

# BMJ Open Epidemiology of major lower limb amputation using routinely collected electronic health data in the UK: a systematic review protocol

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## ABSTRACT

**Introduction** It is estimated that peripheral arterial disease occurs in one in five people aged over 60 years in the UK. Major lower limb amputation is a debilitating and life-changing potential outcome of peripheral arterial disease. A number of risk factors are involved in the development of the disease including smoking and diabetes. There is debate over the prevalence of major lower limb amputation in the UK with regional variations unexplained. The choice of data source can affect the epidemiological calculations and sources can also differ in the ability to explain variation. This study will aim to estimate the prevalence/incidence/number of major lower limb amputation in the UK. It will also identify sources of routinely collected electronic health data which report the epidemiology of major lower limb amputation in the UK.

**Methods and analysis** A systematic search of peer-reviewed journals will be conducted in Medline, Excerpta Medica database, Cumulative Index of Nursing and Allied Health Literature, Allied and Complementary Medicine Database, The Cochrane Library and Scopus. A grey literature search for government and parliament publications, conference abstracts, theses and unpublished articles will be performed. Articles will be screened against the inclusion/exclusion criteria and data extracted using a pretested extraction form by two independent reviewers. Prevalence, incidence or number of cases (depending on data reported) will be extracted. Disagreements will be resolved by discussion. Data synthesis will be performed either as a narrative summary or by meta-analysis. Heterogeneity will be assessed using the  $I^2$  statistic. If heterogeneity is low-moderate, pooled estimates will be calculated using random-effects models. If possible, meta-regression for time trends in the incidence of major lower limb amputation will be performed along with subgroup analysis, primarily in regional variation.

**Ethics and dissemination** Ethics approval is not required for this study as study data are anonymised and available in the public domain. Dissemination will be by publication in a peer reviewed journal and by appropriate conference presentation.

**PROSPERO registration number**  
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## Strengths and limitations of this study

- This review will report estimates of the prevalence/incidence/number of major lower limb amputation in the UK and also provide information on the use of routinely collected electronic health data in the epidemiology of major lower limb amputation.
- The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines will be adhered to for both the systematic review and the PRISMA-Protocol.
- A comprehensive search strategy will be employed in both peer-reviewed and grey literature searches.
- This study only looks at data sources in the UK and as such will only be applicable to use for this population.
- It is expected that only a small number of studies will be included in this systematic review with large amounts of between study heterogeneity which may be in part down to population and methodological differences.

## INTRODUCTION

Peripheral arterial disease (PAD) is the leading cause of all lower limb amputation where the causes are not due to cancer or trauma.<sup>1</sup> PAD occurs when an excess of plaque (atheroma) builds-up in the arteries and restricts blood flow to the limbs. PAD can occur with or without symptoms. The most common symptom of PAD is pain on walking called intermittent claudication.<sup>2</sup> If the disease progresses patients may develop pain at rest that may be complicated by ulceration and gangrene, this is critical leg ischaemia and without urgent treatment to improve the blood supply to the leg, amputation will result. The number of people diagnosed with PAD worldwide is estimated to be over 200 million.<sup>3</sup> In the UK PAD occurs in 20% of people aged over 60 years.<sup>4</sup> The prevalence of amputation in PAD patients is thought to be 3%–4%.<sup>5</sup> In the UK the prevalence of symptomatic PAD is decreasing with figures of 2.4% in 2014 compared with 3.4% in 2000.<sup>6</sup>



This is surprising given the significant increase in diabetes, one of the major risk factors.<sup>7</sup> Other key risk factors for PAD include: smoking, age, hypertension and dyslipidaemia.<sup>8</sup> There is evidence to suggest that, in England, fewer major lower limb amputation operations are performed than minor.<sup>9 10</sup> This may be partly due to the advancement in surgical care including the range and accessibility of revascularisation procedures.<sup>11</sup> As PAD can have debilitating and life-changing outcomes, it is imperative that the scale of outcomes such as major lower limb amputation are known and any variation in prevalence explained so that suitable and targeted preventative measures can be put in place.

Routinely collected electronic health data are a widely used resource for epidemiological studies. Data are collected from primary and secondary care providers, deidentified and stored in a number of different databases. There are many strengths and limitations to using routinely collected health data in epidemiology which need to be taken into account when analysing the data.<sup>12</sup> The main positive aspect of using large datasets in research is that it enables more accurate results. One particularly notable, but improving issue when using routinely collected health data for research is that of coding errors.<sup>13–15</sup> There is some evidence to suggest that including poor-quality data in incidence studies can affect the apparent trends in incidence.<sup>15</sup> Strengths and limitations can vary between databases as they are established for different reasons. For example, the primary objective of the Hospital Episode Statistics (HES)<sup>16</sup> database is to collect secondary care data to allow hospitals to be paid for the care they deliver making it a very complete dataset but lacking in some detail. Whereas the primary objective of the Clinical Practice Research datalink (CPRD)<sup>17 18</sup> database is to extract routinely collected clinical primary care data from GP practices for research purposes meaning that this dataset contains far more detail than HES, but CPRD does not hold the data from all UK practices and there may be bias in the reporting. Given this, it can be expected that the choice of database used in a study has potential to affect the resulting study outcome.

Currently, there is confusion and debate about the incidence of major lower limb amputation due to conflicting reports.<sup>9 10 19</sup> Moxey *et al* give an incidence proportion of 5 per 100 000 in the population with no change in the 5-year period between 2003 and 2008,<sup>10</sup> whereas Ahmad *et al* give an incidence proportion of 25 per 100 000 population with proportions dropping by up to 20% over the period between 2003 and 2013.<sup>19</sup> It is not clear which databases are more frequently being used in the epidemiological reporting of major lower limb amputations and therefore what impact this might be having on the reporting. Other reasons for variation have been explored. For example, a systematic review by Davies *et al* found substantial differences in methodology between studies.<sup>20</sup> Differences included the denominator population, the definitions of major lower limb amputations, standardisation techniques and subgroups analysed. The heterogeneity of these studies made it too difficult to compare the trends over time. As well as estimating the epidemiology of major lower limb

amputation in the UK, this study aims to expand on this by looking more closely at the data sources and identifying which sources are most frequently used and which are under-used and discussing their differences, strengths and limitations.

### Objectives

1. To ascertain the incidence/prevalence/number of major-lower limb amputation in the UK and any changes over time.
2. To determine any regional and subgroup differences in the incidence/prevalence/number of major lower limb amputation.
3. To establish which routinely collected electronic health databases are being used and which are available for use in reporting the epidemiology of major lower limb amputation.
4. To discuss the strengths and limitations of each database used.
5. To explain reasons for variation in the reporting of the epidemiology of major lower limb amputation.

### METHODS

The systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting the results of systematic reviews.<sup>21</sup>

The PRISMA-Protocol checklist for systematic review protocols was used when writing this protocol. Tabulated versions are included in online supplementary files 1 and 2.<sup>22</sup>

### Peer-reviewed literature

The search strategy was developed by a specialist vascular clinical librarian.

The electronic databases Medline, Excerpta Medica database, Cumulative Index of Nursing and Allied Health Literature, The Cochrane Library, Allied and complementary medicine Database and Scopus will be searched using combinations of key words and topics. Full-search strategies are included in online supplementary files 3 and 4. The search strategy was developed in Medline and will then be adapted for use in other databases. The search will limit the date of publication to 2009 onwards, to studies published in English and to studies based on UK data, using filters where possible.<sup>23 24</sup> Search results will be exported to and stored in EndNote. The reference lists of any studies selected for inclusion will be checked for additional studies to include. Searches will be rerun at the end of the review process to check for any publications in the intervening period.

### Grey literature

The grey literature websites [www.opengrey.eu](http://www.opengrey.eu), [openDoar.org](http://openDoar.org), [openAire.eu](http://openAire.eu) and [base-search.net](http://base-search.net) will be searched using the key word 'amputation'/'amput\*'. Electronic databases aforementioned will be used to search conference papers as well as peer reviewed literature. A thesis search will be performed in eTHOS, on [OpenDisserations.org](http://OpenDisserations.org) and in the University of

Leicester thesis database. Government publications will be searched on [www.gov.co.uk](http://www.gov.co.uk) and Parliament publications will be searched using [www.parliament.uk](http://www.parliament.uk) and [www.vvappg.com](http://www.vvappg.com) with searches to include the key words 'amputation'. Publication searches will also be performed on the health record database websites [www.digital.nhs.uk](http://www.digital.nhs.uk), [www.QResearch.org](http://www.QResearch.org), and the bibliography provided at [www.CPRD.com](http://www.CPRD.com). Experts in the field will also be consulted to further identify articles for inclusion potential.

### Inclusion/exclusion criteria

Articles considered for inclusion will provide population-based statistics made available since 2009 that use routinely collected electronic health data as their data source, that are written in English and that provide a measure (eg, prevalence/incidence/number) of major lower limb amputation in adults in the general public or in persons diagnosed with diabetes in England or UK. The decision to only consider for inclusion studies published from 2009 onwards was made to ensure that epidemiological calculations are reflective of current trends in the major risk factors. Studies that only include adults (or report a sub group for adults) are more likely to exclude major lower limb amputations that were performed for reasons other than PAD or diabetes, such as cancer and trauma. Studies of adults that include those that have lost limbs due to cancer and trauma may be included in the study but this information will be explicitly stated where available.

A specific definition of major lower limb amputation will not be used to exclude articles from the review as it is anticipated that the precise definition will vary among studies reporting the epidemiology of major lower limb amputation. There is no apparent, explicit definition of 'major' lower limb amputation. For these reasons, a decision was made to include all studies that report for a major lower limb amputation and to extract, tabulate and discuss the differences in definition. Comparisons will also be made between the extracted definitions and the case ascertainment coding of major lower limb amputation. Further comparisons of the definitions will be made to the Global Vascular Guidelines (GVG) where a minor lower limb amputation is defined but a major lower limb amputation is only inferred.<sup>25</sup> Some studies may report epidemiology statistics for both minor and major lower limb amputation. Where this occurs, data from minor amputations (ie, below the ankle joint, as per the GVG definition) will be excluded, articles that do not report separate statistics for major lower limb amputation will also be excluded. Only articles with comparable definitions will be considered for data pooling.

### Screening

The titles, authors, abstracts and the date and location of publication will be extracted and imported into EndNote X9. Duplicates will be removed at this stage.

The titles and abstracts will then be screened for inclusion by two reviewers independently. The full texts will then be screened by two reviewers for confirmation of suitability. Any disagreement on suitability for inclusion will be resolved by discussion between the two reviewers and, if necessary, with the aid of the third reviewer. Reasons for exclusion will be noted at each stage.

### Outcomes

The main outcome will be an estimate of the incidence, prevalence or absolute number of major lower limb amputation in England (UK) depending on the epidemiological statistics available.

Regional and subgroup measures, any reported trends over time, any standardisation methods used and code lists for the identification of major lower limb amputation in the databases will be analysed where available.

The routinely collected electronic health data source used in each study will be reported and discussed.

### Data extraction

After screening has taken place the extraction will be performed by two reviewers using a pretested tabulated extraction form. Disagreement between the two reviewers will be resolved by discussion and, if necessary, by the involvement of the third reviewer.

Data to be extracted includes:

- ▶ Author, title, publication date and published location.
- ▶ The data sources used in the analysis.
- ▶ Epidemiological measure of major lower limb amputation—prevalence/incidence/number including any CI, SE and variance recorded.
- ▶ Definition of major lower limb amputation.
- ▶ Population studied (England/UK, diabetic/non diabetic, age limits, date limits, comorbidities or reasons for amputation excluded for example, cancer/trauma).
- ▶ Data recorded for any subgroups analysis (eg, sex, age, ethnicity).
- ▶ Any standardisation methods used.
- ▶ Code lists used to identify subjects with major lower limb amputation.

Corresponding authors will be contacted to attempt to retrieve any data that is missing from the full text and available attachments.

### Quality assessment

There are many quality assessment tools available but the most applicable to the type of studies and publications to be included in this systematic review are the increasingly used Joanna Briggs Institute (JBI) Critical Appraisal Instrument for Studies Reporting Prevalence Data and, for any cohort studies, the JBI Critical Appraisal Checklist for Cohort Studies.<sup>26–30</sup> These tools will be used to critically appraise the quality of the studies that have been selected for inclusion. Following the JBI guidelines, two reviewers will independently carry out the critical appraisal using the critical appraisal tool and discuss the results coming to agreement.

on the conclusions with the aid of a third reviewer where necessary. The aim of the quality assessment will not be to further exclude studies from the review but instead to discuss the strengths and limitations of the studies.

### Data synthesis

For the objective of ascertaining the incidence/prevalence/number of major lower limb amputation, where data allow, the statistic will be converted into a consistent measure. Different measures will be pooled independently. The  $I^2$  statistic will be calculated to determine the percentage of variation due to heterogeneity. If heterogeneity levels deem it possible then meta-analysis of prevalence and meta-regression of prevalence time trends will be performed using a random effects model (which allows for differences in estimates due to heterogeneity) with the `metaprop`<sup>31</sup> command in Stata. If possible, these analysis will be repeated for comparison of subgroups reported, primarily for regional subgroups.

For the objective of establishing which routinely collected health databases are being used and which are available for use in reporting the epidemiology of major lower limb amputation, extracted data will be tabulated where applicable and narratively synthesised.

Strengths and weaknesses of each database will be evaluated by using the following sources:

- ▶ Relevant sections of each included article.
- ▶ The data sources themselves (from their websites, etc).
- ▶ Published articles that evaluate the strengths and weaknesses of the databases.

There is potential for the included articles and the data source websites to be positively biased towards their work and so to balance this, published articles that specifically review the potential weaknesses of the data sources will also be used to inform assessment where available.

### Epidemiological calculation definitions

$$\text{Incidence proportion (cumulative incidence)} = \frac{\text{The number of new major lower limb amputations in a specified time period}}{\text{The total population at risk at the start of the time period}}$$

$$\text{Incidence rate} = \frac{\text{The number of new major lower limb amputations during the specified time period}}{\text{The total population time at risk during the specified time period}}$$

$$\text{Point prevalence} = \frac{\text{The number of new and pre existing major lower limb amputations at a specified point in time}}{\text{The population total at the specified point in time}}$$

$$\text{Period prevalence} = \frac{\text{The number of new and pre existing major lower limb amputations over a specified period in time}}{\text{The average or mid interval population for the specified period of time}}$$

Where *population* refers to the population specified by the study.

Definitions taken from the Centers for Disease Control and Prevention and the Health Knowledge website managed by the Public Health Action Support Team.<sup>32 33</sup>

### Patient and public involvement

Patients and the public were not involved in the design of this study.

### ETHICS AND DISSEMINATION

As this study does not involve the analysis of confidential patient data, it does not require formal ethics approval. This systematic review aims to build on previous systematic reviews that report the epidemiology of major lower limb amputation by establishing a current estimate of incidence/prevalence/number with time trends and subgroup estimates reported where available. The sources of routinely collected electronic health data used in reporting the epidemiology of major lower limb amputation will be established and discussed. Extensive systematic searches will strengthen the findings of this review. It is anticipated that the results of this review will be able to inform future research on the epidemiology of and regional variation in major lower limb amputation in the UK. After the expected completion data in October 2020, the study will be submitted to a peer-reviewed journal.

**Author contributions** AM, LJG and RDS were all involved in and accountable for each stage of the writing of the systematic review protocol and thus all contributed to the concept and design, the drafting and revising and approving the final version. The search strategy for grey and peer reviewed literature were created by CJP and AM.

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**Disclaimer** The funder had no role in the development of the systematic review protocol.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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