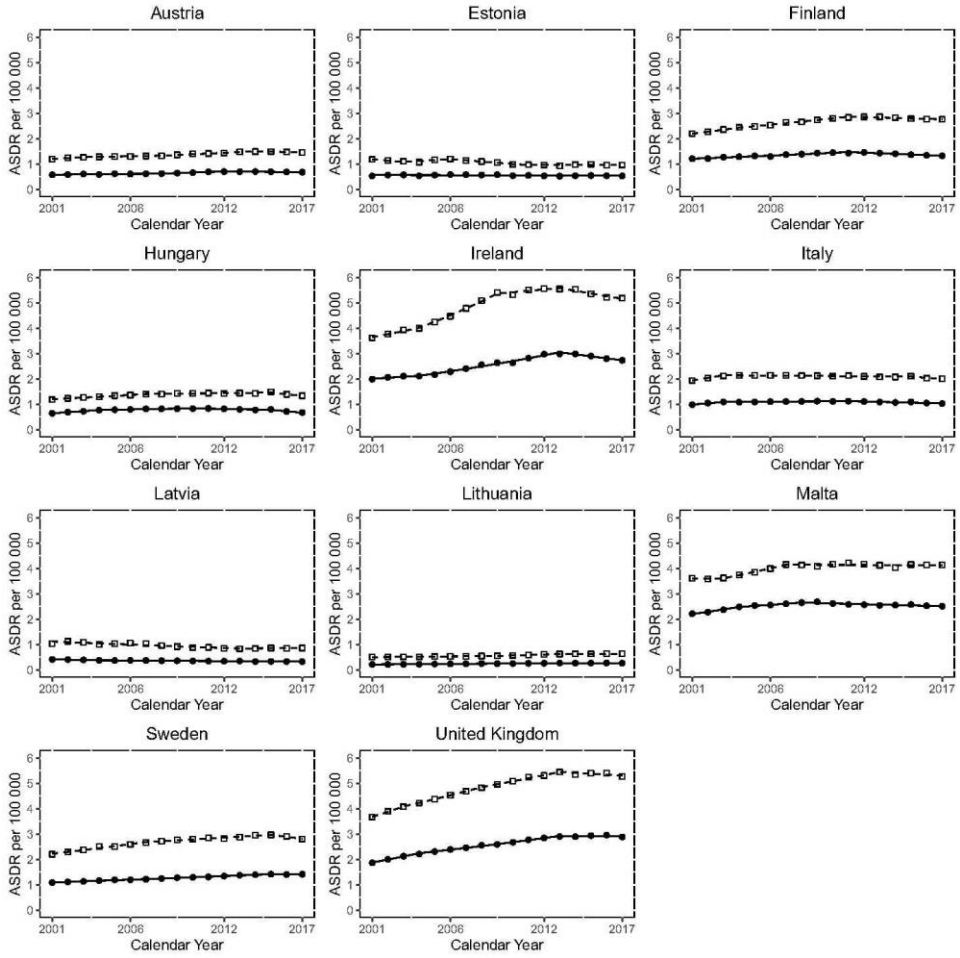
Supplemental Figure 1:



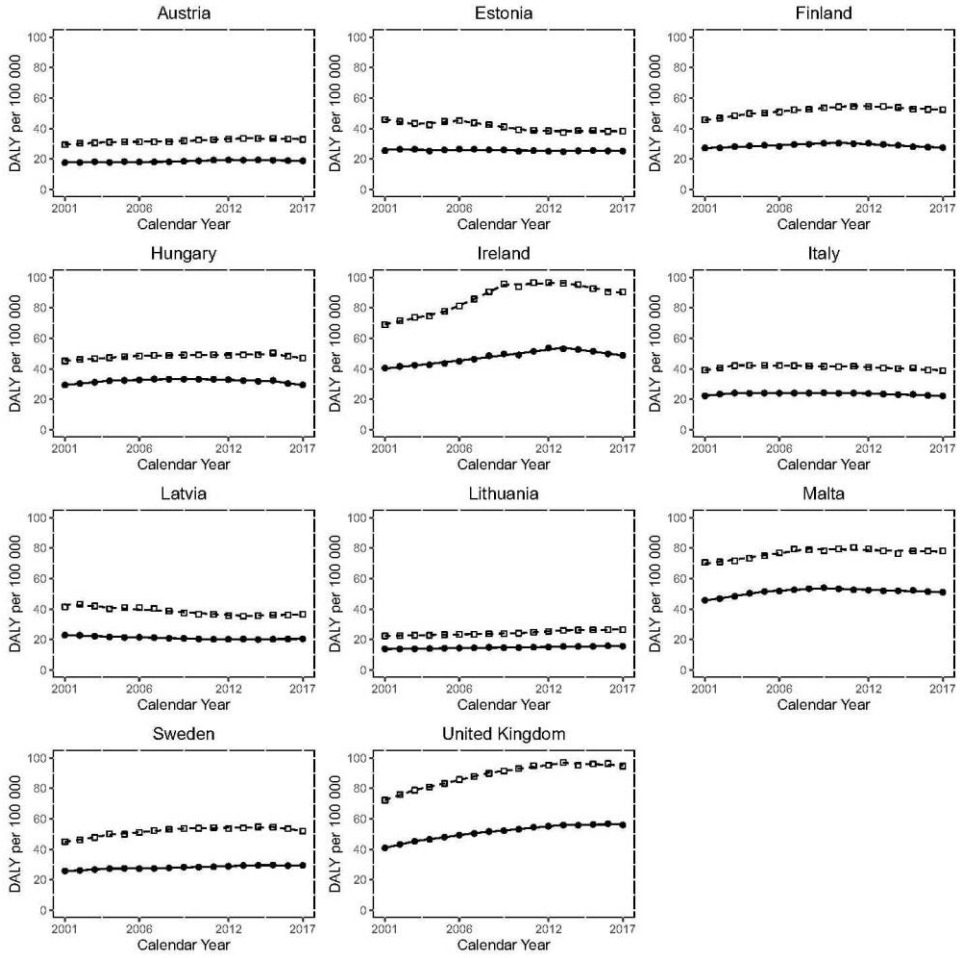
Supplemental Figure 2:



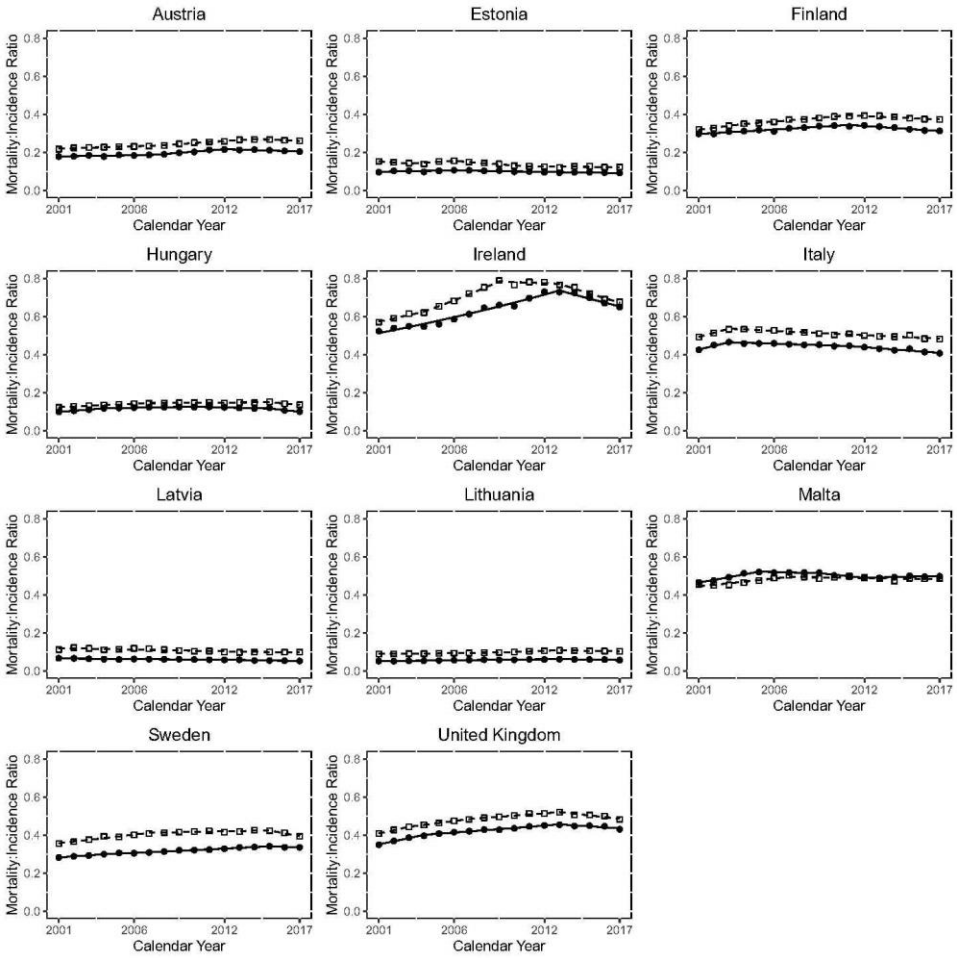
Supplemental Figure 3:



Supplemental Figure 4:



Supplemental Figure 5:



Supplemental Table Legends

Supplemental Table 1: Joinpoint analysis for male incidence of Interstitial Lung Diseases across Europe between 2001 and 2017. EAPC is estimated annual percentage change and CI is confidence interval of the EAPC

Supplemental Table 2: Joinpoint analysis for female incidence of Interstitial Lung Diseases across Europe between 2001 and 2017. EAPC is estimated annual percentage change and CI is confidence interval of the EAPC

Supplemental Table 3: Joinpoint analysis for male mortality of Interstitial Lung Diseases across Europe between 2001 and 2017. EAPC is estimated annual percentage change and CI is confidence interval of the EAPC

Supplemental Table 4: Joinpoint analysis for male mortality of Interstitial Lung Diseases across Europe between 2001 and 2017. EAPC is estimated annual percentage change and CI is confidence interval of the EAPC

Supplemental Table 5: Joinpoint analysis of mortality-to-incidence ratio for men across European countries between 2001 and 2017. EAPC is estimated annual percentage change and CI is confidence interval of the EAPC.

Supplemental Table 6: Joinpoint analysis of mortality-to-incidence ratio for women across European countries between 2001 and 2017. EAPC is estimated annual percentage change and CI is confidence interval of the EAPC.

Supplemental Table 1:

	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)
Austria	2001 – 2005	0.7 (0.6, 0.7)	2005 – 2010	-0.4 (-0.5, -0.3)	2010 – 2017	0.1 (0.1, 0.2)		
Belgium	2001 – 2005	0.5 (0.4, 0.5)	2005 – 2010	1.3 (1.3, 1.4)	2010 – 2017	0.9 (0.8, 0.9)		
Bulgaria	2001 – 2005	0.0 (-0.1, 0.0)	2005 – 2010	-0.4 (-0.5, -0.4)	2010 – 2014	0.0 (0.0, 0.1)	2014 – 2017	0.2 (0.2, 0.3)
Croatia	2001 – 2004	0.2 (0.2, 0.3)	2004 – 2011	0.2 (0.2, 0.2)	2011 – 2014	0.3 (0.3, 0.4)	2014 – 2017	0.4 (0.4, 0.5)
Cyprus	2001 – 2005	0.0 (-0.1, 0.0)	2005 – 2010	0.9 (0.8, 0.9)	2010 – 2014	-0.4 (-0.5, -0.3)	2014 – 2017	-1.3 (-1.4, -1.1)
Czech Republic	2001 – 2003	0.3 (0.2, 0.5)	2003 – 2006	0.5 (0.3, 0.7)	2006 – 2017	1.0 (1.0, 1.0)		
Denmark	2001 – 2005	0.3 (0.3, 0.3)	2005 – 2010	0.1 (0.1, 0.1)	2010 – 2013	0.2 (0.2, 0.3)	2013 - 2017	0.3 (0.2, 0.4)
Estonia	2001 – 2010	-0.1 (-0.2, -0.1)	2010 – 2013	0.2 (0.1. 0.4)	2013 – 2017	0.6 (0.5, 0.6)		`
Finland	2001 – 2006	0.4 (0.4-0.5)	2006 – 2010	0.7 (0.6, 0.7)	2010 – 2014	0.4 (0.3, 0.4)	2014 – 2017	0.3 (0.2-0.3)
France	2001 – 2006	0.3 (0.3, 0.3)	2006 – 2013	0.4 (0.4, 0.4)	2013 – 2017	0.5 (0.5, 0.5)		
Germany	2001 -2006	0.1 (0.1, 0.1)	2006 – 2012	0.7 (0.7, 0.7)	2012 – 2017	1.0 (1.0, 1.1)		
Greece	2001 – 2006	0.7 (0.6, 0.7)	2006 – 2010	2.0 (1.9, 2.1)	2010 – 2013	2.4 (2.2, 2.6)	2013 – 2017	3.0 (3.0, 3.1)
Hungary	2001 – 2005	-0.1 (-0.1, -0.1)	2005 – 2013	0.1 (0.1, 0.1)	2013 – 2017	0.2 (0.1, 0.2)		
Ireland	2001 – 2005	0.6 (0.4, 0.6)	2005 – 2017	1.4 (1.4, 1.4)				
Italy	2001 – 2006	0.6 (0.6, 0.7)	2006 – 2009	0.9 (0.7, 1.0)	2009 – 2013	0.3 (0.2, 0.3)	2013 – 2017	-0.1 (-0.2, -0.1)
Latvia	2001 – 2005	-0.6(-0.7, -0.4)	2005 – 2009	-1.5 (-1.7, -1.3)	2009 – 2013	-0.1 (-0.3, 0.1)	2013 – 2017	0.8 (0.7, 0.9)
Lithuania	2001 – 2011	0.1 (0.0, 0.1)	2011 – 2014	1.1 (0.9, 1.2)	2014 – 2017	1.7 (1.7, 1.8)		
Luxembourg	2001 – 2006	0.5 (0.5, 0.5)	2006 – 2009	0.6 (0.6, 0.6)	2009 – 2014	0.5 (0.4, 0.5)	2014 – 2017	0.4 (0.4, 0.4)
Malta	2001 – 2005	0.5 (0.5, 0.6)	2005 – 2009	1.0 (0.9, 1.1)	2009 – 2013	0.3 (0.2, 0.4)	2013 – 2017	-0.0 (-0.1, -0.0)
Netherlands	2001 – 2005	0.6 (0.5, 0.7)	2005 – 2011	1.7 (1.7, 1.8)	2011 – 2017	1.2 (1.2, 1.3)		
Poland	2001 – 2008	-0.1 (-0.1, -0.0)	2008 – 2011	0.0 (-0.0, 0.1)	2011 – 2014	0.3 (0.3, 0.4)	2014 – 2017	0.6 (0.6, 0.6)
Portugal	2001 – 2006	0.5 (0.5, 0.5)	2006 – 2009	1.0 (0.9, 1.0)	2009 – 2017	0.6 (0.6, 0.6)		
Romania	2001 – 2004	-1.1 (-1.2, -1.1)	2004 – 2011	-0.5 (-0.5, -0.5)	2011 – 2014	-1.0 (-1.1, -0.8)	2014 – 2017	-1.3 (-1.4, -1.3)
Slovenia	2001 – 2006	0.3 (0.3, 0.3)	2006 – 2009	0.8 (0.7, 0.8)	2009 – 2017	0.4 (0.4, 0.4)		
Slovakia	2001 – 2006	0.3 (0.2, 0.3)	2006 – 2009	0.5 (0.5, 0.6)	2013 – 2017	0.4 (0.4, 0.5)		
Spain	2001 – 2006	0.5 (0.5, 0.5)	2006 – 2009	1.0 (0.9, 1.0)	2009 – 2013	0.5 (0.5, 0.5)		
Sweden	2001 – 2006	0.8 (0.8, 0.8)	2006 – 2014	0.9 (0.9, 0.9)	2014 – 2017	0.9 (0.9, 1.0)		
United Kingdom	2001 – 2006	1.2 (1.2, 1.2)	2006 – 2009	1.5 (1.5, 1.6)	2009 – 2014	1.1 (1.1, 1.1)	2014 – 2017	1.0 (1.0, 1.1)

Supplemental Table 2:

	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)
Austria	2001 – 2005	0.6 (0.5, 0.6)	2005 – 2010	-0.4 (-0.4, -0.3)	2010 – 2014	0.2 (0.2, 0.3)	2014 – 2017	0.5 (0.4, 0.5
Belgium	2001 – 2005	0.5 (0.5, 0.6)	2005 – 2009	1.3 (1.2, 1.4)	2009 – 2012	0.7 (0.4, 09)	2012 – 2017	0.3 (0.3, 0.4)
Bulgaria	2001 – 2004	0.4 (0.4, 0.5)	2004 – 2011	0.2 (0.2, 0.2)	2011 – 2014	0.7 (0.6, 0.8)	2014 – 2017	1.1 (1.0, 1.1)
Croatia	2001 – 2006	0.1 (0.0, 0.1)	2006 – 2011	0.2 (0.2, 0.2)	2011 – 2014	0.7 (0.7, 0.8)	2014 – 2017	1.1 (1.1, 1.1)
Cyprus	2001 – 2011	-0.2 (-0.2, -0.1)	2011 – 2014	-1.0 (-1.4, -0.6)	2014 – 2017	-1.6 (-1.8, -1.4)		
Czech Republic	2001 – 2006	0.4 (0.4, 0.4)	2006 – 2009	0.8 (0.7, 0.8)	2009 – 2017	0.6 (0.6, 0.6)		
Denmark	2001 -2005	0.6 (0.6, 0.7)	2005 – 2017	0.0 (0.0, 0.0)				
Estonia	2001 – 2006	0.0 (-0.0, 0.0)	2006 – 2011	0.2 (0.2, 0.3)	2011 – 2014	0.6 (0.5, 0.7)	2014 – 2017	0.8 (0.8, 0.9)
Finland	2001 – 2010	0.5 (0.5, 0.5)	2010 – 2014	0.1 (-0.0, 0.1)	2014 – 2017	-0.2 (-0.3, -0.1)		
France	2001 – 2004	0.5 (0.5, 0.5)	2004 – 2011	0.3 (0.3, 0.3)	2011 – 2014	0.4 (0.3, 0.4)	2014 – 2017	0.4 (0.4, 0.4)
Germany	2001 – 2008	0.4 (0.4, 0.4)	2008 – 2011	0.6 (0.5, 0.7)	2011 – 2014	0.8 (0.7, 0.9)	2014 – 2017	1.0 (1.0,1.1)
Greece	2001 -2003	0.5 (0.0, 0.9)	2003 – 2006	1.0 (0.6, 1.4)	2006 – 2014	2.6 (2.5, 2.6)	2014 – 2017	2.8 (2.6, 3.0)
Hungary	2001 – 2006	0.1 (0.1, 0.1)	2006 – 2009	0.4 (0.3, 0.4)	2009 – 2014	0.1 (0.1, 0.1)	2014 – 2017	0.1 (0.1, 0.1)
Ireland	2001 – 2005	0.4 (0.4, 0.4)	2005 – 2009	0.8 (0.8, 0.8)	2009 – 2017	0.6 (0.6, 0.7)		
Italy	2001 – 2005	0.7 (0.7, 0.8)	2005 – 2010	1.0 (1.0, 1.1)	2010 – 2014	0.3 (0.2, 0.3)	2014 – 2017	-0.1 (-0.1, -0.0)
Latvia	2001 – 2005	-0.5 (-0.6, -0.5)	2005 – 2010	-0.8 (-0.9, -0.7)	2010 – 2014	0.6 (0.5, 0.8)	2014 – 2017	1.6 (1.5, 1.8)
Lithuania	2001 – 2011	0.2 (0.2, 0.2)	2011 – 2014	1.2 (1.1, 1.4)	2014 – 2017	1.8 (1.8, 1.9)		
Luxembourg	2001 – 2006	0.8 (0.7, 0.8)	2006 – 2009	1.2 (1.2, 1.2)	2009 – 2017	1.1 (1.1, 1.1)		
Malta	2001 – 2005	0.6 (0.5, 0.8)	2005 – 2009	1.6 (1.4,1.8)	2009 – 2013	0.1 (-0.1, 0.3)	2013 – 2017	-0.8 (-0.9, -0.7)
Netherlands	2001 – 2005	0.6 (0.6, 0.6)	2005 – 2010	1.2 (1.2, 1.2)	2010 – 2014	0.8 (0.8, 0.9)	2014 – 2017	0.7 (0.7, 0.7)
Poland	2001 - 2005	-0.1 (-0.1, -0.2)	2005 – 2012	0.2 (0.1, 0.2)	2012 – 2017	0.3 (0.3, 0.3)		
Portugal	2001 – 2005	0.4 (0.4, 0.4)	2005 – 2010	1.0 (1.0, 1.1)	2010 – 2014	0.5 (0.5, 0.5)	2014 – 2017	0.3 (0.3, 0.4)
Romania	2001 – 2003	-1.6 (-1.6, -1.6)	2003 – 2008	-1.4 (-1.4, -1.4)	2008 – 2012	-1.4 (-1.4, -1.4)	2012 – 2017	-1.5 (-1.5, -1.5)
Slovenia	2001 – 2003	0.2 (-0.0, 0.4)	2003 – 2006	0.4 (0.2, 0.6)	2006 – 2010	1.1 (1.0, 1.2)	2010 – 2017	0.7 (0.6, 0.7)
Slovakia	2001 – 2006	0.3 (0.3, 03)	2006 – 2010	0.4 (0.3, 0.4)	2010 – 2014	0.1 (0.1, 0.2)	2014 – 2017	-0.0 (-0.1, 0.0)
Spain	2001 – 2005	0.5 (0.5, 0.6)	2005 – 2010	1.5 (1.4, 1.5)	2010 – 2014	0.0 (-0.1, 0.1)	2014 – 2017	-0.8 (-0.9, -0.7)
Sweden	2001 – 2006	0.4 (0.4, 0.4)	2006 – 2009	0.7 (0.7, 0.8)	2009 – 2013	0.6 (0.6, 0.6)	2013 – 2017	0.7 (0.6, 0.7)
United Kingdom	2001 – 2006	1.5 (1.5, 1.5)	2006 – 2009	1.8 (1.7, 1.9)	2009 – 2014	1.3 (1.2, 1.3)	2014 – 2017	1.2 (1.1, 1.2)

Supplemental Table 3:

	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)
Austria	2001 – 2003	2.9 (1.4, 4.4)	2003 – 2008	0.9 (0.4, 1.4)	2008 – 2014	2.1 (1.7, 2.4)	2014 – 2017	-0.9 (-1.7, -0.2)
Belgium	2001 – 2012	2.3 (2.1, 2.4)	2012 – 2017	-0.5 (-1.1, -0.0)				
Bulgaria	2001 – 2006	-6.7 (-7.3, -6.2)	2006 – 2009	-2.4 (-5.0, 0.3)	2009 – 2017	0.3 (-0.0, 0.6)		
Croatia	2001 – 2006	1.9 (0.5, 3.4)	2006 – 2017	-1.8 (-2.2, -1.4)				
Cyprus	2001 – 2003	3.3 (0.5, 6.1)	2003 – 2009	0.4 (-0.2, 1.0)	2009 – 2014	1.5 (0.6, 2.3)	2014 – 2017	-0.8 (-2.2, 0.5)
Czech Republic	2001 – 2012	5.7 (5.4, 6.0)	2012 – 2015	1.8 (-2.1, 5.7)	2015 – 2017	-3.9 (-7.5, -0.1)		
Denmark	2001 – 2007	-0.0 (-0.5, 0.4)	2007 – 2011	1.7 (0.3, 3.0)	2011 – 2017	-0.2 (-0.6, 0.3)		
Estonia	2001 – 2003	-4.6 (-11.2, 2.6)	2003 – 2006	3.4 (-3.8, 11.1)	2006 – 2011	-4.3 (-6.4, -2.1)	2011 – 2017	0.1 (-1.1, 1.3)
Finland	2001 – 2004	3.4 (2.5, 4.4)	2004 – 2011	2.4 (2.1, 2.7)	2011 – 2017	-0.6 (-0.9, -0.3)		
France	2001 – 2007	0.8 (0.6, 1.0)	2007 – 2012	2.0 (1.6, 2.3)	2012 – 2017	-1.3 (-1.5, -1.1)		
Germany	2001 – 2006	1.8 (1.2, 2.3)	2006 – 2010	3.1 (1.9, 4.3)	2010 – 2015	-0.8 (-3.1, 1.6)	2015 – 2017	-0.8 (-3.1, 1.6)
Greece	2001 – 2005	3.0 (1.0, 5.0)	2005 – 2011	10.4 (8.9, 12.0)	2011 – 2015	3.5 (0.4, 6.7)	2015 – 2017	-5.8 (-11.4, 0.2)
Hungary	2001 – 2007	2.7 (2.3, 3.1)	2007 – 2015	0.5 (0.2, 0.8)	2015 – 2017	-4.5 (-6.6, -2.4)		
Ireland	2001 – 2004	3.3 (2.0, 4.5)	2004 – 2009	6.0 (5.1, 6.8)	2009 – 2013	1.0 (-0.2, 2.3)	2013 – 2017	-2.0 (-2.7, -1.2)
Italy	2001 – 2003	5.2 (3.3, 7.2)	2003 – 2015	-0.2 (-0.3, -0.1)	2015 – 2017	-2.1 (-3.9, -0.3)		
Latvia	2001 – 2013	-2.3 (-3.0, -1.7)	2013 – 2017	0.6 (-3.0, 4.3)				
Lithuania	2001 – 2009	1.1 (0.9, 1.3)	2009 – 2013	3.4 (2.6, 4.2)	2013 – 2017	0.3 (-0.2, 0.8)		
Luxembourg	2001 – 2004	2.4 (1.3, 3.5)	2004 – 2017	0.5 (0.4, 0.6)				
Malta	2001 – 2003	0.1 (-3.8, 4.2)	2003 – 2007	3.5 (1.5, 5.6)	2007 – 2017	-0.0 (-0.3, 0.3)		
Netherlands	2001 – 2012	2.4 (2.3, 2.5)	2012 – 2015	1.6 (-0.1, 3.4)	2015 – 2017	-1.9 (-3.6, -0.1)		
Poland	2001 – 2005	-1.0 (-1.3, -0.6)	2005 – 2010	2.5 (2.2, 2.9)	2010 – 2015	-0.0 (-0.4, 0.3)	2015 – 2017	-2.7 (-3.7, -1.6)
Portugal	2001 – 2003	5.1 (3.2, 7.1)	2003 – 2011	3.6 (3.3, 3.9)	2011 – 2014	-0.7 (-2.5, 1.1)	2014 – 2017	-1.9 (-2.8, -1.0)
Romania	2001 – 2007	-2.5 (-2.8, -2.2)	2007 – 2010	-0.7 (-2.4, 1.1)	2010 – 2014	-1.8 (-2.7, -0.9)	2014 -2017	1.8 (0.9, 2.7)
Slovenia	2001 – 2003	7.2 (3.2, 11.5)	2003 – 2009	3.4 (2.5, 4.3)	2009 – 2015	0.2 (-0.7, 1.0)	2015 – 2017	-4.1 (-7.7, -0.3)
Slovakia	2001 – 2004	0.6 (-0.9, 2.2)	2004 – 2012	4.0 (3.5, 4.4)	2012 – 2015	1.0 (-2.1, 4.2)	2015 – 2017	-5.1 (-8.1, -2.1
Spain	2001 – 2005	2.6 (2.2, 3.0)	2005 – 2011	1.2 (0.9, 1.5)	2011 – 2015	0.6 (-0.1, 1.2)	2015 – 2017	-1.5 (-2.7, -0.3)
Sweden	2001 – 2007	3.2 (2.6, 3.8)	2007 – 2015	1.3 (0.8, 1.7)	2015 – 2017	-2.7 (-6.0, 0.7)		
United Kingdom	2001 – 2003	5.4 (2.4, 8.5)	2003 – 2008	3.5 (2.5, 4.4)	2008 – 2013	2.4 (1.4, 3.3)	2013 – 2017	-0.6 (-1.6, 0.3)

Supplemental Table 4:

	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)
Austria	2001 – 2008	1.0 (0.4, 1.6)	2008 – 2012	3.2 (1.1, 5.4)	2012 – 2017	-0.7 (-1.7, 0.2)		
Belgium	2001 – 2003	4.9 (1.9, 7.9)	2003 – 2012	1.1 (0.8, 1.4)	2012 – 2017	-1.6 (-2.3, -1.0)		
Bulgaria	2001 – 2003	-4.6 (-6.9, -2.2)	2003 – 2017	-0.7 (-0.8, -0.6)				
Croatia	2001 – 2015	0.2 (-0.2, 0.5)	2015 – 2017	-5.9 (-12.7, 1.5)				
Cyprus	2001 – 2012	0.5 (0.2, 0.8)	2012 – 2017	-3.0 (-4.1, -2.0)				
Czech Republic	2001 – 2012	4.7 (4.4, 5.0)	2012 – 2017	-1.1 (-2.1, -0.0)				
Denmark	2001 – 2004	1.4 (-0.2, 3.1)	2004 – 2012	-0.8 (-1.2, -0.4)	2012 – 2017	0.4 (-0.3, 1.1)		
Estonia	2001 – 2017	-0.3 (-0.7, 0.0)						
Finland	2001 – 2011	2.0 (1.7, 2.3)	2011 – 2017	-1.7 (-2.3, -1.1)				
France	2001 – 2003	2.2 (0.7, 3.7)	2003 – 2011	0.5 (0.3, 0.7)	2011 – 2017	-1.9 (-2.2, -1.7)		
Germany	2001 – 2006	1.6 (1.1, 2.2)	2006 – 2011	3.2 (2.4, 4.0)	2011 – 2017	-0.2 (-0.8, 0.1)		
Greece	2001 – 2004	6.4 (2.9, 10.0)	2004 – 2012	9.6 (8.6, 10.6)	2012 – 2015	2.9 (-3.7, 10.1)	2015 – 2017	-7.8 (-13.8, -1.3)
Hungary	2001 – 2004	6.3 (5.0, 7.6)	2004 – 2010	1.3 (0.8, 1.9)	2010 – 2015	-1.4 (-2.2, -0.6)	2015 – 2017	-7.3 (-9.5, -5.1)
Ireland	2001 – 2004	1.9 (-0.6, 4.4)	2004 – 2013	4.1 (3.6, 4.7)	2013 – 2017	-2.7 (-4.2 -1.2)		
Italy	2001 – 2003	5.0 (1.7, 8.4)	2003 – 2011	0.4 (-0.0, 0.8)	2011 – 2017	-1.3 (-1.9, -0.8)		
Latvia	2001 – 2004	-3.1 (-5.1, -0.9)	2004 – 2017	-1.1 (-1.4, -0.9)				
Lithuania	2001 – 2013	1.9 (1.6, 2.2)	2013 – 2017	-0.1 (-1.7, 1.6)				
Luxembourg	2001 – 2015	2.8 (2.7, 2.9)	2015 – 2017	0.5 (-1.9, 2.9)				
Malta	2001 – 2004	4.1 (2.5, 5.6)	2004 – 2008	1.7 (0.2, 3.2)	2008 – 2017	-0.6 (-0.9, -0.3)		
Netherlands	2001 – 2010	1.7 (1.3, 2.1)	2010 – 2017	0.6 (0.1, 1.2)				
Poland	2001 – 2005	-1.4 (-2.2, -0.6)	2005 – 2015	1.2 (1.0, 1.5)	2015 – 2017	-4.1 (-6.5, -1.7)		
Portugal	2001 – 2008	5.2 (4.5, 5.8)	2008 – 2011	1.2 (-3.4, 6.1)	2011 – 2017	-2.8 (-3.6, -2.0)		
Romania	2001 – 2007	-6.5 (-6.9, -6.1)	2007 – 2013	-3.6 (-4.1, -3.0)	2013 – 2017	-0.0 (-0.9, 0.8)		
Slovenia	2001 – 2008	4.9 (4.3, 5.4)	2008 – 2013	2.6 (1.4, 3.8)	2013 – 2017	-4.3 (-5.4, -3.1)		
Slovakia	2001 – 2010	4.4 (4.1, 4.6)	2010 – 2015	0.6 (-0.2, 1.4)	2015 – 2017	-3.1 (-5.5, -0.6)		
Spain	2001 – 2005	3.2 (2.3, 4.1)	2005 – 2015	1.1 (0.8, 1.4)	2015 – 2017	-3.4 (-6.1, -0.6)		
Sweden	2001 – 2015	1.9 (1.8, 2.0)	2015 – 2017	-0.3 (-2.3, 1.6)				
United Kingdom	2001 – 2004	6.2 (4.8, 7.6)	2004 – 2013	3.0 (2.7, 3.3)	2013 – 2017	-0.1 (-0.9, 0.7)		

Supplemental Table 5:

	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)
Austria	2001 – 2007	1.1 (0.6, 1.5)	2007 – 2014	2.1 (1.6, 2.5)	2014 – 2017	-1.2 (-2.5, 0.1)		
Belgium	2001 – 2005	2.1 (1.4, 2.8)	2005 – 2013	0.8 (0.5, 1.1)	2013 – 2017	-1.7 (-2.3, -1.0)		
Bulgaria	2001 – 2006	-6.7 (-7.2, -6.1)	2006 – 2009	-1.7 (-4.3, 0.9)	2009 – 2017	0.2 (-0.1, 0.5)		
Croatia	2001 – 2006	1.8 (0.4, 3.2)	2006 – 2017	-2.1 (-2.5, -1.7)				
Cyprus	2001 – 2004	2.6 (1.2, 4.1)	2004 – 2009	-0.6 (-1.5, 0.3)	2009 – 2015	1.6 (1.0, 2.2)	2015 – 2017	-0.0 (-2.8, 2.9)
Czech Republic	2001 – 2011	5.1 (4.7, 5.4)	2011 – 2015	1.6 (-0.8, 4.0)	2015 – 2017	-5.2 (-9.5, -0.7)		
Denmark	2001 – 2007	-0.2 (-0.7, 0.2)	2007 – 2011	1.6 (0.3, 2.9)	2011 – 2017	-0.5 (-0.9, -0.0)		
Estonia	2001 – 2003	-4.4 (-11.2, 2.9)	2003 – 2006	3.5 (-3.8, 11.5)	2006 – 2011	-4.2 (-6.4, -1.9)	2011 – 2017	-0.4 (-1.6, 0.8)
Finland	2001 – 2004	3.1 (2.1, 4.0)	2004 – 2011	1.8 (1.5, 2.1)	2011 – 2017	-0.9 (-1.2, -0.6)		
France	2001 – 2008	0.6 (0.5, 0.7)	2008 – 2012	1.7 (1.2, 2.2)	2012 – 2017	-1.8 (-2.1, -1.6)		
Germany	2001 – 2007	1.7 (1.3, 2.1)	2007 – 2010	2.6 (0.1, 5.2)	2010 – 2015	0.1 (-0.7, 0.9)	2015 – 2017	-1.9 (-4.3, 0.6)
Greece	2001 – 2005	2.5 (0.5, 4.5)	2005 – 2011	8.4 (6.9, 10.0)	2011 – 2015	0.7 (-2.5, 3.9)	2015 – 2017	-8.7 (-14.2, -2.8)
Hungary	2001 – 2007	2.7 (2.3, 3.1)	2007 – 2015	0.4 (0.1, 0.7)	2015 – 2017	-4.7 (-6.8, -2.5)		
Ireland	2001 – 2004	2.9 (1.7, 4.2)	2004 – 2009	4.6 (3.8, 5.4)	2009 – 2013	-0.4 (-1.6, 0.8)	2013 – 2017	-3.3 (-4.1, -2.6)
Italy	2001 – 2003	4.3 (1.6, 7.1)	2003 – 2017	-0.7 (-0.9, -0.6)				
Latvia	2001 – 2017	-1.4 (-1.8, -1.0)						
Lithuania	2001 – 2004	0.6 (-0.0, 1.3)	2004 – 2009	1.3 (0.9, 1.7)	2009 – 2013	2.8 (2.2, 35)	2013 – 2017	-1.3 (-1.7, -1.0)
Luxembourg	2001 – 2004	1.8 (0.7, 3.0)	2004 – 2017	0.0 (-0.1, 0.2)				
Malta	2001 – 2007	1.8 (1.0, 2.5)	2007 – 2017	-0.2 (-0.6, 0.1)				
Netherlands	2001 – 2005	1.8 (1.1, 2.5)	2005 – 2015	0.7 (0.5, 0.9)	2015 – 2017	-3.2 (-5.3, -1.1)		
Poland	2001 – 2005	-0.9 (-1.3, -0.5)	2005 – 2010	2.6 (2.2, 3.0)	2010 – 2015	-0.4 (-0.7, 0.0)	2015 – 2017	-3.3 (-4.5, -2.2)
Portugal	2001 – 2004	4.2 (3.4, 4.9)	2004 – 2011	2.7 (2.5, 3.0)	2011 – 2014	-1.3 (-2.7, 0.2)	2014 – 2017	-2.5 (-3.2, -1.8)
Romania	2001 – 2007	-1.6 (-1.9, -1.3)	2007 – 2014	-0.7 (-1.0, -0.4)	2014 – 2017	3.0 (2.0, 4.1)		
Slovenia	2001 – 2003	7.2 (3.1, 11.4)	2003 – 2009	2.8 (1.9, 3.7)	2009 – 2015	-0.3 (-1.2, 0.6)	2015 – 2017	-4.4 (-8.0, -0.6)
Slovakia	2001 – 2004	0.7 (-0.9, 2.3)	2004 – 2014	3.3 (3.0, 3.6)	2014 – 2017	-4.6 (-6.1, -3.0)		
Spain	2001 – 2005	2.2 (1.6, 2.7)	2005 – 2015	0.3 (0.2, 0.5)	2015 – 2017	-2.0 (-3.6, -0.3)		
Sweden	2001 – 2007	2.4 (1.8, 3.0)	2007 – 2015	0.4 (-0.1, 0.8)	2015 – 2017	-3.6 (-6.9, -0.3)		
United Kingdom	2001 – 2003	4.2 (1.2, 7.2)	2003 – 2007	2.2 (0.8, 3.7)	2007 – 2013	1.2 (0.6, 1.9)	2013 – 2017	-1.7 (-2.6, -0.8)

Supplemental Table 6:

	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)	Years	EAPC (95% CI)
Austria	2001 – 2007	0.6 (-0.1, 1.3)	2007 – 2012	3.1 (1.8, 4.5)	2012 – 2017	-1.1 (-2.0, -0.2)		
Belgium	2001 – 2003	4.5 (1.5, 7.6)	2003 – 2012	0.1 (-0.2, 0.4)	2012 – 2017	-1.9 (-2.5, -1.3)		
Bulgaria	2001 – 2004	-3.9 (-5.0, -2.7)	2004 – 2011	-0.6 (-1.0, -0.2)	2011 – 2017	-1.7 (-2.1, -1.3)		
Croatia	2001 – 2015	-0.1 (-0.5, 0.2)	2015 – 2017	-7.6 (-14.6, -0.1)				
Cyprus	2001 – 2004	1.7 (0.0, 3.4)	2004 – 2007	-0.9 (-4.1, 2.4)	2007 – 2012	1.4 (0.4, 2.5)		
Czech Republic	2001 – 2012	4.1 (3.8, 4.4)	2012 – 2017	-1.6 (-2.7, -0.6)				
Denmark	2001 – 2004	0.6 (-1.0, 2.3)	2004 – 2012	-0.9 (-1.3, -0.5)	2012 – 2017	0.4 (-0.4, 1.1)		
Estonia	2001 – 2006	1.4 (-0.5, 3.3)	2006 – 2017	-1.3 (-1.9, -0.7)				
Finland	2001 – 2011	1.5 (1.2, 1.8)	2011 – 2017	-1.6 (-2.2, -1.0)				
France	2001 – 2003	1.5 (0.1, 3.0)	2003 - 2011	0.2 (0.0, 0.4)	2011 – 2017	-2.3 (-2.5, -2.1)		
Germany	2001 – 2006	1.1 (0.7, 1.6)	2006 – 2010	3.1 (2.0, 4.2)	2010 – 2015	-0.4 (-1.1, 0.2)	2015 – 2017	-2.4 (-4.5, -0.3)
Greece	2001 – 2012	7.0 (6.6, 7.4)	2012 – 2015	0.3 (-5.7, 6.6)	2015 – 2017	-10.3 (-15.6, -4.6)		
Hungary	2001 – 2004	6.2 (4.9, 7.6)	2004 – 2010	1.1 (0.5, 1.6)	2010 – 2015	-1.5 (-2.3, -0.7)	2015 – 2017	-7.4 (-9.7, -5.0)
Ireland	2001 – 2013	3.1 (2.7, 3.4)	2013 – 2017	-3.0 (-4.8, -1.1)				
Italy	2001 – 2003	4.4 (1.2, 7.6)	2003 – 2011	-0.5 (-1.0, -0.1)	2011 – 2017	-1.4 (-1.9, -0.9)		
Latvia	2001 – 2013	-1.0 (-1.4, -0.7)	2013 – 2017	-2.6 (-4.3, -0.9)				
Lithuania	2001 – 2013	1.6 (1.2, 1.9)	2013 – 2017	-2.1 (-3.7, -0.3)				
Luxembourg	2001 – 2004	2.5 (1.2, 3.7)	2004 – 2015	1.6 (1.4, 1.8)	2015 – 2017	-0.5 (-2.9, 1.9)		
Malta	2001 – 2005	2.9 (2.2, 3.7)	2005 – 2009	-0.4 (-1.6, 0.8)	2009 – 2012	-1.6 (-3.9, 0.8)	2012 – 2017	0.4 (-0.2, 0.9)
Netherlands	2001 – 2003	2.7 (0.0, 5.4)	2003 – 2011	0.5 (0.2, 0.9)	2011 – 2014	-1.0 (-3.6, 1.6)	2014 – 2017	0.9 (-0.5, 2.2)
Poland	2001 – 2005	-1.3 (-2.1, -0.5)	2005 – 2015	1.1 (0.8, 1.3)	2015 – 2017	-4.6 (-7.0, -2.0)		
Portugal	2001 – 2008	4.4 (3.8, 5.1)	2008 – 2011	0.2 (-4.5, 5.1)	2011 – 2017	-3.2 (-4.0, -2.4)		
Romania	2001 – 2007	-5.1 (-5.5, -4.7)	2007 – 2013	-2.2 (-2.8, -1.6)	2013 – 2017	1.4 (0.6, 2.3)		
Slovenia	2001 – 2008	4.3 (3.8, 4.7(	2008 – 2013	1.7 (0.5, 2.8)	2013 – 2017	-4.8 (-5.8, -3.7)		
Slovakia	2001 – 2010	4.0 (3.8, 4.3)	2010 – 2015	0.5 (-0.3, 1.3)	2015 – 2017	-3.0 (-5.3, -0.5)		
Spain	2001 – 2005	2.6 (1.7, 3.5)	2005 – 2010	-0.3 (-1.2, 0.6)	2010 – 2015	1.1 (0.2, 2.0)	2015 – 2017	-2.3 (-5.0, 0.5)
Sweden	2001 – 2004	2.0 (1.0, 2.9)	2004 – 2015	1.2 (1.0, 1.3)	2015 – 2017	-0.9 (-2.7, 1.0)		
United Kingdom	2001 – 2004	4.6 (3.2, 6.0)	2004 – 2013	1.4 (1.1, 1.7)	2013 – 2017	-1.2 (-2.0, -0.3)		