Imperial College London

Academic Section of Vascular Surgery
Department of Surgery & Cancer
Imperial College London
4th Floor, East Wing
Charing Cross Hospital
Fulham Palace Road
London W6 8RF, UK

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Dear Prof. Kolh and the *EJVES* editorial team,

Re: Trends in Limb Amputation Incidence in EU15+ Countries 1990-2017
Authors: Will Hughes, Richard Goodall, Justin Salciccioli, Dominic Marshall, Alun Davies, Joseph Shalhoub

We present an observational analysis of limb amputation incidence in European Union (EU) 15+ countries between 1990-2017, using data obtained from the Global Burden of Disease (GBD) Study 2017.

Our hypothesis was that we would identify reducing incidence trends, given previous work from our group using the GBD Study which identified reducing incidence of peripheral arterial disease over the same time period in EU15+ countries (in press). However, the present article identifies variable trends in amputation incidence across EU15+ countries between 1990-2017. We discuss potential contributors to the observed results.

We confirm that:

a) There has been no duplicate publication or submission elsewhere
b) All authors have read and approved the manuscript
c) Subject to acceptance, authors will sign an exclusive license to publish
d) There are no conflicts of interest.

Thank you for your consideration.

Yours sincerely,

Dr Will Hughes
On behalf of the authors

Trends in Lower Limb Amputation Incidence in European Union 15+ Countries *1990-2017*

Will Hughes* (1) BSc MBChB MRCS, Richard Goodall* (2) BSc MBChB MRCS, Justin D Salciccioli (2,3) MA MBBS, Dominic C Marshall (4) BSc MBBS MRCP, Alun Huw Davies (2) MA DM FRCS DSc, Joseph Shalhoub (2) BSc MBBS PhD MEd FRCS FEBVS

*Contributed Equally

(1) Department of Surgery, Broomfield Hospital, Chelmsford, UK
(2) Academic Section of Vascular Surgery, Department of Surgery & Cancer, Imperial College London, UK, and Department of Vascular Surgery, Imperial College Healthcare NHS Trust, London, UK
(3) Department of Medicine, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA 02138, USA
(4) Critical Care Research Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Corresponding author: Will Hughes
ORCID: https://orcid.org/0000-0003-0849-671X
Email: w.hughes1@nhs.net

Address:

Academic Section of Vascular Surgery

Department of Surgery & Cancer

Imperial College London

4th Floor

Charing Cross Hospital

Fulham Palace Road

London W6 8RF, UK

Tel: +44 (0) 7951919537

Fax: +44 (0) 20 3311 7362

Twitter: @imperialvasc

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Short title: Trends in Lower Limb Amputation EU15+ 1990-2017

What does this study/review add to the existing literature and how will it influence future clinical practice?

We present an observational analysis of lower limb amputation incidence in European Union (EU) 15+ countries between 1990-2017, using data obtained from the Global Burden of Disease (GBD) Study 2017.

Our hypothesis was that we would identify reducing incidence trends, given previous work from our group using the GBD Study which identified reducing incidence of peripheral arterial disease over the same time period in EU15+ countries. However, the present article identifies variable trends in lower limb amputation incidence across EU15+ countries between 1990-2017. We discuss potential contributors to the observed results.

Abstract

Objective

Lower extremity amputation (LEA) carries significant mortality, morbidity and health economic burden. In the Western world, it most commonly results from complications of peripheral arterial occlusive disease (PAOD) or diabetic foot disease. Incidence of PAOD has declined in Europe, the United States and parts of Australasia. We aimed to assess trends in LEA incidence in European Union (EU15+) countries for the years 1990 to 2017.

Design

Observational study using data obtained from the 2017 Global Burden of Disease (GBD) Study.

Materials

GBD Results Tool: http://ghdx.healthdata.org/gbd-results-tool

Methods

Age-standardised incidence rates (ASIRs) for LEA (stratified into toe amputation, and LEA proximal to toes) were extracted from the GBD Results Tool for EU15+ countries for each of the years 1990-2017. Trends were analysed using Joinpoint regression analysis.

Results

Between 1990 and 2017, variable trends in the incidence of LEA were observed in EU15+ countries. For LEAs proximal to toes, increasing trends were observed in 6 of 19 countries and decreasing trends in 9 of 19 countries, with 4 countries showing varying trends between sexes. For toe amputation, increasing trends were observed in 8 of 19 countries and decreasing trends in 8 of 19 countries for both sexes, with 3 countries showing varying trends between sexes. Australia had the highest ASIRs for both sexes in all LEAs at all time points, with steadily increasing trends. The USA observed the greatest reduction all LEAs in both sexes over the time period analysed (LEAs proximal to toes: females -22.93%, males -29.76%; toe amputation: females -29.93%, males -32.67%). The greatest overall increase in incidence was observed in Australia.

Conclusions

Variable trends in LEA incidence were observed across EU15+ countries. These trends do not reflect previously observed reductions in incidence of PAOD over the same time period.

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Introduction

Lower extremity amputation (LEA) represents a significant burden on global health systems. Significant morbidity and mortality accompanies both traumatic and non-traumatic amputations[1,2]. One-year mortality rates vary by country, age, gender and anatomical level of amputation, but are estimated at between 12-58%[3]. In a retrospective cohort of 18,463 patients who underwent major peripheral arterial occlusive disease (PAOD) related amputation in the United States between 2003-2010, the mean cost of inpatient care in the year before amputation, including the amputation itself, was $22,405[4]. There are several indications for LEA, including an injured or mal-perfused limb not amenable to salvage (or where attempts at salvage have failed), an injured limb wherein mortality is a risk from infection, or malignancy[5,6]. In developed countries, LEA results primarily from failure of limb conserving interventions in the management of diabetes and/or peripheral arterial occlusive disease (PAOD)[7].

Our group has previously used data obtained from the Global Burden of Disease Study to demonstrate decreasing trends in PAOD incidence across European Union (EU) 15+ countries[8] – a group of countries which have previously been demonstrated to be comparable in terms of their health-expenditure[9,10]. Decreasing PAOD incidence rates in Western European populations have also been reported elsewhere[11]. Conversely, data pertaining to diabetes incidence, a known risk factor for PAOD, demonstrates increasing worldwide trends[12].

Country-specific data for trends in LEA incidence have been published[13–17], however only a few studies have investigated inter-country incidence over a period of time[18,19]. Furthermore, to our knowledge, no study has used the Global Burden of Disease (GBD) database[20,21] to compare trends in age-standardised incidence rates (ASIRs) of LEA in EU15+ countries.

The primary objective of this observational analysis was to compare the incidence rates of LEA across EU15+ countries between 1990 and 2017. Given the reduction in incidence rates of PAOD observed in our earlier analysis[8], we hypothesized that similar temporal reductions would be observed for LEA incidence across these countries.

Methods

Data Source

Data collected for the Global Burden of Disease (GBD) study was used for this observational analysis of LEA incidence. GBD combines multiple data-sources to provide results related to specific diseases: deaths/death rates, years of life lost (YLLs) due to premature mortality, prevalence and incidence. The GBD methodology has been published previously[20,21]. For estimations of disease incidence within a population, the GBD study combines multiple sources of information for a disease (including (but not limited to) systematic reviews, claims data, inpatient hospital admissions data and outpatient encounter data (based on International Classification of Disease (ICD) coding)) using a Bayesian meta-regression tool DisMod-MR 2.1[20]. The DisMod-MR tool evaluates and pools available data, adjusted for systematic bias associated with methods that varied from the reference, and produces estimates by population with corresponding uncertainty intervals using Bayesian statistical methods[20]. The results are then made publicly available online via the GBD Results Tool http://ghdx.healthdata.org/gbd-results-tool. We extracted age-standardised incidence rates for LEA for EU15+ countries between 1990 and 2017 from the GBD Results Tool. The EU15+ countries are as follows: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland6, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom and United States. Age-standardised incidence data were extracted for both toe amputation and LEA proximal to toes.

Data Handling

Age-standardised incidence rates per 100,000 population (ASIRs) were extracted from the GBD Results Tool for each of the years 1990-2017 inclusive for each EU15+ country per sex. For all ASIRs, GBD uses a standard population calculated as the non-weighted average across all countries of the percentage of the population in each five-year age group for the years 2010-2035 from the United Nations Population Division's World Population Prospects (2012 revision)[22]. Put simply, using age-standardised rates accounts for differences in the age structure of different populations and improves the comparability between countries. Absolute and relative changes in ASIRs over the observation period were calculated between the start and end for each sex in each country by computing the difference between the start and end age-standardised incidence rates for males and females independently. The GBD data was analysed for LEAs, which were further stratified into toe amputation and LEA proximal to toes (unilateral and bilateral combined).

Statistical Analysis

Trends in LEAs were analysed by gross percentage change from 1990 to 2017, and using Joinpoint regression analysis (Joinpoint software (Joinpoint Command Line Version 4.5.0.1) provided by the United States National Cancer Institute Surveillance Research Program[23]). Joinpoint regression software analyses trends in data over time and uses a logarithmic scale to connect different line segments in the simplest possible model. Starting with the minimum number of Joinpoints (zero Joinpoints represents a straight line), the addition of more Joinpoints is tested for statistical significance using a Monte Carlo permutation method and, if significant, that Joinpoint is added to the model. Additionally, the software computes estimated annual percent changes (EAPC) for each line segment (with corresponding 95% confidence intervals). EAPCs are evaluated to establish if there is a difference from the null hypothesis of no change. Therefore, for the final model, each Joinpoint represents a statistically significant change in trend (increase or decrease) and each trend is described by the EAPC with confidence estimates. By estimating the annual percentage change, one is able to assess trend changes at a constant percent per year.

Results

1990-2017 Lower Extremity Amputation Incidence

Figure 1 demonstrates LEA ASIRs per country in 1990 and 2017 for males and females. In 1990, Sweden had the lowest incidence of LEA proximal to toes in both males and females (15.3 and 13.9 per 100,000, respectively). In 2017, the USA had the lowest incidence of LEA proximal to toes for both sexes (males 12.4 per 100,000, females 12.8 per 100,000). In 1990, the highest incidence of LEA proximal to toes in both sexes was observed in Australia (males: 37.8 per 100,000; females: 31.4 per 100,000). The highest incidences in 2017 were also seen in Australia, increasing to 41.9 per 100,000 for males and 34.8 per 100,000 for females.

In 1990, the lowest incidences for toe amputation among females were observed in the Netherlands (19.5 per 100,000). For males in 1990, Ireland had the lowest incidences (26.6 per 100,000). In 2017, Italian females had the lowest ASIR (19.4 per 100,000). The lowest incidence for males in 2017 was observed in the Netherlands (31.2 per 100,000). Australia saw the highest toe amputation ASIRs among both sexes in both 1990 and 2017.

Trends in Lower Extremity Amputation Incidence

LEA proximal to toes ASIRs per 100,000 increased between 1990 and 2017 for both sexes in Australia, Belgium, Germany, Ireland, Sweden and the UK. In females, the greatest overall percentage increase was seen in Australia (+11.02%), followed by the UK (+8.52%) and Sweden (+8.35%). In males, the greatest percentage increase occurred in the UK (+11.93%), followed by Belgium, Sweden and Australia (+11.45%, +11.10% and +11%, respectively). Decreasing rates in LEA proximal to toes were seen in both sexes in Austria, Denmark, France, Greece, Italy, Luxembourg, Portugal, Spain and the USA. The USA showed the greatest overall percentage reduction in both males and females (-29.76% and -22.93%, respectively). Considerable percentage reductions were seen in Portugal and Luxembourg in males (-27.34% and -16.42%, respectively), and Denmark and Portugal in females (-18.16% and -15.25%, respectively). Canada, Finland, the Netherlands and Norway all showed <5% increase in incidence in females, but reductions in incidence in males for LEAs proximal to toes.

Toe amputation ASIRs increased between 1990 and 2017 for both sexes in Australia, Belgium, Finland, Germany, Ireland, the Netherlands, Sweden and the UK. In females, the greatest overall percentage increase was seen in Australia (+9.66%), followed by the UK (+6.27%) and Sweden (+6.11%), mirroring the changes seen in LEAs proximal to toes. In males, this greatest percentage increase occurred in Belgium (+16.02%), followed by Australia and the UK (+13.29% and +11.04%, respectively). Decreasing ASIRs in toe amputation were seen in both sexes in Austria, Denmark, France, Italy, Luxembourg, Portugal, Spain and the USA, mirroring LEA proximal to toes except for Greece. The USA showed the greatest overall percentage reduction in both males and females (-32.67% and -29.93%, respectively). Considerable percentage reductions were seen in Portugal and Luxembourg in males (-28.8% and -17.20%, respectively), and Portugal and Italy in females (-13.60% and -11.31%, respectively). Canada and Norway observed percentage increases in females, but decreases in males, with Greece demonstrating decreases in females but increases in males, however all changes were less than +/-5% for these countries.

Joinpoint Analysis for Lower Extremity Amputation Incidence

Figures 2 and 3, and Tables 1 - 4 present the results of the Joinpoint regression analysis for the trends in all LEA ASIRs between 1990 and 2017 in females and males. EAPC in incidence rates for periods covered by each trend are demonstrated. Significant trend changes in ASIRs are reported.

For LEAs proximal to toes, trends in ASIR were variable. Across the included countries, over half of all the observed trends were negative for both males and females. The greatest single reduction was observed in the USA for both males and females (-6.3% for both sexes). The most consistently positive trends were observed in the UK, Canada and Belgium in females, and in the UK and Australia for males.

Trends were also variable for across countries for toe amputation. Just under half of all trends were negative for females, however in males over half of the trends were negative. In both sexes the greatest single reduction was observed in the USA (-8.1% for males and -8.2% for females). The most consistently positive trends were observed in the UK, and Canada in females, and in Sweden and Australia for males.

Discussion

In this 28-year observational study of lower extremity amputation incidence in EU15+ countries, we identify significant variability in amputation incidence both geographically and temporally. For both sexes, Australia has consistently observed the highest incidences of LEAs across the period studied as well as the greatest percentage increase in ASIRs. Meanwhile, the incidence of LEA was consistently low in the Netherlands and the USA, with the greatest percentage reduction in incidence observed in the USA.

The primary objective of this analysis was to compare amputation incidence across the EU15+ countries. Based upon previous analyses of LEA incidence[18,19] and the decreasing incidence of PAOD over the same time period presented elsewhere[8,11] our hypothesis was that amputation incidence would decrease over the studied period. This would match data observed for PAOD and its risk factors[8,24]. The findings from this study do not directly support this hypothesis, with variability in trends differing from the uniformly downward trends observed in the aforementioned previous studies. We discuss several potential reasons for this.

The latest figures from the International Diabetes Federation (IDF) suggest that the global incidence of diabetes has increased from 151 million in 2000, to 425 million in 2017, and is projected to increase further[25]. Harding et al[26] recently reviewed trends in LEA incidence among global diabetic populations from 1988 to 2011. Despite the rising incidence of diabetes, consistent reductions in LEA in a diverse and global population were identified. While the body of evidence is significant, the difficulties in drawing direct comparisons have been highlighted previously[7], and include the use of different denominators (proportion of diabetic vs whole population), healthcare expenditure, population sizes, and data gathered from specialised vascular centres versus district general hospitals or equivalent. It should be noted that there is a significant lack of data from countries outside North America, Europe and the high-income Asia-Pacific countries.

Traumatic amputations in Western countries and countries not affected by conflict are now rare, with amputation occurring in only 1% of trauma patients in the USA[1]. Instead, declining PAOD incidence may be partly responsible for the results of this study. Our group has previously used the GBD Study to demonstrate reducing incidence of PAOD across the EU15+ countries[8], despite concomitant increases in mortality from PAOD over the 27-year-period. Evidence suggests that many patients suffering with symptomatic PAOD are not receiving the recommended secondary preventative medications[27-29].

Failure in treatment of PAOD can ultimately manifest as LEA, however the level of amputation is important. Below , through or above knee amputations result from failure of conservative treatment. Toe or forefoot amputations are often utilised as an adjunct to conservative measures in treating limb-threatening disease, aiming to prevent the need for more proximal amputation[7]. Previous research from VASCUNET identified reductions in major amputations (defined in the VASCUNET Report as a level above the ankle) in 11 of 12 countries over a 4-year period, with corresponding increases in minor amputations (defined by VASCUNET as below ankle level)[18]. While this differs from the results presented in this analysis, it is important to note the length of the analysed period. In countries such as Finland and Belgium, we present increasing incidence rates of amputation from 1996 to 2006 (before the VASCUNET study), which then start to decrease from 2010 to 2017 (the time of the VASCUNET study).

Goodney et al[30] analysed amputation data in the USA using Medicare and Medicaid databases. They found a 45% reduction in amputation incidence over a 15-year period (1996-2011), with a concomitant increase in the number of angiographic revascularisation procedures performed. This reduction corresponds with the dramatic reduction in all LEAs observed in this analysis over a similar time period. It is important to note that amputation rates vary with socio-economic status and healthcare expenditure, with more affluent, insured, non-African-American patients reported as benefiting from earlier limb revascularisation therapies[31,32].

The greatest incidences for all LEAs were observed in Australia in both sexes. Australia also saw the greatest increase in incidence over time for both amputation levels. The IDF data do not suggest that there is a significantly higher prevalence of diabetes in Australia. Previous research has established that nearly half of all amputees in Australia are affected by diabetes[33]. Work using the GBD data identified Australia as having the lowest incidence of PAOD, with the highest PAOD-related mortality[8]. These data suggest an opportunity for improvement in management of PAOD and an at-risk diabetic population. The large land-mass and variable population density could present a challenge in managing at risk limbs, with patients having to travel significant distances for specialist care. Such travel times and the related expenses could result in patients presenting later with more significant disease requiring amputation[34]. In addition to this, recent data (adjusted for socio-economic status) from New Zealand suggests that the considerable 4-fold variation in LEA incidence seen within regions of the same country may be in part due to the variation in quality and availability of diabetic foot management services[35].

Limitations

One of the main limitations specific to the present paper relates to the definition of the level of amputation. Previous studies have described “minor” amputations are those occurring below the ankle, with “major” comprising an amputation at ankle level and above. The GBD does not categorise amputation into the “major” and “minor” categories that have been described in previous studies (including the VASCUNET Report[18]), and instead categorises amputation into “Toes”, “Lower Limb Unilateral” or “Lower Limb Bilateral”. The definition of the level of toe amputation is omitted from the GBD methodology, therefore we are unable to accurately ascertain which category forefoot amputations (i.e. those in which part or all of metatarsals are amputated) fall into. Furthermore, whether bilateral relates to a first presentation requiring two amputations, or a pre-existing unilateral amputee requiring a second amputation of the contralateral limb is unclear. The incidence rate of bilateral limb amputation is, however, largely negligible in comparison to the unilateral rate. For simplicity and comparability, unilateral and bilateral LEAs were therefore combined in this analysis to assimilate LEAs proximal to toes. It has not been possible to establish the exact International Classification of Disease (ICD) 10th revision codes that were used. There are several additional limitations that need consideration when interpreting the data from the GBD Study. We have discussed these previously[8] and include the following important limitations: Firstly, the present analysis presents trends in LEA in EU15+ countries between 1990-2017, however we cannot make causal statements about these data. The observational nature of the study means that numerous confounding factors not discussed in the manuscript will be differentially contributory to the observed trends. To reduce the effects of confounding on the results presented, we used age-standardised, sex-specific incidence rates and chose to compare countries with relatively similar health expenditure/economies. Secondly, the accuracy of death certification may differ across EU15+ countries. Deaths are under-registered globally:

Only 38% were registered in 2012[36], however Europe, Australasia and North America had the best performing systems for civil registration and vital statistics which supports the reliability of the GBD Study data from EU15+ countries presented in this study. Furthermore, the GBD study methodology includes corrections for under-registration and “garbage” code redistribution algorithms (a ‘garbage’ code is a death assigned to either a condition that cannot be the underlying cause of death or a poorly-defined diagnosis). Finally, differences and changes in data-coding practices within the EU15+ countries across the time period may compromise data robustness: of note a transition from ICD-9 to ICD-10 occurred over the study period.

Conclusions

There are variable international trends in the incidence of lower limb amputation among the EU15+ countries over the 28-year study period. These changes do not mirror the decreasing incidence trends observed over the same time period for PAOD[8].

Conflict of Interests

Nil.

References

1. Barmparas G, Inaba K, Teixeira PG, Dubose JJ, Criscuoli M, Talving P et al. Epidemiology of post-traumatic limb amputation: a National Trauma Databank analysis. *Am Surg.* 2010;76(11):1214-1222.
2. Stern JR, Wong CK, Yerovinkina M, Spindler SJ, See AS, Panjaki S et al. A Meta-analysis of Long-term Mortality and Associated Risk Factors following Lower Extremity Amputation. *Ann Vasc Surg.* 2017;42:322-327.
3. Jensen PS, Petersen J, Kirketerp-Møller K, Poulsen I, Andersen O. Progression of disease preceding lower extremity amputation in Denmark: A longitudinal registry study of diagnoses, use of medication and healthcare services 14 years prior to amputation. *BMJ Open*. 2017;7(11):e016030.
4. Goodney PP, Travis LL, Brooke BS, DeMartino RR, Goodman DC, Fisher ES et al. Relationship between regional spending on vascular care and amputation rate. *JAMA Surg.* 2014;149(1):34-42.
5. Björck M, Earnshaw JJ, Acosta S Bastos Gonçalves F, Cochennec F, Debus ES et al. European Society for Vascular Surgery (ESVS) 2020 clinical practice guideline on the management of acute limb ischaemia. *Eur J Vasc Endovasc Surg.* 2020;59(2):173-218.
6. Conte MS, Bradbury AW, Kolh P White JV, Dick F, Fitridge R et al. Global vascular guidelines on the management of chronic limb-threatening ischaemia. *Eur J Vasc Endovasc Surg.* 2019;58(1):S1-109.
7. Moxey PW, Gogalniceanu P, Hinchliffe R Loftus IM, Jones KJ, Thompson MM et al. Lower extremity amputations – a review of global variance. *Diabet Med.* 2011;28(10):1144-53.

8. Goodall RJ, Salciccioli JD, Davies AH, Marshall D, Shalhoub J. Trends in peripheral arterial disease incidence and mortality in EU15+ countries 1990-2017. *Eur J Prev Cardiol.* 2020. DOI: https://doi.org/10.1177/2047487319899626.
9. Viner RM, Hargreaves DS, Coffey C, Patton GC, Wolfe I. Deaths in young people aged 0-24 years in the UK compared with the EU15+ countries, 1970-2008: analysis of the WHO Mortality Database. *Lancet.* 2014;384(9946):880-892.
10. Salciccioli 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.
11. Kreutzburg T, Peters F, Rieß HC Hischke S, Marschall U, Kriston L et al. Comorbidity patterns among patients with peripheral arterial occlusive disease in Germany: a trend analysis of health insurance claims data. *Eur J Vasc Endovasc Surg.* 2020;59(1):59-66.
12. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet.* 2016;387(10027):1513-1530.
13. Witsø E, Lium A, Lydersen S. Lower limb amputations in Trondheim, Norway. *Acta Orthop.* 2010;81(6):737-744.
14. Ikonen TS, Sund R, Venermo M, Winell K. Fewer major amputations among individuals with diabetes in Finland in 1997-2007: a population-based study. *Diabetes Care.* 2010;33(12):2598-2603.

15. Vamos EP, Bottle A, Majeed A, Millett C. Trends in lower extremity amputations in people with and without diabetes in England, 1996-2005. *Diabetes Res Clin Pract.* 2010;87(2):275-282.
16. Icks A, Haastert B, Trautner C, Giani G, Glaeske G, Hoffmann F. Incidence of lower-limb amputations in the diabetic compared to the non-diabetic population. findings from nationwide insurance data, Germany, 2005-2007. *Exp Clin Endocrinol Diabetes.* 2009;117(9):500-504.
17. Calle-Pascual AL, Garcia-Torre N, Moraga I, Diaz JA, Duran A, Moñux G, et al. Epidemiology of nontraumatic lower-extremity amputation in area 7, Madrid, between 1989 and 1999: a population-based study. *Diabetes Care.* 2001;24(9):1686-1689.
18. Behrendt CA, Sigvant B, Szeberin Z, Beiles B, Eldrup N, Thomson IA et al. International Variations in Amputation Practice: A VASCUNET Report. *Eur J Vasc Endovasc Surg.* 2018;56(3):391-399.
19. Unwin N. The LEA Study Group. Comparing the Incidence of Lower Extremity Amputations Across the World: the Global Lower Extremity Amputation Study. *Diabetic Medicine*. 1995;12(1):14-18.
20. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1789-1858.
21. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 282 causes of death in 195 countries and territories,

1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392;1736-1788.

22. United Nations Department of Economic and Social Affairs; Population Division. World Population Prospects. The 2012 Revision. 2013. Available online: https://population.un.org/wpp/Publications/Files/WPP2012_HIGHLIGHTS.pdf. (Accessed June 2019).
23. Kim HJ, Fay MP, Feuer EJ, Midthurne DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med.* 2000;19:335-351.
24. Hartley A, Marshall DC, Salciccioli JD, Sikkel MB, Maruthappu M, Shalhoub J. Trends in mortality from ischaemic heart disease and cerebrovascular disease in Europe 1980 to 2009. *Circulation*. 2016;133:1916-1926.
25. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*. 2017;128:40–50.
26. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. *Diabetologia*. 2019;62(1):3-16.
27. Cea-Soriano L, Fowkes FGR, Johansson S, Allum AM, García Rodriguez LA. Time trends in peripheral artery disease incidence, prevalence and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK. *BMJ Open.* 2018;8:e018184.
28. Subherwal S, Patel MR, Kober L, Peterson ED, Jones WS, Gislason GH et al. Missed opportunities: despite improvement in use of cardioprotective

medications among patients with lower-extremity peripheral artery disease, underuse remains. *Circulation*. 2012;126:1345-1354.

29. Cacoub PP, Abola MT, Baumgartner I, Bhatt DL, Creager MA, Liau CS et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis.* 2009;204:e86-e92.

30. Goodney PP, Tarulli M, Faerber AE, Schanzer A, Zwolak RM. Fifteen-year trends in lower limb amputation, revascularization, and preventive measures among medicare patients. *JAMA Surg.* 2015;150(1):84-86.

31. Eslami MH, Zayaruzny M, Fitzgerald GA. The adverse effects of race, insurance status, and low income on the rate of amputation in patients presenting with lower extremity ischemia. *J Vasc Surg.* 2007;45(1):55-59.

32. Feinglass J, Abadin S, Thompson J, Pearce WH. A census-based analysis of racial disparities in lower extremity amputation rates in Northern Illinois, 1987-2004. *J Vasc Surg.* 2008;47(5):1001-1007; discussion 1007.

33. Lim TS, Finlayson A, Thorpe JM, Sieunarine K, Mwipatayi BP, Brady A et al. Outcomes of a contemporary amputation series. *ANZ J Surg.* 2006;76(5):300-305.

34. Dillon MP, Kohler F, Peeva V. Incidence of lower limb amputation in Australian hospitals from 2000 to 2010. *Prosthet Orthot Int.* 2014;38(2):122-132.

35. Lazzarini PA, Fiteridge R. Regional variations in amputation rates: are regional diabetic foot services the reason? *ANZ J Surg*. 2019;89(7-8):796-797.

36. Mikklesen L, Philips DE, Abouzahr C, Setel PW, de Savigny D, Lozano R et al. A global assessment of civil registration and vital statistics systems: monitoring

data quality and progress. *Lancet*. 2015;386:1395-1406. DOI: 10.1016/S0140-6736(15)60171-4.

Figure 1: Age-standardised incidence rates (ASIRs) per 100,000 for lower extremity amputation (LEA) in the European Union (EU) 15+ countries in 1990 (females, A, males, C) and 2017 (females, B, males D).

Figure 2: Trends in age-standardised incidence rates (ASIRs) per 100,000 for lower extremity amputation (LEA) proximal to toes in European Union (EU) 15+ countries between 1990-2017. Open squares indicate males; and filled circles indicate females.

Figure 3: Trends in age-standardised incidence rates per 100,000 for toe amputation in European Union (EU) 15+ countries between 1990-2017. Open squares indicate males; and filled circles indicate females.

Table 1: Joinpoint analysis for age-standardised incidence rates (ASIRs) for lower extremity amputation (LEA) proximal to toes in European Union (EU) 15+ countries for years 1990-2017 in females.

Table 2: Joinpoint analysis for age-standardised incidence rates (ASIRs) for lower extremity amputation (LEA) proximal to toes in European Union (EU) 15+ countries for years 1990-2017 in males.

Table 3: Joinpoint analysis for age-standardised incidence rates (ASIRs) for toe amputation in European Union (EU) 15+ countries for years 1990-2017 in females.

Table 4: Joinpoint analysis for age-standardised incidence rates (ASIRs) for toe amputation in European Union (EU) 15+ countries for years 1990-2017 in males.

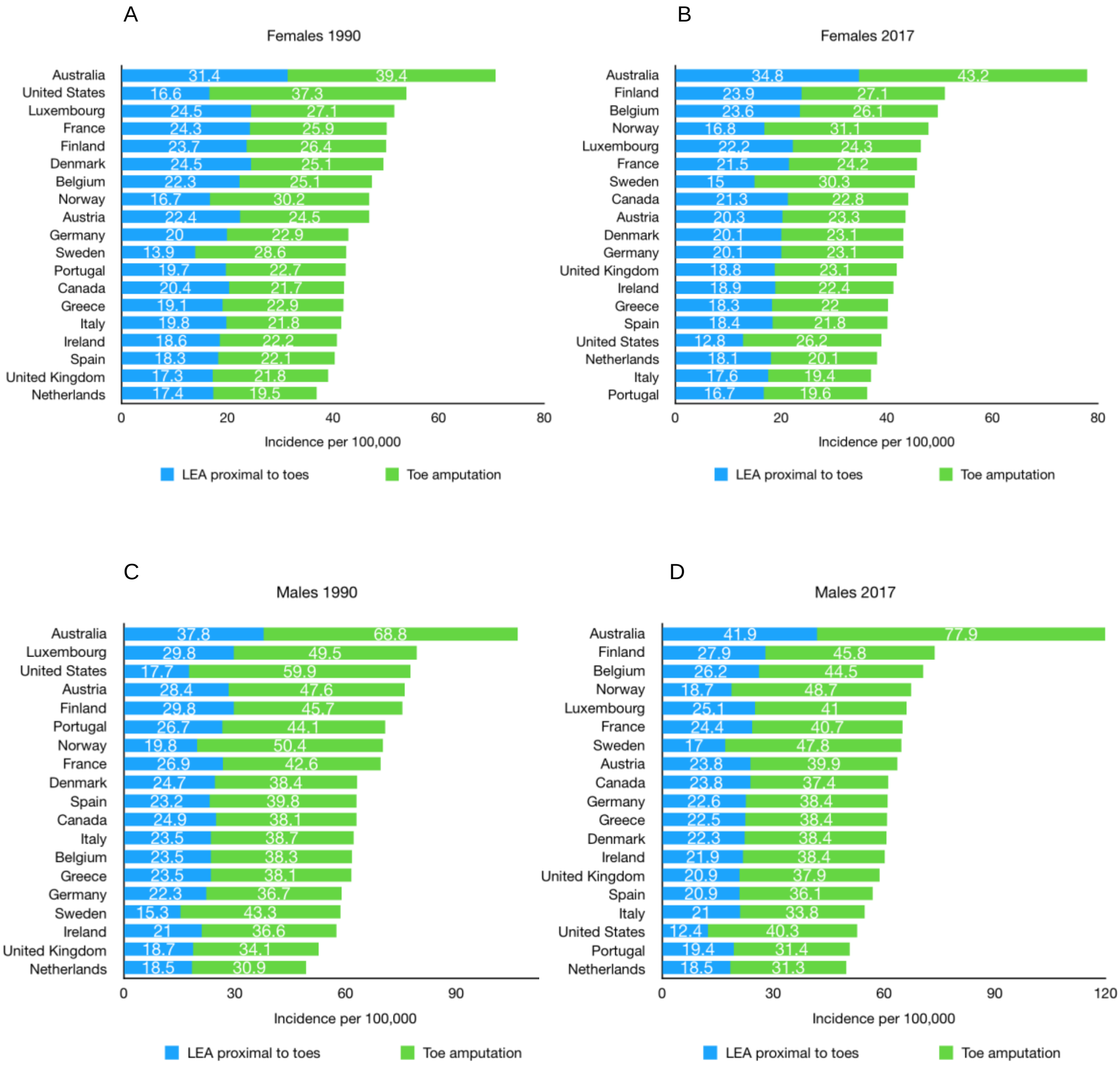

Figure 1: Age-standardised lower extremity amputation (LEA) incidence rates per 100,000 in the EU15+ countries in 1990 (females A, males C) and 2017 (females B, males D).

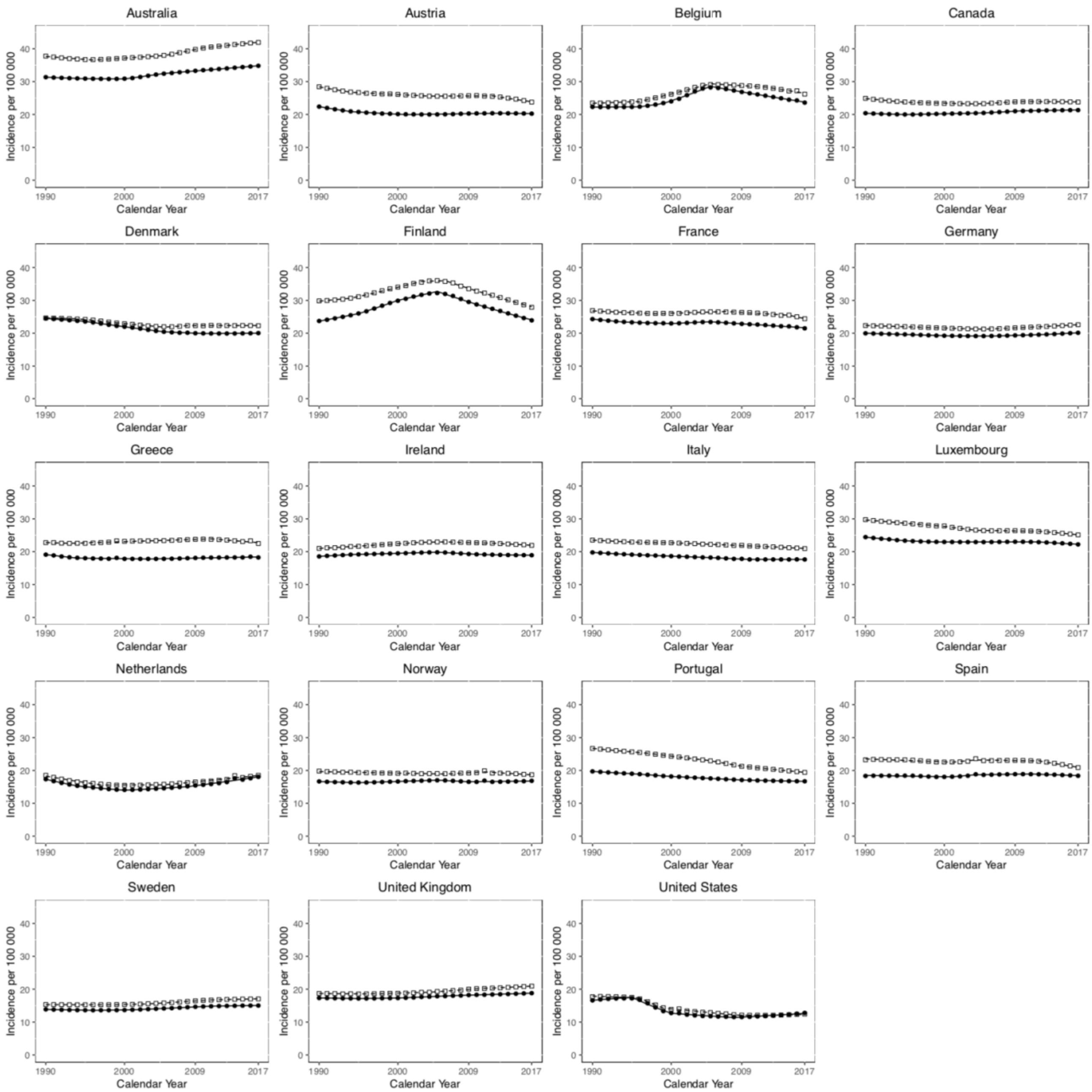

Figure 2: Trends in age-standardised incidence rates per 100,000 for lower extremity amputation proximal to toes in EU15+ countries between 1990-2017. Open squares indicate males; and filled circles indicate females.

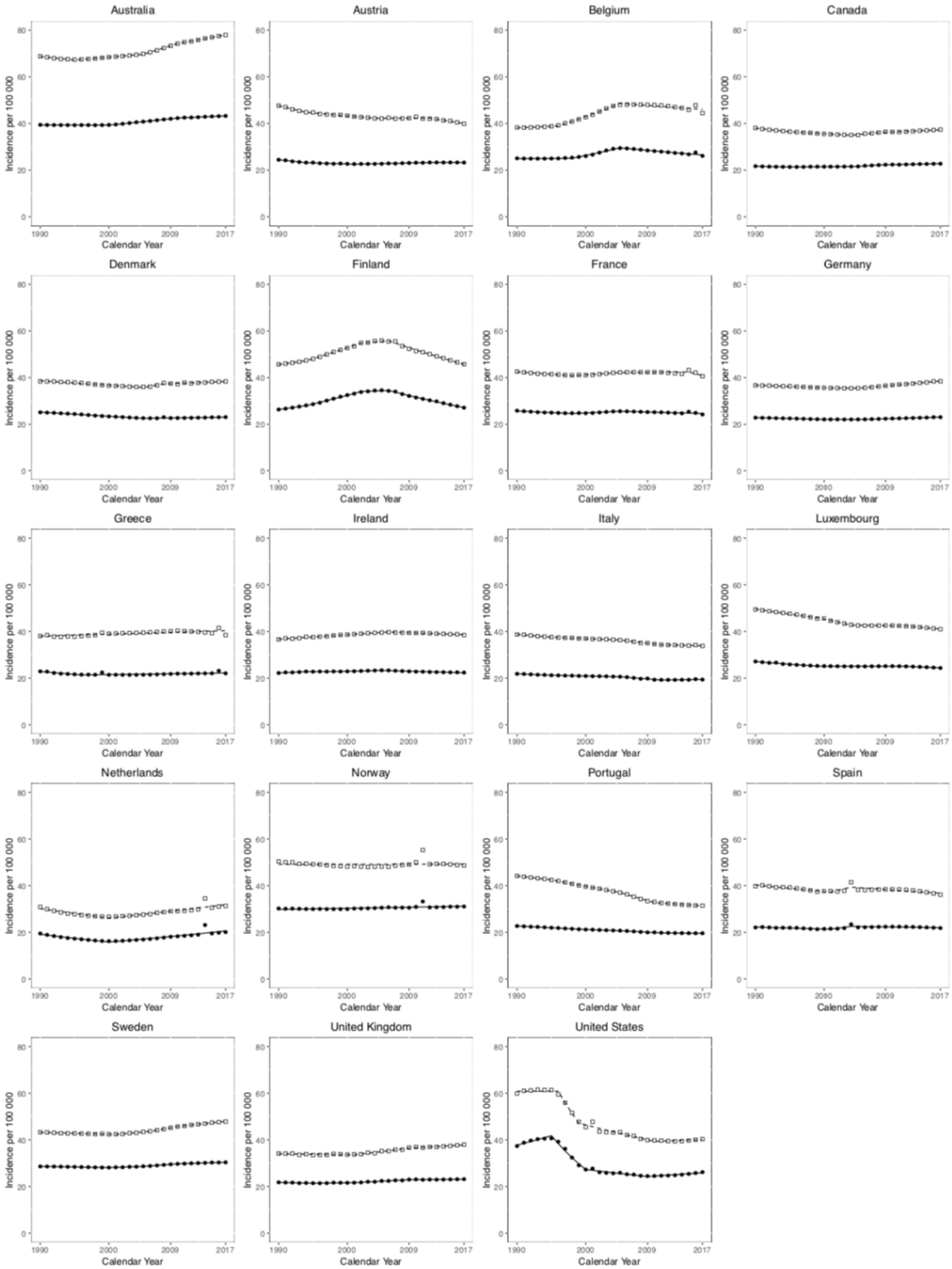

Figure 3: Trends in age-standardised incidence rates per 100,000 for toe amputation in EU15+ countries between 1990-2017. Open squares indicate males; and filled circles indicate females.

Table 1: Joinpoint analysis for age-standardised incidence rates for lower extremity amputation (LEA) proximal to toes in European Union (EU) 15+ countries for years 1990-2017 in females.

Country	Trend 1			Trend 2			Trend 3			Trend 4		
	Years	EAPC	*p* value	Years	EAPC	*p* value	Years	EAPC	*p* value	Years	EAPC	*p* value
Australia	1990-1995	-0.3 (-0.3 - -0.2)	<0.001	1995-2000	-0.1 (-0.1 – 0)	0.10	2000-2005	+1.1 (+1.0 - +1.1)	<0.001	2005-2017	+0.6 (+0.6 - +0.6)	<0.001
Austria	1990-1994	-1.7 (-1.7 - -1.9)	<0.001	1994-2001	-0.6 (-0.8 - -0.5)	<0.001	2001-2013	+0.2 (+0.1 - +0.2)	<0.001	2013-2017	-0.2 (-0.4 - +0.1)	0.10
Belgium	1990-1996	+0.1 (-0.1 - +0.2)	0.40	1996-1999	+1.5 (+0.6 - +2.4)	<0.001	1999-2005	+3.4 (+3.2 - +3.6)	<0.001	2005-2017	-1.5 (-1.6 - -1.5)	<0.001
Canada	1990-1995	-0.4 (-0.4 - -0.4)	<0.001	1995-2005	+0.3 (+0.2 - +0.3)	<0.001	2005-2010	+0.6 (+0.6 - +0.7)	<0.001	2010-2017	+0.2 (+0.1 - +0.2)	<0.001
Denmark	1990-1995	-0.8 (-0.9 - -0.6)	<0.001	1995-2005	-1.4 (-1.5 - -1.4)	<0.001	2005-2010	-0.5 (-0.7 - -0.4)	<0.001	2010-2017	0.1 (0 - +0.1)	0.10
Finland	1990-1995	+1.9 (+1.7 - +2.0)	<0.001	1995-2000	+2.9 (+2.7 - +3.2)	<0.001	2000-2005	+1.7 (+1.5 - +2.0)	<0.001	2005-2017	-2.5 (-2.6 - -2.5)	<0.001
France	1990-1994	-0.9 (-1.2 - -0.7)	<0.001	1994-2000	-0.3 (-0.5 - -0.1)	<0.001	2000-2005	+0.5 (+0.2 - +0.7)	<0.001	2005-2017	-0.7 (-0.7 - -0.6)	<0.001
Germany	1990-2001	-0.4 (-0.4 - -0.4)	<0.001	2001-2006	0 (-0.1 - +0.0)	0.20	2006-2013	+0.4 (+0.3 - +0.4)	<0.001	2013-2017	+0.6 (+0.6 - +0.7)	<0.001
Greece	1990-1994	-1.4 (-1.8 - -10)	<0.001	1994-2003	-0.2 (-0.3 - +0)	<0.001	2003-2017	+0.2 (+0.2 - +0.3)	<0.001			
Ireland	1990-1994	+0.7 (+0.6 - +0.8)	<0.001	1994-2005	+0.3 (+0.3 - +0.4)	<0.001	2005-2011	-0.6 (-0.7 - -0.6)	<0.001	2011-2017	-0.2 (-0.2 - -0.1)	<0.001
Italy	1990-1995	-0.7 (-0.8 - -0.6)	<0.001	1995-2005	-0.5 (-0.5 - -0.4)	<0.001	2005-2010	-0.6 (-0.7 - -0.5)	<0.001	2010-2017	0 (-0.1 - +0)	0.70
Luxembourg	1990-1995	-0.9 (-1 - -0.8)	<0.001	1995-1999	-0.4 (-0.6 - -0.2)	<0.001	1999-2012	0 (0 – 0)	0.40	2012-2017	-0.7 (-0.7 - -0.6)	<0.001
Netherlands	1990-1994	-3.1 (-4 - -2.2)	<0.001	1994-2000	-1.5 (-2.1 - -0.8)	<0.001	2000-2008	+0.9 (+0.5 - +1.3)	<0.001	2008-2017	+2.0 (+1.8 - +2.3)	<0.001
Norway	1990-1995	-0.4 (-0.8 - -0.1)	<0.001	1995-2005	+0.5 (+0.3 - +0.6)	<0.001	2005-2009	-0.7 (-1.5 - +0.1)	0.10	2009-2017	+0.1 (+0 - +0.3)	0.10
Portugal	1990-1996	-0.7 (-0.8 - -0.7)	<0.001	1996-1999	-1.0 (-1.3 - -0.7)	<0.001	1999-2009	-0.7 (-0.7 - -0.7)	<0.001	2009-2017	-0.3 (-0.3 - -0.3)	<0.001
Spain	1990-2001	-0.2 (-0.3 - -0.1)	<0.001	2001-2004	+1.1 (-0.1 - +2.4)	0.10	2004-2011	+0.2 (0 - +0.4)	0.10	2011-2017	-0.4 (-0.6 - -0.2)	<0.001
Sweden	1990-1996	-0.3 (-0.4 - -0.3)	<0.001	1996-2001	+0.2 (+0.1 - +0.3)	<0.001	2001-2011	+0.8 (+0.8 - +0.8)	<0.001	2001-2017	+0.2 (+0.2 - +0.3)	<0.001
United Kingdom	1990-1995	-0.2 (-0.3 - -0.1)	<0.001	1995-2005	+0.2 (0 - +0.3)	<0.001	2000-2007	+0.6 (+0.5 - +0.7)	<0.001	2007-2017	+0.4 (+0.4 - +0.4)	<0.001
United States	1990-1995	+1.1 (+0.5 - +1.6)	<0.001	1995-2000	-6.3 (-7 - -5.6)	<0.001	2000-2008	-1.4 (-1.7 - -1.1)	<0.001	2008-2017	+1.2 (+1 - +1.4)	<0.001

Data presented as Estimated Annual Percentage Change (EAPC %), with 95% confidence intervals in brackets. *P* values deemed significant if <0.05.

Table 2: Joinpoint analysis for age-standardised incidence rates for lower extremity amputation (LEA) proximal to toes in European Union (EU) 15+ countries for years 1990-2017 in males.

Country	Trend 1			Trend 2			Trend 3			Trend 4		
	Years	EAPC	*p* value	Years	EAPC	*p* value	Years	EAPC	*p* value	Years	EAPC	*p* value
Australia	1990-1996	-0.5 (-0.5 - -0.4)	<0.001	1996-2005	+0.4 (+0.4 - +0.4)	<0.001	2005-2010	+1.2 (+1.1 - +1.3)	<0.001	2010-2017	+0.6 (+0.6 - +0.6)	<0.001
Austria	1990-1994	+1.5 (-1.7 - -1.3)	<0.001	1994-2004	-0.4 (-0.5 - -0.4)	<0.001	2004-2012	0 (-0.1 - +0.1)	0.40	2012-2017	-1.4 (-1.6 - -1.3)	<0.001
Belgium	1990-1996	+0.4 (+0.2 - +0.7)	<0.001	1996-2005	+2.3 (+2.1 - +2.4)	<0.001	2005-2012	-0.5 (-0.7 - -0.2)	<0.001	2012-2017	-1.4 (-1.7 - -1.1)	<0.001
Canada	1990-1995	-1.0 (-1.0 - -0.9)	<0.001	1995-2004	-0.2 (-0.3 - -0.2)	<0.001	2004-2010	+0.5 (+0.4 - +0.6)	<0.001	2010-2017	-0.1 (-0.1 – 0)	<0.001
Denmark	1990-1994	-0.3 (-0.5 – -0.1)	<0.001	1994-2005	-1.0 (-1.0 - -0.9)	<0.001	2005-2008	+0.7 (+0.1 - +1.2)	<0.001	2008-2017	0 (0 - +0.1)	0.40
Finland	1990-1994	+0.7 (+0.4 - +1.0)	<0.001	1994-2003	+1.7 (+1.6 - +1.8)	<0.001	2003-2006	0.2 (-0.8 - +1.2)	0.60	2006-2017	-2.2 (-2.3 – -2.2)	<0.001
France	1990-1998	-0.4 (-0.5 - -0.3)	<0.001	1998-2007	+0.3 (+0.2 - +0.4)	<0.001	2007-2015	-0.5 (-0.7 - -0.4)	<0.001	2015-2017	-2.0 (-2.9 - -1.2)	<0.001
Germany	1990-2005	-0.3 (-0.4 - -0.3)	<0.001	2005-2013	+0.5 (+0.5 - +0.5)	<0.001	2013-2017	+0.6 (+0.5 - +0.7)	<0.001			
Greece	1990-1993	-0.4 (-1.3 - +0.5)	0.40	1993-2011	+0.3 (+0.3 - +0.4)	<0.001	2011-2017	-0.8 (-1.1 - -0.5)	<0.001			
Ireland	1990-2003	+0.7 (+0.6 - +0.7)	<0.001	2003-2006	+0.2 (-0.3 - +0.7)	0.50	2006-2012	-0.3 (-0.4 - -0.2)	<0.001	2012-2017	-0.6 (-0.7 - -0.5)	<0.001
Italy	1990-1995	-0.5 (-0.6 - -0.4)	<0.001	1995-2000	-0.2 (-0.3 - -0.1)	<0.001	2000-2013	-0.4 (-0.5 - -0.4)	<0.001	2013-2017	-0.6 (-0.7 - -0.5)	<0.001
Luxembourg	1990-2000	-0.7 (-0.7 - -0.7)	<0.001	2000-2004	-1.1 (-1.3 - -0.9)	<0.001	2004-2012	-0.1 (-0.2 - -0.1)	<0.001	2012-2017	-0.8 (-0.9 - -0.8)	<0.001
Netherlands	1990-1997	-2.3 (-2.7 - -1.8)	<0.001	1997-2005	0 (-0.4 - +0.5)	0.90	2005-2017	+1.4 (+1.2 - +1.6)	<0.001			
Norway	1990-2006	-0.2 (-0.3 - -0.2)	<0.001	2006-2011	+0.7 (+0.3 - +1.0)	<0.001	2011-2017	-0.8 (-0.9 - -0.6)	<0.001			
Portugal	1990-1997	-0.8 (-0.8 - -0.8)	<0.001	1997-2005	-1.2 (-1.2 - -1.1)	<0.001	2005-2009	-1.9 (-2.0 - -1.8)	<0.001	2009-2017	-1.1 (-1.2 - -1.1)	<0.001
Spain	1990-2001	-0.4 (-0.5 - -0.3)	<0.001	2001-2004	+1.0 (-0.4 - +2.4)	0.20	2004-2012	-0.1 (-0.3 – 0)	0.10	2012-2017	-1.8 (-2.1 - -1.5)	<0.001
Sweden	1990-1998	-0.1 (-0.1 – 0)	<0.001	1998-2003	+0.4 (+0.2 - +0.5)	<0.001	2003-2011	+0.9 (+0.9 - +1.0)	<0.001	2011-2017	+0.3 (+0.3 - +0.4)	<0.001
United Kingdom	1990-1996	-0.1 (-0.1 – 0)	<0.001	1996-2004	+0.3 (+0.3 - +0.4)	<0.001	2004-2010	+0.9 (+0.8 - +1.0)	<0.001	2010-2017	+0.5 (+0.5 - +0.6)	<0.001
United States	1990-1996	-0.6 (-0.9 - -0.2)	<0.001	1996-1999	-6.3 (-8.3 - -4.2)	<0.001	1999-2009	-1.7 (-1.9 - -1.5)	<0.001	2009-2017	+0.3 (+0.1 - +0.6)	<0.001

Data presented as Estimated Annual Percentage Change (EAPC %), with 95% confidence intervals in brackets. *P* values deemed significant if <0.05.

Table 3: Joinpoint analysis for age-standardised incidence rates for toe amputation in European Union (EU) 15+ countries for years 1990-2017 in females.

Country	Trend 1			Trend 2			Trend 3			Trend 4		
	Years	EAPC	*p* value	Years	EAPC	*p* value	Years	EAPC	*p* value	Years	EAPC	*p* value
Australia	1990-2000	0 (0 - 0)	0.10	2000-2010	+0.7 (+0.7 - +0.8)	<0.001	2010-2017	+0.3 (+0.3 - +0.3)	<0.001			
Austria	1990-1994	+1.3 (-1.6 - -1)	<0.001	1994-2001	-0.4 (-0.6 - -0.2)	<0.001	2001 - 2013	+0.3 (+0.2 - +0.3)	<0.001	2013-2017	0 (-0.3 - +0.3)	0.70
Belgium	1990-1998	+0.1 (-0.2 - +0.4)	0.60	1998-2005	+2.4 (+1.9 - +2.8)	<0.001	2005-2017	-0.9 (-1.1 - -0.8)	<0.001			
Canada	1990-1995	-0.3 (-0.4 - -0.2)	<0.001	1995-2005	+0.1 (+0.1 - +0.2)	<0.001	2005-2008	+1 (+0.5 - +1.4)	<0.001	2008-2017	+0.3 (+0.2 - +0.3)	<0.001
Denmark	1990-2005	-0.7 (-0.8 – -0.7)	<0.001	2005-2017	+0.2 (+0.1 - +0.2)	<0.001						
Finland	1990-1994	+1.6 (+1.2 - +2)	<0.001	1994-2002	+2.5 (+2.3 - +2.6)	<0.001	2002-2006	+0.3 (-0.3 - +0.9)	0.30	2006-2017	-2.1 (-2.2 – -2.1)	<0.001
France	1990-1998	-0.6 (-0.8 - -0.3)	<0.001	1998-2005	+0.6 (+0.2 - +0.9)	<0.001	2005-2017	-0.3 (-0.4 - -0.2)	<0.001			
Germany	1990-2000	-0.3 (-0.4 - -0.3)	<0.001	2000-2005	-0.1 (-0.2 – 0)	0.40	2005-2017	+0.4 (+0.4 - +0.4)	<0.001			
Greece	1990-1996	-1.1 (-1.9 - -0.4)	<0.001	1996-2017	+0.2 (+0.1 - +0.3)	<0.001						
Ireland	1990-1994	+0.6 (+0.4 - +0.9)	<0.001	1994-1999	0 (-0.2 - +0.3)	0.80	1999-2005	+0.3 (+0.1 - +0.5)	<0.001	2005-2017	-0.4 (-0.4 - -0.3)	<0.001
Italy	1990-1995	-0.6 (-0.9 - -0.3)	<0.001	1995-2005	-0.3 (-0.4 - -0.2)	<0.001	2005-2011	-1.2 (-1.5 - -0.9)	<0.001	2011-2017	+0.2 (0 - +0.4)	<0.001
Luxembourg	1990-1999	-0.8 (-0.9 - -0.8)	<0.001	1999-2012	0 (-0.1 – 0)	0.70	2012-2017	-0.6 (-0.8 - -0.4)	<0.001			
Netherlands	1990-2000	-1.9 (-2.7 - -1.1)	<0.001	2000-2017	-1.6 (+1.2 - +1.9)	<0.001						
Norway	1990-2017	+0.2 (+0.1 - +0.2)	<0.001									
Portugal	1990-2000	-0.7 (-0.7 - -0.6)	<0.001	2000-2005	-0.5 (-0.7 - -0.3)	<0.001	2005-2011	-0.8 (-0.9 - -0.6)	<0.001	2011-2017	-0.1 (-0.2 – 0)	<0.001
Spain	1990-2001	-0.4 (-0.5 - -0.2)	<0.001	2001-2004	+1.9 (-0.2 - +3.9)	0.10	2004-2017	-0.2 (-0.3 - -0.1)	<0.001			
Sweden	1990-2000	-0.2 (-0.2 - -0.2)	<0.001	2000-2005	+0.3 (+0.2 - +0.5)	<0.001	2005-2010	+0.8 (+0.7 - +0.9)	<0.001	2010-2017	+0.3 (+0.3 - +0.4)	<0.001
United Kingdom	1990-1995	-0.3 (-0.6 - -0.1)	<0.001	1995-2001	+0.2 (-0.1 - +0.4)	0.10	2001-2009	+0.7 (+0.6 - +0.9)	<0.001	2009-2017	+0.1 (0 - +0.2)	0.10
United States	1990-1995	+2.1 (+1.2 - +2.9)	<0.001	1995-2000	-8.2 (-9.2 - -7.1)	<0.001	2000-2009	-1.3 (-1.7 - -0.9)	<0.001	2009-2017	+0.8 (+0.4 - +1.2)	<0.001

Data presented as Estimated Annual Percentage Change (EAPC %), with 95% confidence intervals in brackets. *P* values deemed significant if <0.05.

Table 4: Joinpoint analysis for age-standardised incidence rates for toe amputation in European Union (EU) 15+ countries for years 1990-2017 in males.

Country	Trend 1			Trend 2			Trend 3			Trend 4		
	Years	EAPC	*p* value	Years	EAPC	*p* value	Years	EAPC	*p* value	Years	EAPC	*p* value
Australia	1990-1995	-0.4 (-0.5 - -0.4)	<0.001	1995-2005	+0.4 (+0.3 - +0.4)	<0.001	2005-2010	+1.3 (+1.2 - +1.4)	<0.001	2010-2017	+0.7 (+0.7 - +0.8)	<0.001
Austria	1990-1994	-1.5 (-2 - -1.1)	<0.001	1994-2004	-0.6 (-0.7 - -0.5)	<0.001	2004-2012	0 (-0.2 - +0.2)	0.80	2012-2017	-1.1 (-1.4 - -0.8)	<0.001
Belgium	1990-1996	+0.3 (-0.3 - +0.9)	0.30	1996-2005	+2.5 (+2.1 - +2.9)	<0.001	2005-2017	-0.4 (-0.7 - -0.2)	<0.001			
Canada	1990-1995	-0.8 (-1 - -0.7)	<0.001	1995-2004	-0.5 (-0.5 - -0.4)	<0.001	2004-2008	+0.8 (+0.4 - +1.2)	<0.001	2008-2017	+0.4 (+0.3- +0.4)	<0.001
Denmark	1990-2005	-0.5 (-0.6 - -0.5)	<0.001	2005-2008	+1.4 (+0.1 - +2.6)	<0.001	2008-2017	+0.3 (+0.2 - +0.4)	<0.001			
Finland	1990-1994	+0.9 (+0.4 - +1.3)	<0.001	1994-2002	+1.9 (+1.7 - +2.1)	<0.001	2002-2006	+0.4 (-0.3 - +1.2)	0.20	2006-2017	-1.8 (-1.9 - -1.7)	<0.001
France	1990-1998	-0.5 (-0.6 - -0.4)	<0.001	1998-2005	+0.5 (+0.3 - +0.6)	<0.001	2005-2015	0 (-0.1 - +0.1)	0.40	2015-2017	-1.8 (-2.8 - -0.7)	<0.001
Germany	1990-2001	-0.3 (-0.3 - -0.3)	<0.001	2001-2005	-0.1 (-0.3 - +0.2)	0.70	2005-2017	+0.7 (+0.7 - +0.7)	<0.001			
Greece	1990-2017	+0.2 (+0.2 - +0.3)	<0.001									
Ireland	1990-2006	+0.5 (+0.5 - +0.5)	<0.001	2006-217	-0.3 (-0.3 - -0.2)	<0.001						
Italy	1990-1995	-0.6 (-0.8 - -0.4)	<0.001	1995-2005	-0.3 (-0.4 - -0.2)	<0.001	2005-2011	-1 (-1.1 - -0.8)	<0.001	2011-2017	-0.2 (-0.3 - -0.1)	<0.001
Luxembourg	1990-2000	-0.9 (-0.9 - -0.8)	<0.001	2000-2004	-1.5 (-1.9 - -1.2)	<0.001	2004-2012	-0.1 (0.2 – 0)	0.10	2012-2017	-0.7 (-0.8 - -0.5)	<0.001
Netherlands	1990-2000	-1.4 (-2 - -0.8)	<0.001	2000-2017	+1.2 (+0.9 - +1.4)	<0.001						
Norway	1990-2017	0 (-0.1 - +0.1)	0.90									
Portugal	1990-1995	-0.8 (-0.9 - -0.7)	<0.001	1995-2005	-1.4 (-1.4 - -1.3)	<0.001	2005-2010	-2.5 (-2.6 - -2.3)	<0.001	2010-2017	-0.6 (-0.7- -0.6)	<0.001
Spain	1990-2001	-0.7 (-0.9 - -0.5)	<0.001	2001-2004	+1.9 (-1.3 - +5.1)	0.20	2004 -2017	-0.5 (-0.7 - -0.4)	<0.001			
Sweden	1990-2001	-0.2 (-0.2 - -0.1)	<0.001	2001-2006	+0.6 (+0.4 - +0.8)	<0.001	2006-2010	+1.2 (+0.9 - +1.5)	<0.001	2010-2017	+0.7 (+0.6 - +0.8)	<0.001
United Kingdom	1990-2001	-0.1 (-0.2 - 0)	0.10	2001-2009	+1 (+0.8 - +1.3)	<0.001	2009-2017	+0.5 (+0.3 - +0.7)	<0.001			
United States	1990-1996	0 (-0.8 - +0.8)	1.0	1996-1999	-8.1 (-12.4 - -3.6)	<0.001	1999-2010	-1.6 (-2 - -1.3)	<0.001	2010-2017	+0.2 (-0.4 - +0.9)	0.40

Data presented as Estimated Annual Percentage Change (EAPC %), with 95% confidence intervals in brackets. *P* values deemed significant if <0.05.