The Global Disability Burden of Diabetes-related Lower Extremity Complications in 1990 and 2016

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ABSTRACT

Objective No study has reported global disability burden estimates for individual diabetes-related lower extremity complications (DRLECs). The Global Burden of Diseases (GBD) study presents a robust opportunity to address this gap.

Research Design and Methods GBD 2016 data including prevalence and years lived with disability (YLDs) for the DRLECs of diabetic neuropathy, foot ulcer, and amputation with, and without prosthesis were used. GBD estimated prevalence using data from systematic reviews and DisMod-MR 2.1, a Bayesian meta-regression tool. YLDs were estimated as the product of prevalence estimates and disability weights for each DRLEC. We reported global, sex-, age-, region- and country-specific estimates for each DRLEC for 1990 and 2016.

Results In 2016, an estimated 131 million (1.8% of the global population) had DRLECs. An estimated 16.8 million YLDs (2.1% global YLDs) were caused by DRLECs, including 12.9 million (95% uncertainty interval: 8.30 to 18.8) from neuropathy only, 2.5 million (1.7 to 3.6) foot ulcers, 1.1 million (0.7 to 1.4) amputation without prosthesis, and 0.4 million (0.3 to 0.5) amputation with prosthesis. Age-standardised YLDs rates of all DRLECs increased by between 14.6% to 31.0% from 1990 estimates. Male-to-female YLD ratios ranged from 0.96 for neuropathy only to 1.93 for foot ulcers. Aged groups 50-69 years accounted for 47.8% of all YLDs from DRLECs.

Conclusions These first ever global estimates suggest DRLECs are a large and growing contributor to the disability burden worldwide, and disproportionately affect males and middle-to-older aged populations. These findings should facilitate policymakers worldwide to target strategies at populations disproportionately affected by DRLECs.

The International Diabetes Federation estimated that one in every eleven adults (451 million) had diabetes in 2017, and one in ten (693 million) will have diabetes by 2045.(1) People with diabetes are at high risk of developing a range of complications, including cardiovascular, kidney, eye and lower extremity complications.(2, 3) Arguably the most disabling of these are the lower extremity complications of peripheral neuropathy, foot ulceration and amputation.(4, 5)

Diabetes-related lower extremity complications (DRLECs) typically first present as neuropathy.(4, 5) Neuropathy is the critical risk factor for developing foot ulceration, and foot ulceration the critical risk factor for foot infection and amputation.(4, 5) It is estimated that up to 50% of people with diabetes have neuropathy,(6, 7) up to 34% will develop a foot ulcer in their lifetime,(5) around 50% of those ulcers will become infected,(8-10) and 20% amputated.(5, 10, 11) DRLECs also account for up to 80% of global lower extremity amputations, are a leading cause of hospitalisation,(12-14) and result in significant reductions in quality of life.(4, 15) Thus, DRLECs appear to cause considerable global disability burden.

Whilst several narrative reviews have reported basic global epidemiology estimates for some DRLECs, (4-6, 16, 17) only one paper has reported a robust global prevalence estimate based on systematic reviews.(16) In this meta-analysis, the authors reported a pooled global foot ulcer prevalence of 4.6% in the diabetes population and also reported foot ulcer prevalence estimates for five geographical regions and 33 countries.(16) Otherwise, no paper has systematically reported global, regional or country prevalence estimates for the other individual DRLECs, including neuropathy and amputations.

Additionally, to our knowledge, only our group has reported an estimate of the global disability burden of DRLECs.(18) In a brief published letter we used data from the Global

Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2015 to report an overall estimate for the years lived with disability (YLD) caused by aggregated DLRECs in 2015.(18) YLDs is an important population measure of disability burden (or non-fatal health loss) as it enables objective comparisons of disability burden of a condition across different populations or for different conditions within the same population.(19) YLDs are calculated by multiplying the total numbers of people affected by a condition by the average severity of disability for that condition (disability weight).(19) However, in that letter we did not report YLD estimates for individual DRLECs or estimates by sex, age, region, or country.(18) Thus, robust data on the global, regional and country prevalence and disability burden of DRLECs is still not accessible to decision makers. GBD presents a unique and robust opportunity to address this gap.

GBD is a multinational collaborative research project, which systematically integrates all available data to produce consistent, transparent and up-to-date estimates on the disability and mortality burdens of most diseases and injuries impacting the world.(19-23) Initiated in the early 1990s by the World Health Organisation, and since 2010 independently funded by the Bill and Melinda Gates Foundation, it has grown into an international consortium of more than 3,600 researchers, with more than 200 papers published. GBD estimates are now arguably the most well-known, well-used and well-cited burden of disease estimates, and have had a profound impact on health policy and agenda-setting throughout the world, especially as it has brought global attention to otherwise hidden or neglected diseases and injuries.(19-23)

While estimates have been presented for diabetes mellitus in GBD capstone papers, the estimates for the disabling sequelae that make up the diabetes mellitus burden have not been described in detail, including DRLECs.(19) Although it is apparent in these capstone papers that the global burden of diabetes is comparatively large and has markedly increased over recent decades,(19) and it could be expected that the disease burden of DRLECs would have a commensurate increase, to date, global, regional and national estimates and changes over time related to DRLECs remain hidden. Thus, this paper uses GBD data with the primary aim to provide global prevalence and disability burden (YLDs) estimates for individual and overall DRLECs in 2016. Secondary aims are to further explore these 2016 estimates by sex, age, 21 regions, and 195 countries or territories, and over time compared to 1990 estimates. Such estimates should enable health service providers and researchers to evaluate the comparative disease burden DRLECs have on their population of interest, and in turn inform decisions about resource allocation to target cost-effective prevention and treatment at populations disproportionately affected.

Research Design and Methods

Research design

This study was a secondary analysis of GBD 2016 data obtained from the Institute for Health Metrics and Evaluation (IHME), Seattle, USA. IHME provided prevalence and YLD estimates for diabetes mellitus and DRLEC-related sequelae by sex, 20 age groups, 21 regions and 195 countries or territories, for the years 2016 and 1990. Prevalence and YLDs were provided in counts, rates and age-standardized rates, with 95% uncertainty intervals (UI). Results of this study were reported according to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement (eTable 1).(24)

GBD framework

Since 1990, GBD has been estimating global disease burden by quantifying the health loss from premature mortality and non-fatal disability.(19-23) GBD attributes the health loss to hundreds of causes (diseases and injuries that cause death or disability) which are made up of thousands of sequelae (complications of those causes) using a mutually-exclusive and exhaustive list of causes organised into a hierarchy of levels.(19) Level 1 causes consist of three broad overarching cause groups, such as *Non-communicable diseases*.(19) These are disaggregated into >20 Level 2 cause groups, such as *Diabetes, urogenital, blood and endocrine diseases*.(19) These are further disaggregated into >100 Level 3 causes, such as *Diabetes mellitus*, and again into >200 Level 4 causes, such as *Chronic kidney disease (CKD) due to diabetes mellitus*.(19) Finally, these Level 4 causes are disaggregated into >2,000 sequelae, such as the DRLEC-related sequelae of *Diabetic neuropathy and amputation with treatment*.(19) Thus, the prevalence and YLD estimates for all the sequelae of a particular Level 4 cause should sum exactly to the prevalence and YLD estimate of that Level 4 cause, respectively, and so on up the hierarchy of levels.

GBD is now remeasured and republished at least every three years. For each new iteration, GBD provides new estimates not only for more recent years, but also for all previous years as improvements in GBD methodology are implemented. These new estimates for previous years supersede any previously published result estimates for those years, including 1990 estimates. GBD 2016 estimated global prevalence, incidence, and YLDs for 328 causes and 2982 sequelae, for 21 regions, and 195 countries or territories during 1990-2016.(19, 25) The extensive GBD 2016 methodology has been published in detail elsewhere.(19, 25) For the purpose of this paper, we summarise the methodology used in the prevalence and YLD estimations for *diabetes mellitus* and its eight mutually exclusive sequelae: *uncomplicated diabetes mellitus*, *moderate vision loss due to diabetes mellitus*, *severe vision loss due to diabetes mellitus, blindness due to diabetes mellitus*, *diabetic neuropathy*, *diabetic foot due to neuropathy*, *diabetic neuropathy and amputation with treatment*, and *diabetic neuropathy and amputation without treatment*.(19)

Case Definitions

As a cause in GBD 2016, *Diabetes mellitus* was defined as those with a fasting plasma glucose (FPG) > 126 mg/dL (7 mmol/L) or being on treatment for diabetes.(19) DRLECs were defined as the four mutually exclusive DRLEC-related sequelae of *Diabetes mellitus*: 1. *Diabetic neuropathy*, defined as cases of diabetes mellitus with diagnosed neuropathy that do not currently have a foot ulcer or previous major amputation;(19) 2. *Diabetic foot due to neuropathy*, cases of diabetes mellitus that currently have a foot ulcer;(19) 3. *Diabetic neuropathy and amputation without treatment*, cases of diabetes mellitus that have previously had major leg amputation(s) (above or below the knee) that do not have a prosthetic limb to ambulate (and instead require crutches or similar aide to move around); 4. *Diabetic neuropathy and amputation with treatment*, cases that have previously had major leg amputation(s) (above or below the knee) that do have a prosthetic limb to ambulate.(19) Amputation was broken down into with and without treatment (i.e. with and without prosthesis) to more accurately estimate disability burden, based on studies that those with major amputation without a prosthesis had markedly worse quality of life and disability burdens than those with a prosthesis.(19, 26-28) Cases with multiple DRLEC-related sequelae were assigned the most severe of their DRLECs as their only DRLEC so as to be counted only once. Full case definitions and diagnostic criteria with associated ICD 9 and ICD 10 codes are presented in eTable 2. Shortened terms are used to denote these four sequelae for the remainder of this paper as *neuropathy*, *foot ulcer*, *amputation with prosthesis,* and *amputation without prosthesis*, respectively.

Prevalence estimation

In GBD, prevalence was estimated firstly for causes, and then split into sequelae. For all included causes, GBD initially performed systematic reviews to identify all available data sources from published articles and unpublished registry data prior to December 31, 2016.(19) All accessible information identified on disease occurrence, natural history, and any sequelae based on severity for a cause such as diabetes, then passed a strict set of inclusion criteria and adjustments, to maximise the comparability of the data, despite if different collection methods or case definitions were used in the included studies over time. For diabetes, data from 806 prevalence articles were extracted and processed, including time, age and sex splitting. A series of adjustments were then made if required, this involved crosswalking data inputs from studies with less desirable methods to data inputs from optimally conducted studies. Crosswalks between several different case definitions with different thresholds of FPG or glycated hemoglobin levels for diabetes mellitus were used based on available data with individual records of the actual measurements. The adjusted input data were entered into a validated Bayesian meta-regression tool DisMod-MR 2.1 to produce adjusted pooled prevalence estimates for diabetes for each age-sex-country-year combination.(19) To predict estimates for countries with sparse or no available data, GBD uses a ‘wrapper’ code that bases country estimates on the regional estimates from the geographical parent region for that country. Furthermore, in the case of countries with no data, the coefficients for the parent geographical region were also used to take advantage of the predictive power of the covariates in a meta-regression. In the case of diabetes, a range of covariates were systematically tested, and two covariates were chosen to further inform estimates for data-sparse countries based on statistical fit (AIC and adjusted R^2): prevalence of obesity per country and lag-distributed income per capita.(19)

For DRLEC-related sequelae, GBD included 89 prevalence articles for neuropathy, 43 for foot ulcer and 12 for amputation. Separate DisMod-MR 2.1 models were used to produce pooled estimates of the proportion of diabetes population affected by each different sequela. These proportion estimates were multiplied by the estimated prevalence of diabetes to determine prevalence estimates for each sequela after a series of adjustments.(19) Crosswalks were again performed to adjust for any studies using different DRLEC diagnostic criteria to that used as the case definition by GBD for each DRLEC (see eTable 2). A series of "squeeze" adjustments were then made to ensure firstly that the sum of all complicated sequelae did not exceed 90% of the diabetes prevalence, and secondly that the sum of foot ulcer and amputation did not exceed 90% of the total neuropathy prevalence.(19) Finally, the amputation prevalence was split into those with and without prosthesis, based on a standardised scaled country-specific health system access covariate developed by GBD and the assumption that at least 10% of amputees will not receive a prosthetic, supported by data from a pivotal historical study reporting the proportion of prosthetic treatment for major amputations(26) and since supported by multiple contemporary studies.(29-31) A population-weighted average was then performed to obtain a regional estimate for the proportion of amputees that receive a prosthetic. This adjusted regional proportion was then used as the proportion of amputation with prosthesis for each country and a conservative confidence interval of ±50% applied to adjust for any uncertainty of these prosthesis proportion assumptions.(19)

Adjusted prevalence estimates were then produced using DisMod-MR 2.1 for each DRLEC-related sequelae for each age-sex-country-year combination, based on the GBD reference population, a standard global reference population structure used to facilitate such age-standardised rate comparisons.(32, 33) For countries with sparse or no DRLEC data the aforementioned wrapper code was again used to adjust estimates based on the estimates of geographical parent region. All GBD 2016 estimates have been estimated with uncertainty. Uncertainty comes from many sources, including heterogeneity in the empirical data that are available and identified through systematic reviews, and uncertainty in the indirect estimation models used to make predictions for populations with little or no data. Because the empirical basis for estimating prevalence is much weaker for some DRLECs sequelae than for others, uncertainty varies substantially between sequelae, and within sequelae across regions and countries.

Years lived with disability (YLDs) estimation

The disability burden resulting from a sequela or cause within a population is measured using YLDs.(19) YLDs are calculated by multiplying the prevalence estimate of a sequela by a disability weight for the same sequela.(19) The disability weight represents the average severity of non-fatal health loss associated with the particular sequela on a scale of 0 (equivalent to perfect health) to 1 (equivalent to death).(19, 34) For example, *uncomplicated diabetes* has a comparatively low disability weight of 0.049, whereas, *blindness due to* *diabetes* has a comparatively high disability weight of 0.187.(19) Disability weights were determined from a series of multinational, household-based or web-based surveys, “which used paired comparison questions in which respondents considered two hypothetical individuals with different health states and specified which person they deemed healthier”.(34) Data from these surveys were analysed and rescaled to disability weight units between 0 and 1.(34) Lay descriptions of the four DRLEC-related sequelae used to frame the comparison questions can be found in eTable 2. The final stage in the estimation of YLDs is a micro-simulation that adjusts for comorbidity. It is performed by simulating 40,000 individuals for each age-sex-country-year. Based on the prevalence estimates of sequelae, these simulated individuals end up having none to multiple disease sequelae. The disability weight for each individual is estimated based on the sequelae they acquired and the disability weight is then attributed to each sequela. The disability weight determined for neuropathy was 0.133 (0.089–0.187).(19) The disability weights for the other three sequelae were calculated as a combination of two health states: neuropathy and foot ulcer (0.02 (0.01-0.034)) or amputation with prosthesis (0.039 (0.023 – 0.059)), or amputation without prosthesis (0.173 (0.118 – 0.24)). (19)

Analysis

We transformed all data provided by IHME into tables and figures to display the global prevalence and YLDs of individual and overall DRLECs in 2016 and 1990, and the composition by sex, 20 age groups, 21 regions, and 195 countries or territories. Prevalence and YLDs were presented in counts, all-age rates and age-standardized rates, with 95% uncertainty intervals (UI). Overall DRLEC prevalence and YLDs were calculated by summing mean estimates of the four DRLECs-related sequelae. Mean percentage changes between 1990 and 2016 were calculated for all outcomes in counts, all-age rates, and age-standardized rates. Change in counts reflects the combined effects of population growth, population ageing, and epidemiological change.(19) Population ageing and epidemiological change explain the mean percentage change in all-age rates, while the change in age-standardised rates reflects epidemiological change that is not due to ageing or population growth.(19) Male-to-female ratios were also calculated across age groups. Estimates were considered significantly different if their 95% UIs did not overlap.

RESULTS

Global findings

Tables 1 displays global prevalence and YLD estimates for diabetes, individual and overall DRLECs in 2016, and percentage changes from 1990 to 2016. In 2016, there were an estimated 131.0 million people (1.77% of the global population) affected by overall DRLECs, including 105.6 million (95% UI, 85.5 to 128) with neuropathy only, 18.6 million (15.0 to 22.9) with foot ulcers, 4.3 million (3.7 to 4.9) amputation without prosthesis, and 2.5 million (2.1 to 3.0) amputation with prosthesis. The age-standardized prevalence rates showed that 1,848 per 100,000 were affected, including 1,480 (1,201 to 1,783) with neuropathy only, 270 (217 to 332) foot ulcers, 60.6 (52.6 to 69.2) amputation without prosthesis, and 36.7 (30.2 to 43.9) amputation with prosthesis.

An estimated 16.8 million YLDs (2.07% of global YLDs) were caused by DRLECs in 2016, including 12.9 million (8.30 to 18.8) from neuropathy only, 2.5 million (1.7 to 3.6) from foot ulcers, 1.1 million (0.7 to 1.4) from amputation without prosthesis, and 0.4 million (0.3 to 0.5) from amputation with prosthesis. The age-standardized YLD rates for DRLECs was 237 per

100,000, including 180 (116 to 263) from neuropathy only, 36.3 (23.8 to 51.4) foot ulcers, 15.1 (10.6 to 20.4) amputation without prosthesis, and 5.4 (3.6 to 7.6) amputation with prosthesis.

Compared to 1990 estimates, counts of prevalence and YLDs in 2016 increased significantly by between 110.4% (neuropathy) and 140.3% (amputation without prosthesis). Age-standardised rates of prevalence and YLD also increased by between 14.9% (neuropathy) and 31.5% (amputation without prosthesis) from 1990 to 2016, though statistical significance of these increases is unclear due to overlapping 95% UIs.

Insert Table 1

Sex & age findings

Figure 1 shows sex and age composition in YLD counts (A) and rates (B) in 1990 and 2016. In 2016, male-to-female ratios for age-standardised YLD rates were 1.11 for overall DRLECs, 0.96 for neuropathy, 1.56 for amputations (both with and without prosthesis) and 1.93 for foot ulcers. See eTable 3 for male-to-female ratios for YLD counts and rates in each age group. Age groups accounting for most YLD counts of individual DRLECs were: neuropathy, 50-54 years in males and 55-59 years in females; foot ulcers, 60-64 years in both sexes; amputation without prosthesis, 60-64 years in both; and amputation with prosthesis, 65-69 years in both (eTable 3). In summary, the 50-69 years-old accounted for most (47.8%) of the overall DRLEC YLD counts in 2016, while people aged >70 years had higher YLD rates. YLD rates in 2016 increased in nearly all age groups compared to 1990 (eTable 3).

Insert Figure 1 here

Regional findings

Figure 2 shows broad variation in age-standardised YLD rates across the 21 regions in 1990 and 2016. In both 1990 and 2016, highest YLD rates of overall DRLECs were in North Africa and Middle East, Central Latin America, Oceania and Caribbean, whilst lowest rates were in East Asia, Western Sub-Saharan Africa, Australasia and Western Europe. The largest increases from 1990 to 2016 were in Southern Sub-Saharan Africa, South Asia and Southeast Asia, whereas a decrease was only observed in High-income Asia Pacific region .

For individual DRLECs in 2016, highest YLD rates of neuropathy were in North Africa and Middle East (493.9, 318.9 to 726.2 per 100,000), of foot ulcers in Oceania (103.8, 68.6 to 147.9), amputation without prosthesis in Southern Sub-Saharan Africa (44.4, 30.1 to 59.7), and with prosthesis in High-income North America (20.3, 12.3 to 28.8). Figure 3 displays world maps of age-standardised YLD rates for overall DRLECs across 195 countries or territories in 1990(A) and 2016(B). The country with the highest overall DRLECs rate was the Marshall Islands (1096.4 per 100,000), while the lowest was Switzerland (97.1). World maps for prevalence and YLDs of individual DRLECs can be found in eFigure1 and 2, with specific data presented in eTable 5 and 6.

Insert Figure 2 and Figure 3 here

DISCUSSION

We have presented detailed estimates on the disability burden caused by DRLECs for the first time. Based on GBD 2016 data, an estimated 131.0 million (1.77%) people worldwide had DRLECs in 2016, including 105.6 million with neuropathy only, 18.6 million with foot ulcers and 6.8 million with amputations (with or without prosthesis). This resulted in 16.8 million YLDs (2.07% of all YLDs), including 12.9 million from neuropathy only, 2.5 million from foot ulcers and 1.6 million from amputations. Overall, the DRLEC disability burden appeared to disproportionately affect males, 50-69 year aged groups and those living in the regions of North Africa and Middle East, Central Latin America, Oceania and Caribbean. Compared to 1990 estimates, the 2016 global estimates for age-standardized YLD rates increased by 16.7% for overall DRLECs, and for individual DRLECs the increases ranged from 14.9% for neuropathy to 31.5% for amputation without prosthesis. Regional changes in age-standardized YLD rates of overall DRLECs also varied over time for different regions, from 45.4% increase in Southern Sub-Saharan Africa to 11.6% decrease in High-income Asia Pacific.

To our knowledge our previous brief letter was the first to highlight the contribution of DRLECs to the global burden of disability. In this paper, we report an estimated 16.8 million YLDs resulted from DRLECs based on GBD 2016 data, a lower estimate than the 20.5 million in 2015 based on GBD 2015 data in the previous letter.(18) This apparent decrease is most likely explained by lower prevalence estimates of diabetes and DRLECs in GBD 2016: estimates decreased from 435 million(35) in 2015 to 383 million(19) in 2016 for diabetes prevalence, which resulted an decrease from 159 million(18) to 131 million for DRLECs. Unlike previous GBD estimates,(35) GBD 2016 excluded all articles using self-reported diabetes diagnosis which are known to overestimate prevalence of diabetes.(19) Thus, the remeasured GBD 2016 estimates reported in this paper, for the new estimation year 2016 and for the previous year 1990 using new data from annual updates, improved case definitions and modelling, should be the more robust.

As YLDs are a product of prevalence and disability weight, and disability weight has remained the same, it is also reassuring that our prevalence estimates appear to be similar to those reported in the very few other previous papers.(5, 6, 16) We report 131 million people with diabetes had DRLECs, i.e. neuropathy either alone or with foot ulcers or amputations, equalling 34% of diabetes population. Somewhat reassuringly our 34% finding seems to plausibly fit within the neuropathy range, reported in a recent review, of 10%-15% in newly diagnosed diabetes patients and up to 50% in those with >10 year diabetes duration.(6) Additionally, we report an estimated 18.6 million (4.8%) people with diabetes have a foot ulcer which aligns very closely with a 4.6% global pooled prevalence estimated in a meta-analysis.(16) Although studies have investigated diabetes-related major amputations, as per the combined definition of our amputation outcomes (with or without prosthesis), they did so using incidence and thus we are unable to compare our prevalence findings for amputations.(17)

Our estimate of 16.8 million YLDs from DRLECs equates to 59% of the diabetes YLDs (28.6 million). Interestingly, when compared to all 271 Level 4 causes in GBD 2016, in terms of the proportion of overall YLDs (805.4 million) by each cause, diabetes mellitus (3.54%) was the 8th leading cause, made up of DRLECs (2.07%), diabetes-related vision loss (0.03%) and uncomplicated diabetes (1.43%).(19) If we further compare DRLECs (2.07%) with all Level 4 causes, DRLECs would rank between the 10th leading cause (falls: 2.35%) and the 11th leading cause (chronic obstructive pulmonary disease: 2.06%).(19) Furthermore, DRLECs would rank as having a higher global disability burden than ischemic stroke (17th; 1.47%), ischemic heart disease (29th; 0.86%) and CKD due to diabetes (52nd; 0.46%) which is listed in GBD as a separate cause rather than a sequela of diabetes (eTable 4).(19) Thus, our estimate indicates that DRLECs make up a very large proportion of the diabetes disability burden, and a comparatively large proportion of the overall global disability burden in 2016. In an ageing global population, diseases largely affecting the elderly such as diabetes will become more prominent causes of YLDs. The increase in diabetes and the improved survival in people with diabetes through prevention of deaths from cardiovascular complications will most likely lead to further increases in prevalence and a need to prevent these disabling complications of diabetes, in particular DRLECs.

This comparatively large disability burden of DRLECs appeared to disproportionately affect males, and the largest proportion (47.8%) of this burden affected 50-69 years-old population. These are not unique findings as diabetic foot ulcers and amputations have consistently been reported to be much higher in the male population, with median ages of disease onset in this same middle-to-older aged bracket.(16, 36, 37) The previous meta-analysis on diabetic foot ulcer prevalence reported a male-to-female ratio equating to 1.3.(16) While, a recent systematic review on diabetic amputation incidence reported a male-to-female ratio range between 1.5 to 3.0,(36, 37) and attributed this to males having a higher prevalence of smoking, peripheral neuropathy, peripheral artery disease and foot ulceration.(36) We did not find this for neuropathy, although neuropathy did appear to affect males more so in middle-aged groups than females,(38) but did for foot ulceration. Similarly, increasing proportions of diabetes-related complications have been reported in the middle-aged populations. A recent review identified that the proportional contribution of 45-64 year olds to all diabetes-related strokes increased from 20.1% to 31.4% and amputation from 32.4% to 52.8% during 1990 and 2010.(3) It could be suggested that the large proportional contribution of middle-aged groups may partly be attributed to the relatively large size of middle-aged groups compared with other age groups, as suggested by the changing shapes of counts and rates over time in figure 1.

Our findings also showed that almost all regions were faced with increased burden of DRLECs. Along with the global epidemic of diabetes and interventions to prevent death and prolong life, more people were living with diabetes, and this increasingly complicated population are placing extra challenge on health systems worldwide. The most affected regions found in this study were North Africa and Middle East, Central Latin America and Oceania, perhaps not surprisingly, as these were the same regions most affected by diabetes,(19) however inadequate healthcare provision might be another underlying factor. An attempt to evaluate healthcare system performance in GBD is via a ratio of actual disease burden to expected disease burden. If the ratio is larger than one (actual burden exceeds expected burden), it is suggested that healthcare systems in those geographical locations are not performing to levels necessary to cope with the specific disease.(19) In both Central Latin America and Oceania, actual YLDs from diabetes significantly outnumbered the expected by two-fold, indicating that the quality of local healthcare are not meeting the needs of their diabetes population.(19) Another attempt GBD has made to assess healthcare is via the establishment of Health Access Quality index which assesses personal healthcare access and quality for regions and countries.(39) GBD reports that Oceania scored 36.0 out of 100 possible total score. Though North Africa and Middle East scored a higher 55.8, large between-country variation exists, ranging from Afghanistan (25.9) to Lebanon (85.6).(39) Interestingly, only High-income Asia-Pacific (Japan, South Korea, Singapore and Brunei) saw reductions in disability burden from almost every DRLEC since 1990. Perhaps researchers could investigate the strategies employed in this region that may have led to their apparent DRLEC success, and in turn employ in those regions most affected.

Several limitations should be taken into consideration when interpreting these findings. First, our estimates for diabetic neuropathy may be an over-estimate. Unlike the other three outcomes, neuropathy can affect more than just lower extremities. Whilst, the GBD definition of diabetic neuropathy included only peripheral neuropathy, this does mean that upper as well as lower extremities were included. However, peripheral neuropathy is known to overwhelmingly affect lower extremities so any over-estimate should be minimal.(6) Conversely, if we chose to exclude neuropathy it would have resulted in a significant underestimate of the overall burden.(4, 5) Second, we did not have data to include other diabetic complications of the lower extremity that also cause significant disability, such as peripheral artery disease, foot infections and minor amputations.(4, 5) Thus, our overall DRLEC burden may in fact be an under-estimate of the actual overall DRLECs, and there's a need to improve the way DRLECs are captured and categorized in future GBD iterations so that the overall DRLEC burdens are more comprehensively estimated. Third, we were reliant on GBD data, and caution is needed when interpreting the results, particularly in data-sparse countries with wide 95% UI around estimates. While there has been significant investment in improving GBD global disease modelling approaches, there is still a need for more investment to improve vital registration and data in developing countries. The accuracy of DRLECs estimates depend on the availability of reliable and comparable information, and as better-quality evidence becomes available, future disease modelling at a global level will be more accurate and reliable. Fourth, disability weights, a crucial component of YLDs, were derived from models using survey data, and responses from these surveys were sensitive to details included in the lay descriptions.(34) Further improvements on disability weight methodology may also improve the precision of estimates in future. Fifth, some results, including the overall DRLEC prevalence and YLDs estimates were a simple summation of individual DRLECs by the authors, and 95%UI for these findings were not estimated. Last, diabetes is also associated with increased risk of mortality, however given the complex inter-relationships between diabetes complications and other comorbidities causing mortality, estimating the impact of individual complications on mortality remains challenging, hence we were unable to investigate the mortality burden of DRLECs.

Despite these limitations, results from this study adds significant novel knowledge on the global burden of DRLECs. DRLECs appear to be a large contributor to the global disability burden, and this age-standardized burden has increased by 15-31% since 1990. Disability from DRLECs appeared to disproportionately affect males, the middle-to-older aged groups, and specific regions. It is recommended that these populations are targeted by DRLEC strategies shown to reduce these burdens. Whilst general diabetes management strategies may help to reduce the DRLEC disability burden via prevention of complications, evidence suggest that the most significant DRLEC burden reductions were from DRLEC-specific strategies, such as the introduction of interdisciplinary foot care services adhering to evidence-based guidelines.(4, 5, 11) Thus, in a similar manner to how *CKD due to diabetes mellitus* is treated as a separate cause by GBD and others, we also recommend that DRLECs should be monitored and addressed separately. This would allow ongoing interpretations of DRLECs and will particularly facilitate worldwide policy makers and clinicians to tackle DRLECs, a leading cause of global disability burden.

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Duality of interest

We declare no competing interests

Contribution Statement

YZ contributed to data acquisition, analysis and interpretation, drafted and critically reviewed the paper for intellectual content. PAL contributed to conception and design of the study, data analysis and interpretation, drafted and critically reviewed the paper for intellectual content. SMM contributed to data analysis and interpretation and critical reviewed the paper for intellectual content. JJvN and DGA contributed to conception and design of the study and critical reviewed the paper for intellectual content. REP contributed to conception and design of the study, data acquisition, analysis and interpretation, drafted and critical reviewed the paper for intellectual content. All authors reviewed and approved the final version of the article. The corresponding author had full access to all the data and final responsibility for publication submission.

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Table 1 Global prevalence, years lived with disability (YLDs) in 2016, and percentage change from 1990 to 2016, of diabetes and diabetes-related lower extremity complications (DRLECs)

	Diabetes	Neuropathy	Foot ulcer	Amputation without prosthesis	Amputation with prosthesis	Overall DRLECs
Prevalence in 2016						
counts	383,453,015 (352,587,613 to 414,576,179)	105,576,315 (85515449 to 127846934)	18,582,635 (14,983,869 to 22,879,466)	4,259,294 (3,693,664 to 4,869,809)	2,533,616 (2,089,427 to 3,035,649)	130,951,860
rates	5.187% (4.769 to 5.608)	1.428% (1.157 to 1.730)	0.251% (0.203 to 0.310)	0.058% (0.050 to 0.066)	0.034% (0.028 to 0.041)	1.771%
ASR	5334.8 (4908.6 to 5759.7)	1479.8 (1200.7 to 1782.6)	269.7 (217.1 to 331.6)	60.6 (52.6 to 69.2)	36.7 (30.2 to 43.9)	1848.0
Mean change in prevalence from 1990 to 2016^						
of counts	112.6%	110.4%	129.8%	140.7%	116.3%	114.0%
of rates	51.4%	49.0%	63.2%	71.7%	53.5%	63.0%
of ASR	19.5%	14.6%	20.5%	31.0%	15.4%	15.9%
YLDs in 2016						
counts	28,583,685 (19,533,803 to 39,574,719)	12,880,541 (8,300,709 to 18,842,744)	2,510,297 (1,655,321 to 3,562,773)	1,066,553 (753,179 to 1,436,595)	380,147 (255,740 to 528,955)	16,837,538
Proportion*	3.51% (3.05 to 4.05)	1.582% (1.019 to 2.314)	0.308% (0.203 to 0.437)	0.131% (0.092 to 0.176)	0.047% (0.031 to 0.065)	2.068%
ASR	398.8 (273.6 to 550.9)	179.9 (115.9 to 262.7)	36.3 (23.8 to 51.4)	15.1 (10.6 to 20.4)	5.4 (3.6 to 7.6)	236.7
Mean change in YLDs from 1990 to 2016^						
of counts	113.7%	110.4%	129.7%	140.3%	115.8%	114.9%
of proportion	41.0%	49.8%	63.3%	71.1%	53.4%	53.0%
of ASR	18.8%	14.9%	20.6%	31.5%	15.8%	16.7%

ASR, age-standardized rate.

Prevalence and YLDs of diabetes, neuropathy, foot ulcer, amputation without prosthesis, and amputation with prosthesis are presented as mean (95% uncertainty intervals) in counts, rate/proportion and age-standardized rate (ASR) was presented; mean estimates were presented for overall DRLECs. Rates and age-standardized rates were calculated based on the GBD 2016 reference population.(19),(32) *Proportion means the proportion of overall global YLDs from all causes in the corresponding year. Overall global YLDs are 532,835,179 in 1990 and 805,393,000 in 2016, and are sourced from GBD Compare Viz Hub (https://gbd2016.healthdata.org/gbd-compare/)

^: Mean change of counts, rate/proportion or age-standardized rates was calculated with the formula: [(value in 2016 – value in 1990)/value in 1990]*100%

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Figure 1: Sex and age composition of global YLD counts (A) and rates (B) for diabetes-related lower extremity complications (DRLECs) in 1990 and 2016.

Figure 2: Regional YLD rates (age-standardized, per 100,000) of diabetes-related lower extremity complications (DRLECs) in 1990 ,2016, and percentage change from 1990 to 2019.

Legend: *% change is for the region denoted in 2016.

Figure 3: World map of age-standardized YLD rates (per 100,000) for overall diabetes-related lower extremity complications (DRLECs) in 1990(A) and 2016(B)