Diabetes-related lower-extremity complications are a leading cause of the global burden of disability

Short Title: Diabetic leg complications a leading cause global disability

Globally ~435 million people have diabetes (1), with 19-34% (~83-148 million) of those estimated to develop foot ulcers in their lifetime (2). Foot ulcers are typically precipitated by other diabetes-related lower-extremity complications (DRLECs) including peripheral neuropathy and peripheral vascular disease (2, 3). Collectively, DRLECs are a leading cause of infection, hospitalisation and amputation outcomes (2-5); yet, these outcomes are readily preventable with evidence-based DRLEC care (6, 7). This suggests the burden caused by DRLECs is a large, yet reducible, cause of the global burden of disease.

Burden of disease is measured in disability-adjusted life-years (DALYs) (8). One DALY represents one year of healthy life lost (8). DALYs are estimated by summing the years of life lost (YLLs) due to premature mortality, and years lived with disability (YLDs) (1, 8). YLLs are estimated by multiplying the number of deaths from a cause, by the years lost between the age at death from that cause and the longest normal life expectancy age (8); YLDs are estimated by multiplying the prevalence of a cause, by a disability weight that reflects the severity of that cause (1).

The Global Burden of Disease Study (GBD) has published global YLD, YLL and DALY estimates for >300 disease and injury causes and >2,600 sequelae in several iterations over the last decade (GBD2010-GBD2016) (1, 8, 9). Of most interest to the global diabetes community were ongoing estimates for “diabetes mellitus” and “chronic kidney disease (CKD) due to diabetes mellitus” (1, 8, 9). However, estimated YLDs, YLLs and DALYs for

DRLECs remained hidden within the aggregated “diabetes mellitus” estimates presented in all these GBD publications, except for the GBD2015 YLD publication (1, 8, 9).

The GBD2015 YLD publication presented disaggregated findings for “diabetes mellitus” in three summary sequelae: “uncomplicated diabetes”, “vision loss due to diabetes”, and “neuropathy and other complications of diabetes” (1). According to GBD2015 methodology, “neuropathy and other complications of diabetes” consisted of a total of four specific sequelae, i.e. those with diagnosable neuropathy: i) only, “diabetic neuropathy”; ii) and current foot ulcer, “diabetic foot due to neuropathy”; iii) and leg amputation with prosthetic limb, “diabetic neuropathy and amputation with treatment”; iv) and leg amputation without prosthetic limb, “diabetic neuropathy and amputation without treatment (1). The last three of these four specific sequelae are exclusively DRLECs, with perhaps “diabetic neuropathy” the only exception (2,3).

However, GBD2015 goes on to define “diabetic neuropathy” as being diagnosed via “validated neuropathy screening, vibration perception threshold test, nerve conduction velocity, (or) clinical exam only” in people with “pain, tingling and numbness in arms, legs, hands or feet” (1). That being the case, we suggest that not only do peripheral neuropathies make up >75% of all diabetic neuropathy cases anyway (10), but the GBD2015 publication is only referring to the diabetic peripheral neuropathies in its definition of “diabetic neuropathy” (1). Whilst, diabetic peripheral neuropathies can present in the upper extremity after the lower extremity, it nearly exclusively disables the lower extremity (10). Because it is defined by three exclusively and one nearly exclusively DRLEC sequelae (2,3), we suggest that the GBD2015 summary sequelae of “neuropathy and other complications of diabetes” (1) is suitable to use for the purposes of reporting the estimated global YLD burden caused by

DRLECs. Thus, we report the GBD2015 "neuropathy and other complications of diabetes" YLD publication findings as DRLECs findings to provide estimates of the magnitude of the global disability burden of DRLECs and compare these estimates to other causes for the first time (1).

First, GBD2015 published that diabetes affected 435 million people (1) (~5.9% of the 7.38 billion global population), ranking it 17th of all causes for prevalence (1). When diabetes was disaggregated into summary sequelae, we estimate DRLECs affected 159 million people (~2.2%) (1). As such, DRLECs would rank within the top-40 causes for prevalence; lower than CKD (~4.4%), but higher than ischaemic heart disease (IHD) (~1.5%), and cerebrovascular disease (CVD) (~0.6%) (1).

Second, GBD2015 published that diabetes accounted for 33.4 million YLDs, ranking it 6th of all causes for YLDs (1). When diabetes was disaggregated, we estimate DRLECs accounted for 61% (20.5 million) of YLDs due to diabetes, equalling 2.6% of all 792 million global YLDs (1). YLDs due to DRLECs would rank within the top-10 causes of global YLDs; higher than CKD (8.2 million), IHD (7.3 million), and CVD (6.5 million) (Figure 1) (1).

Third, GBD2015 published that diabetes had the third largest increase (32.5%) of the top-30 level 3 (disease and injury) YLD causes between 2005 and 2015 (1). When diabetes was disaggregated, we estimate DRLECs would rank as the second largest increase (35.6%) of the top-30 causes of global YLDs; higher than IHD (30.2%), CKD (23.8%), and CVD (20.7%) (1).

After interrogating the GBD2015 YLD publication, we estimate that the disability burden caused by DRLECs would rank within the top-10 leading causes of the global disability burden (1). Whilst there is a possibility that our estimated DRLEC disability burden may contain a small proportion attributable to upper extremity diabetic peripheral neuropathies, we note we were unable to include additional DRLECs in our YLD estimates as they were not disaggregated in GBD2015, such as diabetes-related "peripheral vascular disease" (1). Thus, if anything our DRLEC estimates are likely to be an underestimate. With DRLECs also resulting in mortality rates worse than many cancers (2,4,5), we recommend future GBD publications should present YLD, YLL and DALY estimates for "lower-extremity complications due to diabetes" to highlight the potentially significant overall global burden of DRLECs to policymakers, as they do for "chronic kidney disease due to diabetes" (1). In the meantime, these findings highlight the need for policymakers to prioritise policies that improve evidence-based care for people with DRLEC (6, 7), and thus, potentially reduce a large cause of the global burden of disease.

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Conflict of interest

PAL is Co-Chair of Diabetic Foot Australia.

Novelty Statement

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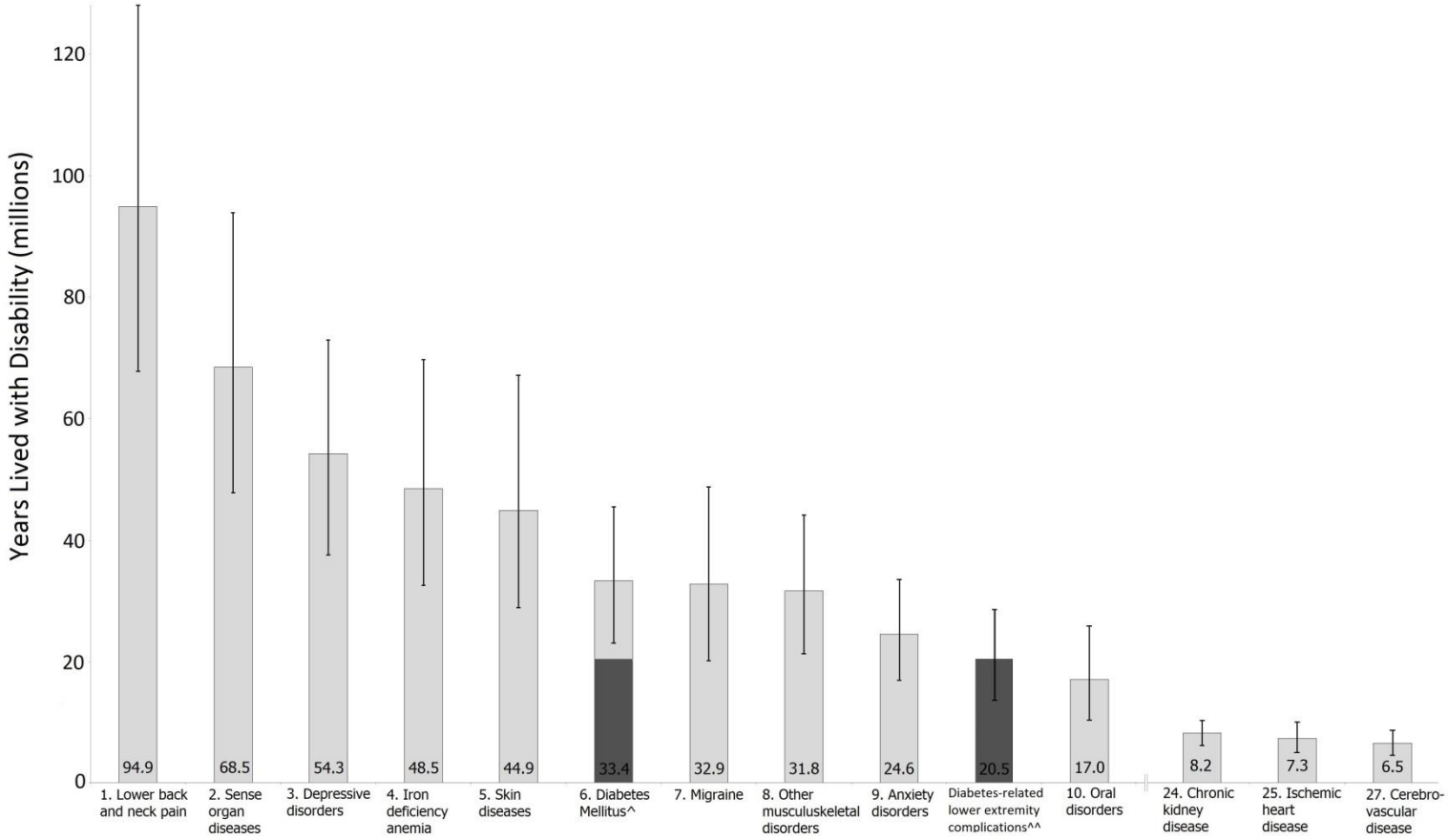

Figure 1: Leading causes of global years lived with disability (YLDs) for both sexes combined in 2015*

*Number refers to ranking of leading causes of global YLDs in 2015, using the cause breakdowns at Level 3 of the GBD cause hierarchy (e.g. 6 is 6th highest cause of global YLDs) (1); ^Diabetes mellitus includes diabetes-related lower-extremity complications YLDs (dark shading); ^^Diabetes-related lower-extremity complications defined as diabetic (peripheral) neuropathy, diabetic foot (ulcer) due to neuropathy, diabetic neuropathy and amputation with treatment, and diabetic neuropathy and amputation without treatment (1).