The epidemiology of major lower-limb amputation in England: a systematic review highlighting methodological differences of reported trials

Maria Davies, Lauren Burdett, Frank Bowling, Naseer Ahmad and Joanne McClennon

Non-traumatic major lower-extremity amputations (LEA) are a common consequence of long-term diabetes mellitus, with risk factors for LEA including coronary heart disease, cerebrovascular disease or peripheral arterial disease (Crawford et al, 2015). The authors of this systematic review aimed to highlight all epidemiology studies from England that describe the population prevalence of major lower-limb amputation in those with and without diabetes. Time trends across populations are highlighted in those studies where such comparison is possible.

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Article points

1. This review highlights the studies' main methodological variances, namely the lack of consensus when defining amputation, lack of inclusion of age groups studied, or the denominator population used for calculating prevalence.
2. The results were rarely presented with age- and gender-specific breakdowns.
3. The overall rate was rarely age standardised and some used incorrect denominator populations.
4. The differences in the methodology used between studies make it difficult to compare. This means the comparison of prevalence over time and across populations is not possible.

Key words

- Diabetes Mellitus
- Epidemiology
- Lower extremity amputation
- Peripheral Arterial Disease
- Prevalence

Authors

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Non-traumatic major lower-extremity amputations (LEA) are a common consequence of long-term diabetes mellitus. Other well-known risk factors for LEA include coronary heart disease, cerebrovascular disease, or peripheral arterial disease (Crawford et al, 2015). A major lower limb amputation is defined as the surgical removal of a part or whole limb proximal to the ankle (Ajibade, 2013). They are performed in cases of excessive tissue loss, sepsis or if there are no further surgical or endovascular options for revascularisation (Rümenapf and Morbach, 2014). Further reasons for amputation are following trauma or accident, cancer or tumour, or orthopaedic deformity (Lazzarini et al, 2011). They are additionally classified as major and minor depending on whether the amputation is above (major) or below (minor) the ankle joint.

Prevalence rates help to identify the extent and depth of a problem. Establishing how prevalence rates may have changed over time is important, as it allows public health professionals to target their resources, implement preventative strategies and plan their services on a local, regional and national level (Hoffmann et al, 2013).

Published data globally demonstrates considerable variation in the incidence of major LEA ranging from 5.6–600 per 100,000 in the population with diabetes and from 3.6–58.7 per 100,000 in the total population (Moxey et al, 2010). More recent studies are within the range reported by Moxey et al (2010), with the average reported major amputation incidence (from 20 international reports worldwide) of 14.5 per 100,000 in the total population (Kolossvary et al, 2016). Fortunately, in England, the rates of major amputation have reduced overall by approximately 18% over the past 10 years, but still remain six times higher in the diabetic population (Ahmad et al, 2016). The excess risk of amputation in the diabetic compared with the non-diabetic population has been reported as ranging between 7.4 and 41.3 times higher with the variation explained by differences in study design and definitions used (Narres et al, 2017). Most variation in the prevalence of any condition in a population can, however, be explained by age, sex and social class (Bhopal, 2008). It is important, therefore, that any explanation of differences, for example, excess amputation rates in people with

Page points

1. Systematic review using PRISMA, STROBE guidelines.
2. Reported prevalence of major LEA in England showed a 475-fold variation in the diabetic population and 25-fold variation in the non-DM population, most of which can be explained by differences in methodology and definitions of major LEA.

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Table 1. The inclusion and exclusion criteria for the purposes of this systematic review.

Inclusion criteria for studies:
• All population-based studies analysing prevalence, incidence or amputation rates
• Both the diabetic and/or non-diabetic populations
• Studies from England only
• Studies published between January 1, 1988 until December 31, 2018
• Peer-reviewed publications reporting original data
Exclusion criteria for studies:
• Studies published in a language other than English
• Full-text studies unavailable
• Conference abstracts, editorials or comments
• Individual case studies and meta-analysis

diabetes, are compared using the same definitions of diabetes, amputation, as well as across the same age, sex and social class groups.

In order to compare rates across populations and time, it is imperative epidemiological principles in calculating and reporting prevalence are followed. These include using the same numerator and denominator populations and age standardising the overall population rate. Further, age and gender specific rates should be provided as they are far more accurate than the age standardised rate and, additionally, allow variations to be explored.

Aim

The aim of this systematic review was to highlight all epidemiology studies based in England that describe the population prevalence of major lower-limb amputation in those with and without diabetes. The authors describe time trends across populations in those studies where such comparison is possible.

Methods

Systematic searches were performed using PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines, from a comprehensive range of databases: PubMed, Cumulative index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), Medical Literature Analysis and Retrieval Online (MEDLINE), Cochrane database, NHS Digital, Diabetes UK and Healthcare Quality Improvement Partnership (HQIP). The search included studies performed in England, published in English, between January 1, 1988 until December 31, 2018.

The key search terms (combined by Boolean operators) were: (amputation) AND (Lower limb) OR (lower extremity) AND (prevalence) OR (Incidence) OR (epidemiology) OR (frequency) NOT (cancer) NOT (trauma) AND (England) OR (UK) OR (British).

A forward citation search using Google Scholar was performed to identify new research that has yet to be indexed in any database. A grey literature search (research that is either unpublished or has been published in non-commercial form such as government reports, fact sheets, theses and dissertations) was performed to identify any further publications. In addition to the electronic searches, reference lists of the included articles were used as a source to hand-search for relevant citations.

The preliminary search yielded a total of 207 journal articles conducted by the primary author (Maria Davies; MD) and repeated by a secondary author (Lauren Burdett; LB). After removing duplicates and those papers published prior to 1988, the two screeners (MD and LB) reviewed the titles and abstracts for their eligibility based on the defined inclusion and exclusion criteria (*Table 1*); this led to the exclusion of 162 studies. The full-texts of the remaining articles were then assessed for their eligibility, resulting in a further 31 studies being excluded. Any disputes were settled by a third screener (Naseer Ahmad; NA). Eleven studies were deemed to meet the eligibility criteria and included in the review (*Table 2*). Eight of the papers provided results specific to both the diabetic and non-diabetic population, the remaining three did not differentiate between the two populations.

Quality assessment was performed on the remaining studies using the STROBE (STrengthening the Reporting of Observational studies in Epidemiology) checklist.

Results

Eleven studies reporting on amputation rates from within England between 1988 and 2018 were included in the analysis. *Table 3* summarises the main methodological weaknesses of these studies.

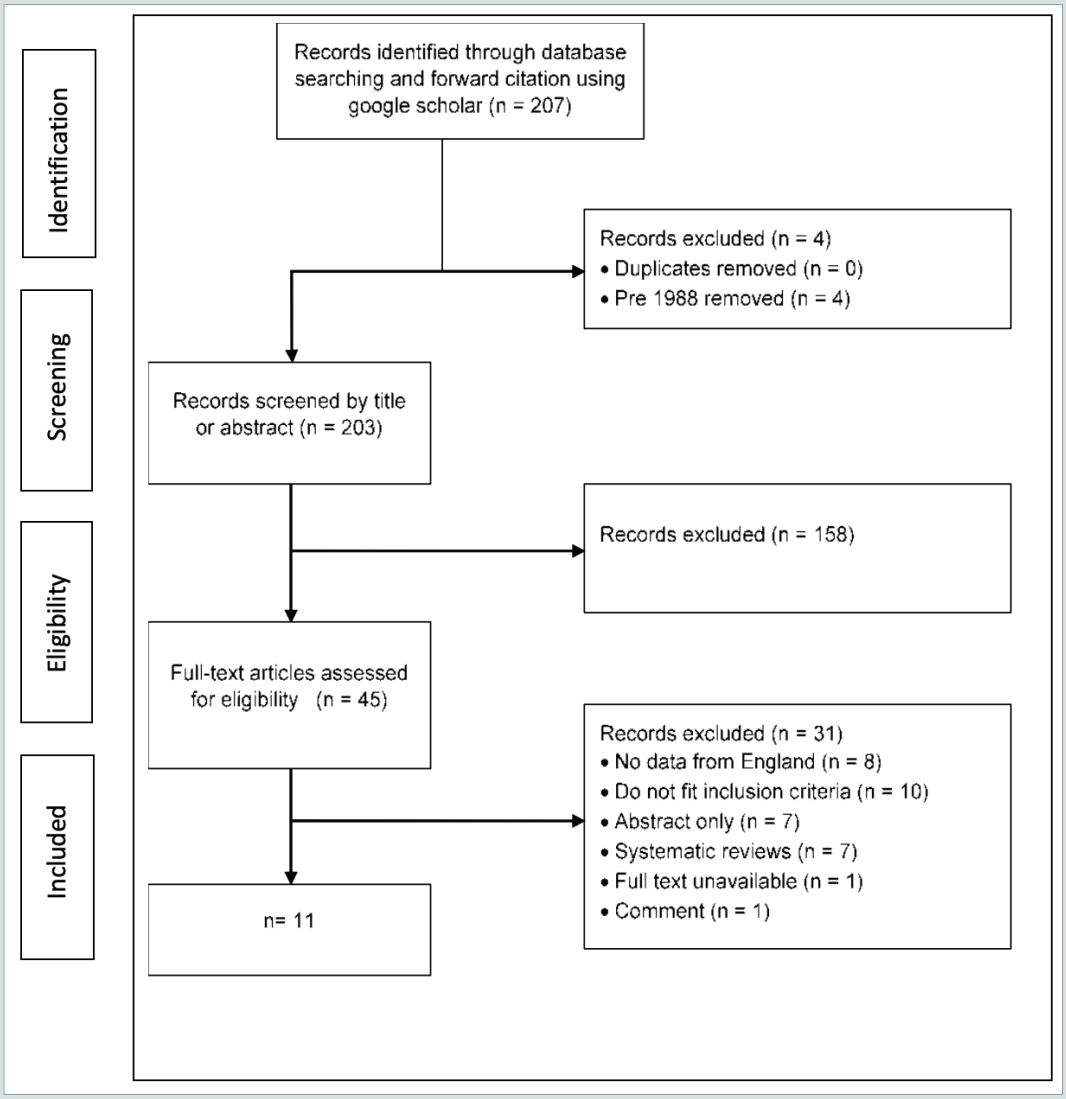

Figure 1. Flow diagram of screening process.

There was considerable variation in the reported prevalence of major LEA, ranging from 0.7 to 332.4 per 100,000 in the diabetic population and 3.0 to 76.1 per 100,000 in the general population.

There were four different definitions describing major LEA in the literature. Canavan et al (2008), Leggetter et al (2002), Unwin (2000) and Vamos et al (2010a; 2010b) defined major LEA at a level through or distal to the ankle joint. The remaining studies agreed that any amputation through or distal to the ankle joint is classified as a minor amputation.

Moxey et al (2010) and Vamos et al (2010a) made a mistake with the denominator populations by using the population of England as the numerator but the entire population of Great Britain as the denominator. Moxey (2010) was the only paper to publish enough methodological data to check the prevalence rate was calculated correctly. They provided rates per 10,000 rather than 100,000. They also used only 1-year population data (2008) and not five-year averages. If calculated correctly then they would have reported a national prevalence rate of 51/100,000 not 5.1/100,000.

Canavan et al (2008), Holman et al (2012), Leggetter et al (2002), Moxey et al (2010), Rayman et al (2004) and Vamos et al (2010a) did not define the denominator population age groups, while Rayman et al (2004) and Vamos et al (2010a; 2010b) did not provide the source of the denominator population.

There were inconsistencies in the age groups studied, ranging from all ages, including children, to only those in the age bracket 50–84 years. Leggetter et al (2002), Moxey et al (2010), Rayman et al (2004) and Vamos et al (2010a) did not define the age group studied, and Leggetter et al (2002), Moxey et al (2010), Rayman et al (2004) and Vamos et al (2010a; 2010b) did not age standardise their results. Results were rarely presented with age and gender specific breakdowns, with only Ahmad et al (2016), McCaslin et al (2007) and Unwin (2000) providing age specific results and Ahmad et al (2014; 2016), Unwin (2000) and Vamos et al (2010b) providing gender specific results.

Cavanan et al (2008), Rayman et al (2004) and Unwin (2000) gathered their numerator data from medical records. The remaining eight studies by Ahmad et al (2014; 2016), Holman et al (2012), Leggetter et al (2002), McCaslin et al (2007), Moxey et al (2010) and Vamos et al (2010a; 2010b) extracted amputation numbers from the Hospital Episode Statistics (HES) database using the Office of Population Censuses and Surveys — 4th Revision (OPCS-4), Classification of Surgical Operation Codes to record the level of amputation. Leggetter et al (2002), McCaslin et al (2007) and Vamos et al (2010a) published OPCS-4 codes that did not correlate with their written definition.

Canavan et al (2008), Leggetter et al (2002), and Unwin (2000) identified people with diabetes through their medical records, as did the prospective study by Rayman et al (2004). The World Health Organization's International Classification of diseases (ICD-10) is used to code conditions such as diabetes mellitus. The remaining studies by Ahmad et al (2014; 2016), Holman et al (2012), McCaslin et al (2007), Moxey et al (2010) and Vamos et al (2010a; 2010b) used ICD-10 codes to identify people with diabetes mellitus. Vamos et al (2010a; 2010b) excluded three (E12–E14) of the five codes that the other papers included.

Discussion

There was wide variation in those studies presenting amputation prevalence in England. Generally rates were higher in the diabetic than non-diabetic population but the range of presented rates varied such that there was significant overlap. The variation stemmed from differences in the definitions of major LEA and denominator populations, different amputation capture techniques and lack of both age standardisation of overall rates and presentation of age and gender specific rates. These variations also made comparison of amputation rates over time difficult.

The only way to describe time trends is if two papers calculate prevalence in the same way. Only one paper by Ahmad et al (2016) provided both age standardised and age-sex specific results over a 10-year period. This found major amputation rates to be falling overall, faster in the population with diabetes than those without and interestingly minor amputation rates (defined as those below the ankle) to be rising in both populations but at a faster rate in those without diabetes and also men compared with women. The effect of age standardisation was also shown in Germany where Spoden et al (2019) investigated amputation rates between 2005–2015. There was an overall increase in lower-limb amputations, however, after age-sex standardisation an overall decrease of 11% was revealed. The increase in amputation numbers is attributed to the aging German population.

The same can be seen in the study by Ahmad et al (2016); amputation numbers increased, yet after age-sex standardisation there was an overall decrease in major LEA by 40% in the population with diabetes and 26% in the population without diabetes. This may explain why McCaslin et al (2007) and Vamos et al (2010b) reported lower rates of major LEA in people with diabetes, however, without the demographic data this cannot be proven.

Conclusion

Significant variation in methodology and reporting of results hinders evaluation of time trends of amputation rates. A standard method of reporting amputation rates is urgently required. The next step is to create a standard to which future amputation data should be presented. ■

Ahmad N, Thomas G, Chan C, Gill P (2014) Ethnic differences in lower limb revascularisation and amputation rates. Implications for the aetiopathology of atherosclerosis? *Atherosclerosis* 233(2): 503–7

Table 2: Summary of studies describing prevalence of major lower-limb amputation in England, 2000-2012.

Author	Setting and study period	Aims	Prevalence rate per 100,000		
			Group (age/sex)	Diabetic	Non-diabetic/general population
Unwin (2000)	Multi-centre globally, 4 in England 1995–1997	A comparison of LEA incidence rates between different centres around the world	All ages Age specific rates Age standardised to European population		Men Leeds: 19.9 Leicester: 7.2 Middlesbrough: 27.8 Newcastle: 20.2 Women Leeds: 10.2 Leicester: 4.3 Middlesbrough: 8.4 Newcastle: 8.8
Leggetter (2002)	3 boroughs in South East London, England 1992–1997	To determine diabetes-related amputation rates in African Caribbeans versus Europeans in the UK	Age not stated Insufficient data for sex-stratified analysis	50–64 yrs 147 African Caribbeans 219 Europeans	50–64 yrs 47 African Caribbeans 14 Europeans
Rayman (2004)	Ipswich 1997–2000	To determine the incidence of LEA using prospective data and comparing to retrospective	Age not stated	1997–98 228 1998–99 152 1999–00 108 Major LEA 162	1997–98 6.3 1998–99 4.2 1999–00 3.0 Major LEA 4.5
McCaslin (2007)	England 1989–2004	To establish national data for lower-limb revascularisation and major amputation in England	>45	45-64 yrs: 1993 2.3 2004 1.9 65-74 yrs: 1996 7.8	45–64 yrs: 1989 10.0 2004 11.5 65–74yrs: 1994 40.0 2004 30.9 >75 yrs: 1989 60.1 1993 76.1 2004 51.5
Cavanan (2008)	South Tees 1995–2000	Trends in Diabetes-related LEAs and Non-DM related LEAs in South Tees	All ages	1995–96 310.5 1996–97 190.2 1997–98 132.9 1998–99 272.8 1999–00 75.8	1995–96 8.7 1996–97 9.6 1997–98 12.4 1998–99 8.1 1999–00 15.3
Vamos (2009)	England 1996–2005	To examine trends in non-traumatic lower-extremity amputations over a 10-year period in people with and without diabetes (DM) in England	Age not stated	T1 DM 1996 1.3 T1 DM 2005 0.7 T2DM 1996 2.0 T2DM 2005 2.7	1996 7.0 2005 4.9
Vamos (2009)	England 2004–2008	To describe trends in the incidence of non-traumatic amputations in patients with and without DM	>16	2004–2005 118 2008–2009 102	2004–2005 7.7 2008–2009 6.9

Table 2: Summary of studies describing prevalence of major lower-limb amputation in England, 2000-2012 (continued).

Author	Setting and study period	Aims	Prevalence rate per 100,000		
			Group (age/sex)	Diabetic	Non-diabetic/general population
Moxey (2010)	England 2003–2008	To investigate the prevalence of lower-extremity amputation in England	Age not stated		Total 5.1 East Midlands 4.9 East of England 4.4 London 3.9 North East 7.2 North West 6.2 South Central 4.7 South East Coast 4.4 South West 5.4 West Midlands 5.1 Yorkshire and Humberside 6.0
Holman (2012)	England 2007–2010	To explore the variation in the recorded incidence of LEA in England	17+	251	111
Ahmad (2014)	England 2003–2009	To describe the prevalence of major LEA across England and the association of ethnicity to amputation, both with and without revascularisation	50–84 yrs Age and sex standardised		Men 37.7 Women 15.9 Overall 26
Ahmad (2016)	England 2003–2013	To determine the prevalence of amputation and revascularisation among people with and without diabetes	50–84 yrs Age and sex standardised	Men 50–64 yrs 2003 119.7 2013 82.2 65–74 yrs 2003 222.3 2013 127.8 75–84 yrs 2003 332.4 2013 193.6 Women 50–64 yrs 2003 74.9 2013 34.6 65–74 yrs 2003 99.9 2013 60.1 75–84 yrs 2003 134.9 2013 94.6	Men 50–64 yrs 2003 11.8 2013 10.1 65–74 yrs 2003 31.5 2013 24.5 75–84 yrs 2003 60.0 2013 40.4 Women 50–64 yrs 2003 3.4 2013 4.1 65–74 yrs 2003 12.3 2013 9.2 75–84 yrs 2003 31.5 2013 22.5

Table 3: Summary of weaknesses of studies.

Methodological weakness	Number of studies	Studies
Did not define age group studied	4	Leggetter, 2002 Rayman, 2004 Vamos, 2009 Moxey, 2010
Definition of major amputation included those below the ankle	5	Unwin, 2000 Leggetter, 2002 Canavan, 2008 Vamos, 2009 Vamos, 2010
Did not define denominator population age groups	6	Rayman, 2004 Canavan, 2008 Vamos, 2009 Moxey, 2010 Holman, 2012 Leggetter, 2002
Did not provide source of denominator population	3	Rayman, 2004 Vamos, 2009 Vamos, 2010
Did not age standardise results	5	Leggetter, 2002 Rayman, 2004 Vamos, 2009 Vamos, 2010 Moxey, 2010
Did not provide age specific results	8	Leggetter, 2002 Rayman, 2004 Canavan, 2008 Vamos, 2009 Vamos, 2010 Moxey, 2010 Holman, 2012 Ahmad, 2014
Did not provide gender specific results	7	Leggetter, 2002 Rayman, 2004 McCaslin, 2007 Vamos, 2009 Moxey, 2010 Holman, 2012 Canavan, 2008
Did not record OPCS-4 codes accurately	3	Leggetter, 2002 McCaslin, 2007 Vamos, 2009
Did not exclude amputations caused by trauma and cancer	5	Ahmad, 2014 Ahmad, 2016 Holman, 2012 McCaslin, 2007 Moxey, 2010

Ahmad N, Thomas GN, Gill P, Torella F (2016) The prevalence of major lower limb amputation in the diabetic and non-diabetic population of England 2003–2013. *Diab Vasc Dis Res* 13(5): 348–53

Ajibade A, Akinniyi OT, Okoye CS (2013) Indications and complications of major limb amputations in Kano, Nigeria. *Ghana Med J* 47(4): 185–8

Bhopal R (2008) *Concepts of Epidemiology*. Oxford University Press: Oxford pp7

Canavan RJ, Kelly WF, Unwin NC, Connolly VM (2008) Diabetes- and non-diabetes-related lower extremity amputation incidence before and after the introduction of better organized diabetes foot care. *Diabetes Care* 31(3): 459–63

Crawford F, Cezard G, Chappell F et al (2015) A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). *Health Technol Assess* 19(57): 1–210

Hoffmann F, Claessen H, Morbach S et al (2013) Impact of diabetes on costs before and after major lower extremity amputations in Germany. *J Diabetes Complications* 27(5): 467–72

Holman N, Young RJ, Jeffcoate WJ (2012) Variation in the recorded incidence of amputation. *Diabetologia* 55(7): 1919–25

Kolossvary E, Farkas K, Colgan MP (2017) "No more amputations": a complex scientific problem and a challenge for effective preventive strategy implementation on vascular field. *Int Angiol* 36(2): 107–115

Leggetter S, Chaturvedi N, Fuller JH, Edmonds ME (2002) Ethnicity and Risk of diabetes-related lower extremity amputation. *Arch Intern Med* 162(1): 73–8

McCaslin JE, Hafez HM, Stansby G (2007) Lower limb revascularization and major amputation rates in England. *Br J Surg* 94(7): 835–9

Moher D, Liberati A, Tetzlaff J, Altman D (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6(7): e1000097

Moxey PW, Hofman D, Hinchliffe RJ et al (2010) Epidemiological study of lower limb amputation in England between 2003 and 2008. *Br J Surg* 97(9): 1348–53

Narres M, Kvitkina T, Claessen H et al (2017) Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: A systematic review. *PLoS One* 12(8): e0182081

Rayman G, Krishnan S, Baker NR et al (2004) Are we underestimating diabetes-related lower-extremity amputation rates? Results and benefits of the first prospective study. *Diabetes Care* 27(8): 1892–6

Rümenapf G, Morbach S (2014) What can I do with a patient with diabetes and critically impaired limb perfusion who cannot be revascularized? *Int J Low Extrem Wounds* 13(4): 378–89

Spoden M, Nimptsch U, Mansky T (2019) Amputation rates of the lower limb by amputation level — observational study using German national hospital discharge data from 2005 to 2015. *BMC Health Serv Res* 19(1): 163

Unwin N (2000) Epidemiology of lower extremity amputation in centers in Europe, North America and East Asia. *Br J Surg* 87(3): 328–37

Vamos EP, Bottle A, Majeed A, Millett C (2010a) Trends in lower extremity amputations in people with and without diabetes in England, 1996–2005. *Diabetes Res Clin Pract* 87(2): 275–82

Vamos EP, Bottle A, Edmonds ME et al (2010b) Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. *Diabetes Care* 33(12): 2592–7

Online CPD activity

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Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The new CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. According to Ajiibade (2013), above which level is lower-limb surgical amputation defined as MAJOR as opposed to MINOR? Select ONE option only.

   A. Knee
   B. Mid shaft tibia
   C. Ankle
   D. Forefoot
   E. Toe

2. Which one of the following is the most appropriate definition of 'prevalence'? Select ONE option only.

   A. The number of individuals who develop a specific disease during a particular time period
   B. The percentage of people with a positive test who truly have the condition
   C. The percentage of people with a negative test who truly do not have the condition
   D. The probability that subjects with a positive screening test truly have the disease
   E. The total number of people in a population who have a disease at a specific period of time

3. According to Ahmad et al (2016), approximately how many times higher are the rates of lower-limb amputation in people with diabetes compared to the total population? Select ONE option only.

   A. 3
   B. 6
   C. 9
   D. 12
   E. 15

4. According to Bhopal (2008), which single one of the following variables best explains the variation in the prevalence of any medical condition within a population? Select ONE option only.

   A. Access to healthcare
   B. Age
   C. Attitude of healthcare professionals
   D. Public awareness
   E. Quality of healthcare provision

5. Study A quotes a rate of major lower-limb amputations as 75/100,000 for a population of people with diabetes aged 50 or above, while Study B quotes a rate of 150/200,000 for people with diabetes aged over 50.

   Which one of the following is different between the two studies? Select one option only.

   A. Age-standardisation
   B. Denominator
   C. Incidence
   D. Numerator
   E. Prevalence

6. Which one of the following most accurately reflects a 'grey literature search'? Select ONE option only.

   A. A standard 'Google' search
   B. Exclusion of academic research papers
   C. Inclusion of drug company sponsored research
   D. Unpublished or non-commercial published reports
   E. Use of non-electronic databases

7. When reviewing the prevalence of major lower limb amputations in England over a 10-year period, how many studies met Davies et al's (2019) (this study's) eligibility criteria?

   A. 11
   B. 59
   C. 106
   D. 207
   E. 1012

8. Ahmad et al (2016) was the only study in Davies et al's (2019) (this study's) review with both age-standardised and age-specific results.

   According to this study, which single one of the following population groups has the fastest rising rate of minor lower-limb amputations, if any? Select ONE option only.

   A. Men with diabetes
   B. Men without diabetes
   C. Women with diabetes
   D. Women without diabetes
   E. No difference between men and women, with or without diabetes

9. According to Spoden et al's (2019) study, which one of the following is the most appropriate explanation of why Germany has seen an overall decrease in age-standardised lower-limb amputation rates yet has an increase in lower-limb amputation rates overall? Select ONE option only.

   A. Changes in the threshold definition of 'amputation'
   B. Differences in hospital coding of surgical procedures
   C. Improved standards of postoperative care
   D. Increasing proportion of females in the population
   E. The ageing population

10. Which is the single most appropriate statement about the concluding recommendations of Davies et al's (2019) (this study's) review of lower-limb amputation rates in England over a 10-year period? Select ONE option only.

    A. A standard method of reporting amputation rates is urgently required
    B. Evaluation of time trends of amputation rates is currently accurate
    C. Further studies are unnecessary
    D. The review included data across all four home nations
    E. There was insignificant variation in study methodologies