The Impact of Diabetic Foot Problems on Health-related Quality of Life of People with Diabetes

by

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Abstract

People with diabetes are at a greater risk of developing foot complications and this chronic condition continues to be the leading cause of non-traumatic amputations in Canada. The purpose of this thesis was to examine the impact diabetic foot problems have on health-related quality of life of people with diabetes, through a systematic review and a cross-sectional analysis of a population with type 2 diabetes living in Alberta. Both studies found an association between reduced HRQOL and diabetic foot problems. Mainly, lower physical health, measured with the SF-36/12, correlated with the severity of foot complications in people with diabetes. The highest decrement on mental health was found in people with diabetes reporting ulceration, which also had the lowest index score, measured with the EQ-5D-5L in the cross-sectional study. Individuals with either or both risk factors for diabetic foot problems, neuropathy and peripheral vascular disease were also associated with lower physical, mental and perceived health compared to individuals with diabetes but no foot complications.

This research implies that interventions to promote better quality of life are needed throughout the different stages of foot problems in people with diabetes.

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List of Abbreviations

ABCD study	Alberta's Caring for Diabetes study
ABI	Ankle Brachial Index
BMI	Body Mass Index
BP	Bodily Pain
CINAHL	Current Nursing and Allied Health Literature
DARTS	Diabetes Audit and Research in Tayside Scotland
DCCT	Diabetes Control and Complications Trial
DFU	Diabetic Foot Ulcer
DQOL	Diabetes Quality of Life
EPHPP	Effective Public Health Practice Project
EQ-5D	EuroQol 5-Dimension Questionnaire
EQ-5D-5L	5-level EuroQol 5-Dimension Questionnaire
FAAM	Foot and Ankle Ability Measure
GH	General Health
HbA1c	Glycated Hemoglobin
HRQOL	Health-related Quality of Life
HUI-3	Health Utility Index Mark 3
IDF	International Diabetes Federation
IWGDF	International Working Group on the Diabetic Foot
MCS	Mental Component Summary
MEPS	Medical Expenditure Panel Survey

MH	Mental Health
MID	Minimal Important Difference
OECD	Organization for Economic Co-operation and Development
PAID-5	Short Form of the Problem Areas in Diabetes Scale
PCS	Physical Component Summary
PF	Physical Functioning
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-analysis Protocols
PVD	Peripheral Vascular Disease
RE	Role Limitations due to Emotional Problems
RP	Role Limitations due to Physical Problems
SF	Social Functioning
SF-12	Medical Outcome Study 12-item Short Form Health Survey
SF-36	Medical Outcome Study 36-item Short Form Health Survey
SMD	Standardized Mean Difference
UKPDS	United Kingdom Prospective Diabetes Studies
VAS	Visual Analogue Scale
VT	Vitality
WHO	World Health Organization
WHO-BREF	World Health Organization Quality of Life

Chapter 1. Introduction

This thesis is in a paper format and in line with the guidelines from the Faculty of Graduate Studies and Research, University of Alberta. The thesis is separated into 4 chapters:

Chapter 1. The introductory chapter of the thesis. It reports on the background, definitions, prevalence, health-related quality of life, and economic burden of diabetic foot problems, and objectives of the thesis.

Chapter 2. A manuscript of a systematic review on the impact that foot problems have on the health-related quality of life (HRQOL) for people with diabetes.

Chapter 3. A manuscript on the impact foot problems have on health-related quality of life in people with type 2 diabetes living in Alberta, Canada.

Chapter 4. The final chapter is the general discussion and conclusion of the thesis. It shows the overall findings, their implications, strength and limitations of this thesis.

1.1. Background

Worldwide, 415 million people were diagnosed with diabetes in 2015 and it is expected that 1 out of 10 adults will have diabetes by 2040[1]. The prevalence of this chronic condition is also on the rise in Canada, which has one of the highest prevalence rates among the Organization for Economic Co-operation and Development (OECD) countries[1, 2].

Diabetes represents a major economic burden in developed countries. The Canadian health expenditure for this illness was estimated to be around US$ 14 billion in 2015[1]. A conservative economic model estimated that the direct and indirect costs of diabetes in Alberta were around 1.3 billion dollars in 2014 and by 2024 these costs could increase to 1.7 billion dollars[3]. The increase in costs are mainly due to the rise on the prevalence of type 2 diabetes which represents 90 to 95% of diabetic cases[2].

This chronic condition also represents a major clinical and societal burden. About 2.8% of all causes of death in 2012 were attributed to diabetes, that ranked as the 6th leading cause of mortality in Canada[4]. The main reasons are its association with several complications, including nerve damage, vision loss, cardiovascular disease and lower extremity problems, leading to increase in morbidity and mortality. Moreover, all of these conditions require treatment during an individual's lifetime and continuous use of health-care resources[5].

One of the most serious and costly consequences of diabetes are the development of foot problems which, if not treated, can lead to amputation[6].

1.2. Economic Burden of Diabetic Foot Disease

Diabetic-foot related complications represent a major cost for the health-care system as chronic ulcers, if infected, require extensive treatment and in worst case scenario, lead to amputations, a costly procedure. An international review published in 2005 estimated diabetic foot accounted for 7% to 20% of total expenditure on diabetes[7].

A recent study on economic burden of diabetic foot disease in Canada reported an hospitalization rate due to diabetic foot ulcers of 88 per 100,000 population[8]. The authors estimated the total cost of diabetic foot related problems in 2011 to be CND$547 millions[8]. However, this is probably an underestimation since it does not account for outpatient visits and indirect costs such

as productivity loss. The addition of indirect costs could represent an addition of 8.7% to 18.7% of total costs[9].

1.3. Diabetic foot: definition and clinical pathway

The International Working Group on the Diabetic Foot (IWGDF) defines diabetic foot as the "infection, ulceration or destruction of tissues associated with neuropathy and/ or peripheral artery disease in the lower extremity of people with diabetes"[10]. In fact, the main risk factors for diabetic foot ulcers are peripheral neuropathy, foot deformities (i.e. Charcot arthropathy), trauma and peripheral vascular disease[11, 12]. Reiber et al. identified that the combination of loss of sensation, foot deformity and trauma was the most common pathway to foot ulceration in diabetes[13].

Neuropathies are the most prevalent complications of diabetes and the main risk factors are poor glycemic control and diabetes duration[14-17]. Different nerves are affected by neuropathy resulting in a range of symptoms and clinical signs[14]. The most common types of this chronic condition are sensorimotor diabetic peripheral neuropathy (or simply peripheral neuropathy) and autonomic neuropathy[18, 19].

The majority of peripheral neuropathy cases in diabetes are asymptomatic, but around 15-25% will develop symptoms ranging from paraesthesia to hyperaesthesia, with symptoms of sharp and burning pain[20]. All these manifestations are accompanied by loss of protective sensation[18]. As a results, subjects are more likely to develop ulcers, though cohort studies on this matter had different results, mainly due to different methodologies for measuring neuropathy[21]. A recent meta-analysis reported that patients with a loss of sensation related to neuropathy had approximately 3.2 times higher odds of ulceration than those without neuropathy[22]. Peripheral neuropathies are also associated with weakness and muscle atrophy which also increases the risk for ulceration[23].

The second most common type of neuropathy is the autonomic neuropathy, which can result in reduced sweating and dryer skin that make feet more prone to callus and increase of foot temperature in the absences of peripheral vascular disease (PVD)[18, 20]. Both types of neuropathy are often found in the clinical pathway of ulceration[18].

Another consequence of neuropathy is the development of Charcot arthropathy, a foot deformity that begins with signs of local inflammations that can eventually lead to bone and joint destruction[10, 24]. This continuous process triggers foot abnormalities which increase the risk of diabetic foot ulcers, particularly when associated with loss of protective sensation[24, 25].

The second most important factor in diabetic foot ulcers is the presence of PVD, a condition in which the blood flow of lower extremities is obstructed. The diabetic population are 2 to 8 times more likely to have PVD and at a younger age and with more rapid progression of the disease than non-diabetes population[26, 27].

The diagnosis and management of PVD is extremely important because, beyond being a risk factor, studies have found worse outcomes such as longer ulcer duration, and higher prevalence of amputation and mortality in which PVD was present with ulceration[20, 28, 29]. In addition, PVD is also a risk factor for cardiovascular and cerebrovascular diseases[27]. However, the diagnosis of PVD is challenging as most diabetic people are asymptomatic and may have a false ankle brachial index (ABI) measurement because of arterial calcification[30-32]. The management of PVD in diabetes also poses another challenge as currently there are no guidelines or studies on revascularization or treatment on these specific conditions[27, 33].

Other risk factors of diabetic foot ulcers include age, previous history of ulcer, poor glycemic control, visual impairment and diabetes duration. As a results of these different factors, diabetic foot ulcers can vary in clinical signs, symptoms, size and duration. Though the majority of foot ulcers will heal, around 10 to 15% will persist and 5 to 24% of them will require amputation[26]. Worse outcomes are associated with the presence of infection which occurs after ulceration[18].

Around 85% of amputations are preceded by foot ulcerations in diabetes and most cases are preventable[34].

1.4. Prevalence, incidence and clinical burden of diabetic foot

The accurate prevalence of diabetic neuropathy is unclear because of variation in study settings and instruments used for diagnosing neuropathy. A compilation of population-based studies found that the prevalence of neuropathy ranges in a population of type 1 and type 2 diabetes from 12.8% to 54.0% and 13.1% to 45.0%, respectively[35]. Within this range, the prevalence of

diabetic neuropathy in Canada was estimated to be around 37.5% of the population with diabetes in 2008[36, 37]. A study conducted by Pirart J reported a prevalence of 50% of neuropathy in a cohort of diabetic patients followed for 25 years[38]. An accurate measure on incidence of this condition is also unclear due to the previous reasons and the fact that many cases are asymptomatic and underdiagnosed. A review based on data from the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) reported an annual incidence of neuropathy in a diabetes population to be approximately 2%[39].

Accurate measurements on the prevalence and incidence of PVD in diabetic individuals are also difficult to find. Studies on this area usually measure the prevalence within the general population and do not report it specifically for diabetes. Other methodological issues include variation on the definition and diagnosis of PVD and settings which the sample was drawn[27]. The Fremantle Diabetes Study, a large population-based study conducted in Australia, reported a 13.6% prevalence of PVD in type 2 diabetes[40]. Another large population-based study, the Framingham Heart study, found a prevalence of 20% of PVD in diabetes, although authors suggest that this is an underestimation as they only measured patients presenting PVD symptoms[41]. A Scottish based study, the DARTS study, found the incidence of PVD in type 1 and type 2 diabetes to be 5.5 and 13.6 per 1,000 subjects, respectively[42]. In Canada, PVD remains underdiagnosed and the true prevalence of the disease in the population remains unclear[43].

A serious consequence of diabetic neuropathy and PVD along with environmental factors is the diabetic foot ulcer (DFU). Studies suggest that the prevalence of ulceration in the diabetic population is from 4% to 10% and the annual incidence could range from 1.0% to 4.1%[44, 45]. The incidence becomes higher (5% to 7%) in individuals with neuropathy. The lifetime risk of foot ulcers in individuals with diabetes could be 15% to 25%[45, 46]. Based on these estimates, around 42,976 people with diabetes in Alberta had experienced a foot ulcer in 2014[47]. On a recent study using administrative data across Canada, the prevalence and incidence of diabetic foot ulcers in Alberta in 2011 were 1.9% and 1.0%, respectively[8, 37]. These results were higher compared to the national prevalence of 1.4% and incidence of 0.8%, though these numbers are probably an underestimation of the true values[8, 37].

The prognosis of diabetic foot ulcers is poor, as those with previous ulceration are at higher risk of developing another ulcer. One meta-analysis also reported that the odds of diabetic foot ulcer is 6.6 times higher in individuals with previous history of ulceration or amputation[22]. A Swedish cohort study of 558 patients with healed foot ulcers found 70% of them had a new foot ulcer and 12% had an amputation after 5 years of follow up[48]. The prognosis of foot ulcers is also poor because of the high mortality among these subjects. Two cohort studies found a mortality rate ranging from 42 to 44% after 5 years, regardless of presence of amputation[47, 48].

Diabetic foot ulcers, if not treated, can lead to amputation, another serious sequelae of diabetes. In Canada, the diabetic population was 20 times more likely to have an amputation compared to the general population[2]. Between 2011-2012, diabetes accounted for 60.3% of amputations performed in hospitals in the country[49]. Consequently, diabetes is the leading cause of non-traumatic amputations[2]. The rates of amputation are different across Canada as rates of diabetes and amputations are found to be higher among First-Nations[49]. A publication from Alberta Health reported that since 2004, the First Nations population had an amputation rate three times higher than non-First Nations[50].

Amputation represents a major clinical burden with high mortality rates. A study from 1988 found a mortality rate of 50% after two years on diabetic patients undergoing amputation[51]. More recent studies found that after five years the cumulative mortality rate ranges from 68% to 78.7%[52, 53]. Patients undergoing amputation also reported higher morbidity and lower quality of life compared to the general diabetic population[2].

1.5. Health-related Quality of Life (HRQOL)

The definition of health, according to the World Health Organization (WHO) is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[54].

There have been some criticisms on the definition of health by WHO as it is very broad and it has not been updated since its creation (1948). Most argue that it does not account for the current state of increased prevalence of chronic conditions such as diabetes in which there is no cure and the "state of complete" and "absence of disease" cannot be achieved[55]. It also does not take into

account the patient's perspective and its ability to adapt and live with the disease[55]. Nonetheless, the definition raises awareness on the importance of measuring different domains of health such as mental, social and physical function.

The need for improving measurements on health and the acknowledgement of the limitations of the concept of health in chronic conditions are some of the reasons that lead to the development of research on health-related quality of life (HRQOL).

HRQOL is a multi-dimensional concept that is mainly concerned with a person's well-being through different health domains (physical, mental and social functioning)[56]. One study reported that in 2005 over 5,300 articles were published on HRQOL, an increase of 10% on publication from the previous year, demonstrating the increase on researchers interest on HRQOL[57].

Clinical measurements such as HbA1c or presence of complications in diabetes does not fully capture the health status of the diabetic population. It does not take into consideration a patient's perception on health and their capability to adapt to the disease[58]. Thus, the use and importance of HRQOL has increased in this area. There are three main purposes for measuring HRQOL: (1) to monitor the health status of a population; (2) to measure effectiveness of an intervention; (3) to use as a potential predictor for health outcomes and death.

Studies have shown that self-rated health and HRQOL predict mortality in diabetes and other disease-specific populations (i.e. cancer)[59-61]. Other studies suggest the potential use of HRQOL as a predictor of morbidity, health-care utilization and adverse health events[62-65]. Clarke et al[62] and Li et al[64] found that HRQOL measures predicted respectively, cardiovascular hospitalizations and all-cause hospitalizations in a diabetic population. Both studies utilized different study settings, type of diabetes and different HRQOL instruments. In addition, the Eurodiale study found that the mobility domain of the EQ-5D can be used as a predictor of death and amputations which could also be associated with higher hospitalization rates[65].

The diabetic population has rated their health lower than the general population but higher compared to some other chronic diseases[66]. However, when combined with other diabetic complications[67] such as foot ulcers and amputations, we can see a higher decrement on HRQOL, especially in the physical domain[68-71].

One literature review from 2004 included qualitative and quantitative measures of HRQOL in diabetes but was mainly focused on qualitative results[69]. The study found that diabetic patients with foot ulcer had lower HRQOL than diabetic amputees[69]. It also found that peripheral neuropathy and negative feelings toward the lower extremities increased probabilities of development of ulcers[69]. However, it is important to notice that these observations came from a limited number of studies and the author did not mention how the literature search was conducted.

In 2005, Goodridge et al published a literature review on HRQOL in diabetic foot ulcers[72]. The search was conducted with a limited search strategy and in two electronic databases: The Current Nursing and Allied Health Literature (CINAHL) and Medline[72]. The review included qualitative and quantitative studies published until 2004[72]. Both type of studies reported the impact of ulcer on physical functioning, social and psychological well-being[72]. The authors also concluded there was a lack of studies on diabetic foot ulcers, in particular in the number of longitudinal studies[72].

Both literature reviews were mainly focused on different stages of diabetic foot ulcers (i.e. healed, unhealed) and amputations as there were no descriptions on impact of PVD and peripheral neuropathy on HRQOL in the diabetic population. In addition, they were prone to meta-bias as they did not follow steps of guidelines on systematic review (i.e. PRSIMA[73]) and were likely conducted by just one reviewer and limited electronic databases.

Hogg et al conducted a systematic review of studies, published until February 2011, assessing the validity and reliability of quantitative HRQOL measures on diabetic foot[68]. As a secondary aim, authors assessed the impact of HRQOL on patients with diabetic foot using the same included studies[68]. The authors reported decrements on HRQOL of diabetic patients with ulcer, regardless of it etiology, and their scores were lower compared to those without foot problems, healed ulcers and with minor amputation[68]. Decrements on health were also found in major amputations and symptomatic neuropathies[68]. The systematic review concluded lacked longitudinal studies and consequently provided limited proof of the causal relationship of diabetic foot and HRQOL[68].

The systematic review[68] did not result in any reports on quality of life of the diabetic population living in Alberta, Canada. It also did not describe the impact of PVD on HRQOL of diabetic individuals as this foot problem was not included in the systematic search, though it is an

important risk factor for ulceration and can have an impact on physical functioning. The authors did not describe whether the systematic review was according to guidelines such as the Cochrane handbook on systematic review. Thus, it is unclear how the selection, extraction and quality assessment were conducted and the presence or not of more than one reviewer during this process.

With the limitations of the current reviews, rapid increase of studies on HRQOL and changes on treatments for diabetic foot, it is important to improve the quality of systematic reviews and keep the information up to date. Additionally, studies on HRQOL of people with type 2 diabetes with or without foot problems are lacking in Alberta.

1.6. Objectives

The objectives of this thesis were to:

(1) Identify and synthesize the current evidence on the impact of diabetic foot problems on health-related quality of life through a systematic review.

(2) Assess and compare the health-related quality of life of people with type 2 diabetes with or without foot problems living in Alberta.

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Chapter 2. Systematic Review of Foot Problems and Health-related Quality of Life of People with Diabetes

2.1. Introduction

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[1]. Measurements on clinical data, morbidity and mortality are not capable of expressing all those dimensions on health. Health-related quality of life (HRQOL) measures, though, are multi-dimensional and take a person's subjective perspective of their well-being through different health domains including, but not limited to, physical, mental and social functioning.

Patients with diabetes have generally rated their quality of life lower than the general population, but higher compared to people with other chronic diseases. However, when diabetes is associated with other comorbidities, there is a significant decrement on quality of life[2]. A review on the EQ-5D conducted by Janssen et al. showed that diabetic subjects with no complications had a utility score of 0.76 (0.68, 0.83) while patients with microvascular and macro vascular complications had 0.73 (0.57–0.89) and 0.73 (0.57–0.88), respectively[3]. Some studies have also shown that diabetic individuals with foot ulcer have even lower HRQOL scores than the general diabetic population, particularly in the mobility domain that may then impact other domains such as daily activities, emotional and social functioning[4-6]. Two literature reviews also reported that ulceration and amputation decreases quality of life due to limitations on physical functioning[4, 7].

Individuals with diabetes are at constant risk of developing foot ulcers that if not treated lead to longer treatment, depression and in more seriuous cases to lost of lower limbs. In fact, diabetes has been the leading cause of non-traumatic amputations in Canada for years, even though most of them are considered preventable. This shows the need for improvement of health-care towards patients with diabetes at risk of foot problems and implementation of new interventions. Foot problems in diabetes, however, are complex and range in symptomatology and clinical diagnosis, which in turn reflect in different care and needs. Current clinical measurements are not able to capture these nuances and HRQOL measures play an important role in assessing different health domains and taking the patients'perspective into consideration for improving the quality of care.

The systematic review by Hoggs et al. (2012) examined the impact of foot diseases on diabetic patients as a secondary objective[8]. His main objective was to assess the reliability and validity of HRQOL instruments on diabetic foot diseases. The review searched for studies published until 2011 and the authors did not conclude whether there is a causal relationship or association between diabetic foot conditions and HRQOL[8].

Most studies reported on those reviews were cross-sectional and presented an association between foot problems and HRQOL. However, due to the nature of the design of these studies, authors could not conclude a causal relationship between the condition and HRQOL[4, 7, 8].

The current reviews on HRQOL in patients with diabetic foot problems did not conduct a meta-analysis and were unclear as to whether they followed guidelines on the selection, extraction and quality assessment. With this limitations in mind and the increase of studies on HRQOL, it is important to conduct a comprehensive review conforming with the guidelines.

The aim of this study was to conduct a systematic review to assess the association of diabetic foot problems and HRQOL.

2.2. Methods

The study protocol was developed before conducting the systematic review and it followed the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (Prisma-P)[9]. Conducting and reporting this review followed the Cochane and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[10, 11]. The protocol was registered at the Prospero database (CRD42015024748), an international database managed by CDR for registering protocols of systematic reviews.

2.2.1. Eligibility criteria

Studies were included if they examined the relationship between diabetic foot problems, including amputation, and HRQOL.

Studies were selected according to the following inclusion criteria, based on the PCOS framework:

- Population: Adults (over 18 years old) medically diagnosed with type 1 or 2 diabetes and presenting one of the following medically diagnosed foot problems: distal symmetrical neuropathy with confirmed signs of sensory loss, peripheral vascular disease, foot ulcer, Charcot foot and/ or amputation.
- Comparator: adults medically diagnosed with type 1 or 2 diabetes without the previously mentioned foot problems, or with a different foot complication than the case group.
- Outcome: HRQOL was measured with a previously validated self-administrative instrument.
- Studies: observational (cohort, case-control and cross-sectional studies) and experimental studies published in scientific journals until July 2015, either in English, Spanish or Portuguese.

Distal symmetrical neuropathy in diabetes is a complex disease and it can range from painful symptoms to numbness with or without loss of sensation in the toes or foot[12, 13]. In this review, we were interested in investigating neuropathy as one of the main risk factors for diabetic foot ulcer and one of the first stages of diabetic foot complications. Therefore, we included only studies with confirmed diagnosis of loss of sensation and excluded studies that defined neuropathy based on presence of pain, exclusively.

Studies were excluded if: (1) they were case-series, case-reports and editorials; (2) they qualitatively measured health-related quality of life (i.e: interviews and group assessments); (3) the HRQOL was measured using a proxy (i.e. physicians, caregivers or relatives) and it was not self-assessed; (4) studies in which the objective was to analyze the psychometric properties of HRQOL measures; (5) studies that used self-report measures on diabetes and foot problem diagnosis as those are prone to information bias; (6) studies that reported magnitude, duration and frequency of pain without associating its impact on quality of life.

2.2.2. Search Strategy

We accessed the following databases until July/2015: Medline (via Pubmed), Embase, CINAHL, PsycInfo, Scopus and Web of Science. The search strategy was developed with the assistance of a librarian. It included a combination of keywords, their synonyms and controlled vocabulary (i.e.

Mesh terms) such as “diabetic foot”, “foot ulcer”, “foot complications”, “quality of life”, “SF-36”, “EQ-5D” (Figure 2.1). The references of included studies were also searched for further studies.

1. exp diabetic foot/
2. exp diabetic neuropathy/
3. exp foot ulcer/ or ((foot or feet) and ulcer*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
4. exp foot disease/
5. exp gangrene/
6. exp osteomyelitis/
7. exp leg amputation/
8. foot amputation/
9. ("foot complication" or "foot problem" or "foot infection" or necrosis).sh.
10. ("charcot foot" or "charcot arthropathy" or "charcot osteoarthropathy" or "neuro-osteoarthropathy" or "neuropatic osteoarthropathy").sh.
11. peripheral occlusive artery disease/
12. exp peripheral vascular disease/
13. exp peripheral neuropathy/
14. ((foot or feet) and diabet*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
15. exp foot/
16. exp diabetes mellitus/
17. 15 and 16
18. 1 or 2
19. diabet*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
20. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
21. 19 and 20
22. 14 or 17 or 18 or 21
23. exp "quality of life"/
24. exp wellbeing/
25. exp quality adjusted life year/
26. ("health-related quality of life" or qol or hrql or hrqol or qaly or "health status" or "patient report outcome").sh.
27. (assess* or evaluat* or tool or instrument or scale or measure* or index or battery or questionnaire or "self-report" or "self-administration" or "survey").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
28. 26 and 27
29. short form 36/
30. exp Short Form 12/
31. ("EQ-5d" or "euroqol" or "SF-6d" or "short form" or DFS or "diabetic foot ulcer scale" or "rand-36" or norfolk or neuroqol or "cardiff wound impact schedule" or CWIS).sh.
32. 29 or 30 or 31
33. 22 and 28
34. 22 and 32
35. 33 or 34

Figure 2.1. Search strategy used on Embase. Similar search strategy was used on all databases

2.2.3. Selection Process, Data Extraction and Quality Assessment

Two reviewers independently screened the titles and abstracts. Both reviewers retrieved and assessed the full-text articles for inclusion and exclusion according to the eligibility criteria. In case of any discrepancies between reviewers, a third party was consulted. The references of included studies were assessed for additional material. Kappa statistics was calculated to

measure the agreement between reviewers and the agreement was considered fair, good and excellent if kappa was between 0.40 and 0.59, 0.60 and 0.74, and 0.75 or over, respectively[14].

One reviewer extracted the data from included studies using an extraction form and the second reviewer checked entries. The standardized form included information on general characteristics of the study (design, setting, sample size), description of HRQOL measures, and characteristics of participants.

Two reviewers independently appraised the quality of included studies using the "Quality Assessment Tool For Quantitative Studies" created by the Effective Public Health Practice Project (EPHPP)[15]. Both reviewers discussed their evaluation and resolved any discrepancies consulting a third party. The software EndNote (www.myendnoteweb.com) was used to store and manage all references found from the previously mentioned databases.

2.2.4. Meta-analysis

We conducted a meta-analysis with HRQOL measures as continuous outcomes using standardized mean difference (SMD) as the measure of effect. SMD was calculated for each outcome measure as the mean difference divided by the pooled standard deviation. Furthermore, we considered 0.2 as a small, 0.5 as a moderate and 0.8 as a large effect size[16]. We performed the random-effect model as described by the DerSimonian and Laird method to calculate the summary statistics and considered a p-value<0.05 for statistical significance[17]. To investigate heterogeineity of results, chi-squared test and I^2 statistics were calculated. We considered presence of significant heterogeineity across studies when I^2 was equal or greater than 50%, coupled with Chi-squared test p-value achieving statistical significance ($p<0.10$)[11, 18].

We chose to pool only outcome of same HRQOL instrument to facilitate interpretation of results and because each measure may have different structures and scoring system. We hypothesized that even measures with similar content would create great heterogeinity and inconsistence in the summary stiatistics.

The software Review Manager (Revman), version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to conduct the meta-analysis.

2.3. Results

The literature search identified 5,921 studies and 298 of them were included for full-text review. After examination, 22 papers describing 21 studies were included in this systematic review with 9 of them included for quantitative synthesis. The agreement between reviewers resulted in a kappa of 0.52 which is considered fair. The main reason for exclusion of studies were: no analysis of the association between foot problems and HRQOL measures and no reports on HRQOL measurements (Figure 2.2).

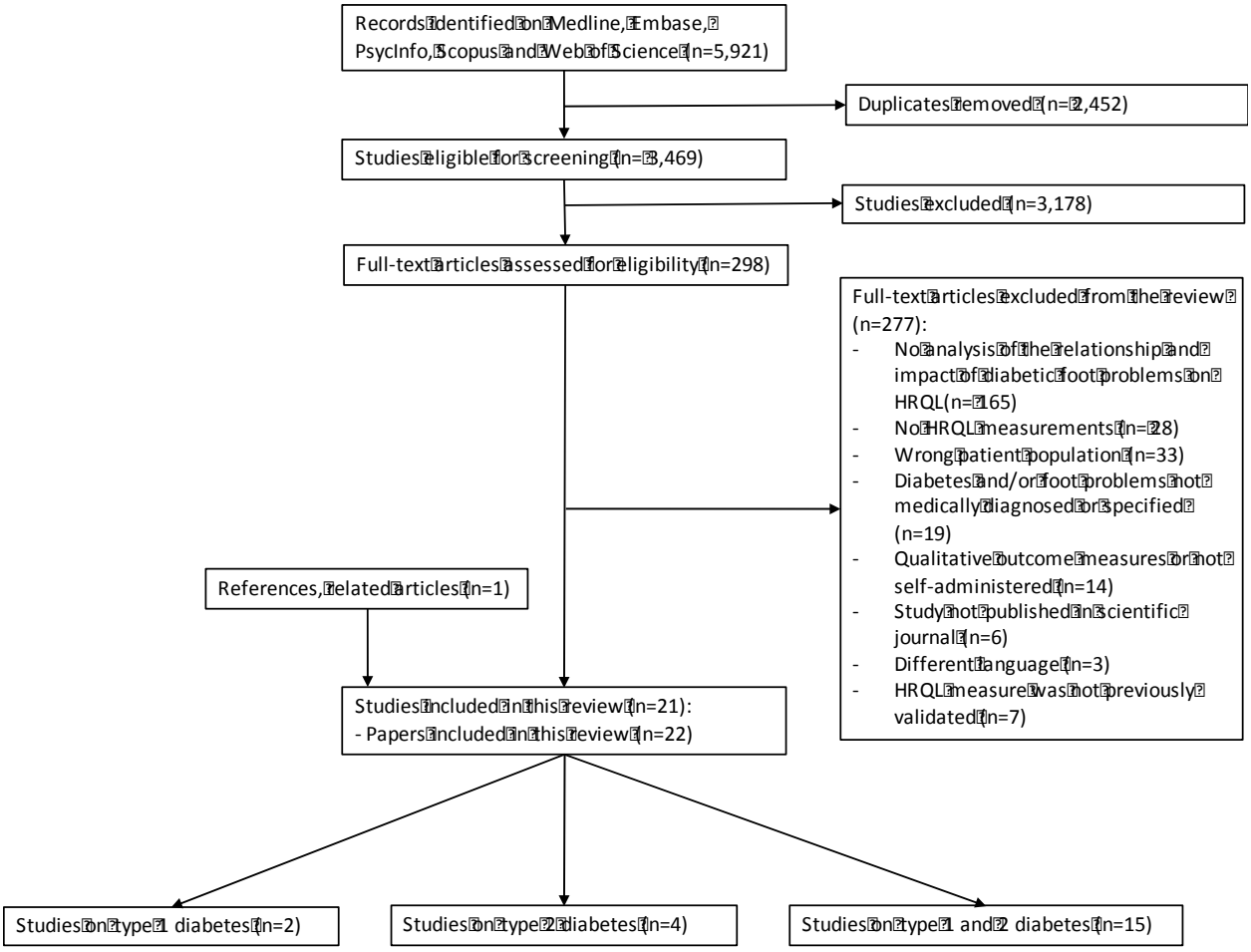

Figure 2.2. PRISMA flowchart of the systematic review search

Table 2.1. Characteristics of included studies

Reference	Study design	Population, sample n, (%male), mean diabetes duration (sd)	Diabetic foot problem criteria, sample n (%)	HRQL instrument	Overall quality
Diabetes type 1					
Lloyd, 1992[35]	Cross-sectional	Individuals with diabetes type 1 with a duration of over 25 years and registered at the Children's Hospital of Pittsburgh (USA); N = 175 (50.3); Diabetes duration = NR (NR)	DPN defined as patients with at least two criteria symptoms, decrease or absence of tendon reflexes, signs of sensory loss (light touch, pinprick, and vibration perception examination); n= 102 (58.3);	DQOL: diabetes specific instrument	Moderate
Trento, 2013[30]	Cross-sectional	Individuals with diabetes type 1 in the diabetes registry of Turin (Italy); N= 310 (53.5); Diabetes duration = 17.3 (6.3)	DPN was assessed through medical tests, though there are no details of type of tests; n= 34 (11.0)	DQOL: diabetes specific instrument	Weak
Diabetes type 2					
Altenburg, 2011[19]	Cross-sectional	Individuals with type 2 diabetes visiting an university clinic in Dresden (Germany); N=94 (74.5); Diabetes duration= 17 (NR)	Medical assessment for the presence of ulcers; n= 47 (50.0)	SF-12: generic instrument (health profile) NeuroQoL: disease-specific instrument	Moderate
Clarke, 2002[20]	Cross-sectional	Individuals newly diagnosed with type 2 diabetes participating in the UKPDS study in the United Kingdom; N= 3,192 (NR); Diabetes duration= 10.6 (2.8)	Medical assessment for the occurance of amputation; n= 19 (0.6)	EQ-5D-3L and VAS: generic instrument (preference-based)	Moderate
Ijzerman, 2012[24]	Cross-sectional	Individuals with type 2 diabetes over 50 years attending one of the 5 listed hospitals at Netherlands; N= 156 (73.7); Diabetes duration = NR (NR)	DPN was diagnosed with the standard clinical neurological examination. A cut off of 5 was used to indicate presence of DPN; n= 98 (62.8)	SF-36: generic instrument (health profile)	Weak
Wexler, 2006[37]	Cross-sectional	Individuals with type 2 diabetes attending one of the two outpatient clinics listed in the study located in Boston (USA); N= 909 (51.1); Diabetes duration= NR (NR)	PVD was assessed through medical records and billing claims; n= 130 (14.3)	HUI-3: generic instrument (preference-based)	Weak
Diabetes type 1 and 2					
Lewko, 2007[26]	Cross-sectional	Individuals with well controlled diabetes type 1 or type 2 attending the medical centre at the university of Bialystok (Poland); N= 59 (35.6); Diabetes duration: Without DPN = 13.0 (9.3); With DPN = 16.6 (11.3)	No mention on what tests were used to diagnose neuropathy; n= 22 (37.3)	SF-36: generic instrument (health profile)	Weak

Van Acker, 2009[32]	Cross-sectional	Individuals with a diagnosis of diabetes type 1 or 2 of more than one year attending one of the 40 outpatient clinics across Belgium; N= 1,111 (56.0); Diabetes duration: Type 1: 16.5 (NR); Type 2: 11.0 (NR)	DPN was considered present if patients did not feel the stimulus on more than one of the tested sites in the monofilament test or if the pinprick stimulus was not felt in at least one foot. The diagnosis of painful neuropathy was based on the presence of neuropathy and a DN4 score higher than 4; n= 478 (43.0)	SF-12: generic instrument (health profile)	Moderate
Ali Alzhrani, 2011[34]	Cross-sectional	Individuals with type 1 or 2 diabetes attending King Abdelaziz university (Saudi Arabia); N=180 (64.4); Diabetes duration: Without foot ulcer = 11.1 (1.0) With foot ulcer = 15.9 (1.3)	Foot ulcer was assessed through medical records; n= 60 (33.3)	SF-36: generic instrument (health profile)	Moderate
García-Morales, 2011[22]	Cross-sectional	Individuals with type 1 or 2 diabetes attending one of two centres in Madrid (Spain); N= 421 (58.9); Diabetes duration: Without foot ulcer = 14.6 (10.9); With foot ulcer = 15.8 (10.8)	Foot ulcer were considered present after a medical diagnosis confirmed an ulcer located bellow the malleoli; n= 163 (38.7)	SF-36: generic instrument (health profile)	Weak
Ragnarson Tennvall, 2000[28]	Cross-sectional	Individuals with type 1 or 2 diabetes treated for foot ulcer at Lund university hospital (Sweden); N= 130 (65.5); Diabetes duration= 19 (NR)	Medical records were assessed for the presence of ulcer and amputation; diabetic foot: foot ulcer: 56 (43.1); minor amputation: 52 (40.0); major amputation: 26 (20.0)	EQ-5D-3L and VAS: generic instrument (preference-based)	Weak
Raspovic, 2014[39]	Cross-sectional	Individuals with type 1 or 2 diabetes hospitalized with a diabetic foot infection at an university hospital and diabetic people who volunteered without any foot problems in the United States; N= 86 (79.1); Diabetes duration: Without foot ulcer = 9.2 (8.3) With foot ulcer = 15.0 (9.6)	Medical assessment for the presence of diabetic foot ulcers and infection; n= 43 (50.0)	SF-36: generic instrument (health profile) FAAM: disease-specific instrument	Weak
Sanjari, 2011[36]	Cross-sectional	Individuals with type 1 or 2 diabetes attending one of the four clinics in Kerman (Iran); N= 132 (62.1); Diabetes duration: Without foot ulcer = 10.4 (6.7); With foot ulcer= 11.6 (7.6)	Medical assessment for the presence of diabetic foot ulcers; n= 54 (40.9)	SF-36: generic instrument (health profile)	Weak
Valensi, 2005[31]	Cross-sectional	Individuals with type 1 or type 2 diabetes who visited one of the 98 clinicians registered in France;	Medical assessment for the presence of diabetic foot ulcers; n= 239 (67.3)	SF-36: generic instrument (health profile)	Weak

		N= 355 (60.8) Diabetes duration: Without foot ulcer = 12.6 (8.6); With foot ulcer = 17.3 (11.1)		DFU: disease-specific instrument	
Davies, 2000[21]	Cohort study	Individuals with a diagnosis of diabetes type 1 or 2 attending diabetic clinics in southeast Wales (UK); N=280 (NR); Diabetes duration= NR (NR)	Medical assessment of neuropathy through the absence of vibration, foot ulcer and amputation; DPN= 150 (53.6); foot ulcer= 20 (7.1); amputation= 10 (3.6)	SF-36: generic instrument (health profile)	Weak
Happich, 2008[23]	Cohort study	Individuals with type 1 or 2 diabetes diagnosed on or before January 2002 and treated for DPN in 2002 in Germany; N= 185 (58.9); Diabetes duration= 15 (NR)	Medical records were assessed for the presence of neuropathy with and without symptoms, foot ulcer and amputation; DPN without symptoms = 35 (18.9); DPN with symptoms= 47 (25.4); foot ulcer= 47 (17.3); amputation= 71 (38.4)	SF-12: generic instrument (health profile) Norfolk-QoL: disease-specific instrument	Moderate
Ikem, 2009[38]	Cross-sectional	Individuals with type 1 or 2 diabetes with a diabetic foot ulcer or DPN and without history of amputation and peripheral vascular disease attending an univeristy hospital in Nigeria; N= 39 (64.1); Diabetes duration= 7.4 (8.0)	Assessment of presence of ulcer. DPN was defined as patients who scored higher than 3 at the neuropathy disability score; foot ulcer= 21 (53.8); DPN= 18 (46.1)	WHO-BREF: generic instrument (health profile)	Weak
Ribu, 2008[29] Jelsness-Jorgensen, 2011[25]	Cohort study	Individuals with diabetes type 1 or 2 attending outpatient clinics in Norway; N= 257 (66.5); Diabetes duration: Without foot ulcer = 15.5 (12.2); With foot ulcer = 19.0 (13.0)	Clinical assessment for the presence of an ulcer on or bellow the malleolus; n= 127 (49.4)	SF-36: generic instrument (health profile)	Moderate
Nabuurs-Franssen, 2005[27]	Cohort study	Patients with type 1 or 2 diabetes with an unhealed ulcer for at least 4 weeks in one of the 81 centres in the US and Europe; N= 454 (NR); Diabetes duration= NR (NR)	Clinical evalution for the presence, duration and size of foot ulcer; persistent ulcer= 132 (29.1); healed ulcer= 162 (35.7)	SF-36: generic instrument (health profile)	Moderate
Winkley. 2009[33]	Cohort study	Diabetic patients with type 1 or 2 with their first ulcer presenting at hospitals foot and community chiropody clinics in four health authorities in South London; N= 241 (64.3); Diabetes duration= 14.7 (13.3)	Diabetic foot ulcer were defined as an ulcer in the anatomical foot, with a full-thickness break in the epithelium with a minimum width of 5mm	SF-36: generic instrument (health profile)	Moderate

NR: not reported

2.3.1. Description and Quality Assessment of Included Studies

The majority (67%) of studies were conducted in Europe[19-33] and were funded by health research institutes[20, 21, 24, 25, 28, 29, 34-37] (43%)(Table 2.1). The overall quality of studies was week to moderate (Table 2.1). Given that majority (67%) of studies were cross-sectional[19, 22, 24, 26, 28, 30-32, 34-39] they would be considered as a weak design for inference of causality. In addition, most studies controlled for age, gender and diabetes duration as confounding variables, but lack measurement or control for other possible confounders such as comorbidities, economic and smoking status[21-25, 27-29, 31, 37, 39, 40]. As a result, the majority were also considered weak for control of confounders.

2.3.2. Participants

The included sample sizes varied from 59 to 6,251 and the number of participants with foot problems ranged from 19 to 239. Most studies were on patients with diabetic foot ulcers, followed by subjects with diabetic peripheral neuropathy. 19% of studies included amputees and only one study was on patients with Charcot foot and another one studying the association of peripheral vascular disease and HRQOL (Table 2.1).

Figure 2 shows that only 2 studies[30, 35] were on type 1 diabetes with the mean age ranging from 32.8 to 37.3, while 4 studies[19, 20, 24, 37] were on exclusively on type 2 diabetes patients and these patients were older as their mean age ranged from 62 to 68 years old. 15 studies[21-23, 25-29, 31-34, 36, 38-40] were on both type of diabetes with majority of participants diagnosed with type 2 diabetes and with mean age varying from 46 to 68 years old (Table 2.1).

2.3.3. Health-related Quality of Life

The methods to assess HRQOL varied and 10 different instruments were used in the 21 included studies. All studies, apart from two, applied a generic instrument and the most common measures were: the SF-36 (n=11), followed by the SF-12 with 3 studies and the EQ-5D-3L with 2 studies (Table 2.1). A total of five specific HRQOL instruments were used: three were specific to diabetic foot problems (DFU[31], Norfolk-QoL[23], NeuroQol[19]), one was specific to foot problems (FAAM[39, 40]) and one was a diabetic specific measure (DQOL[30, 35]) (Table 2.1).

Two studies[30, 35] with subjects with type 1 diabetes that assessed the association and impact of neuropathy in HRQOL measured with the diabetes quality of life instrument (DQOL). Both studies did not find significant differences on the overall DQOL score between patients with and without neuropathy after controlling for confounding variables[30, 35]. Trento et al[30] also did not find any differences for each of the four domains of DQOL.

Welxler et al found that type 2 diabetes participants with peripheral vascular disease had lower HRQOL compared to those without the vascular disease[37]. However, the results were based on simple descriptive statistics prone to confounding variables.

Studies on neuropathy with type 2 or both types of diabetes used different diagnostic tools and criteria for defining the presence of this foot problem. The majority of these studies found no statistical difference between patients with and without neuropathy on physical and mental health[24, 26, 32]. Van Acker et al[32] and Happich et al[23] found that while asymptomatic patients had no differences in the physical and mental scores of SF-12, patients with neuropathic symptoms had significant decrements in both domains. Happich et al also reported worse health in symptomatic neuropathy measured through a disease speficic instrument[23].

The progression of neuropathy can lead to the diabetic Charcot foot, which, according to Raspovic and Wukich,[40] had lower scores on physical functioning, physical role, bodily pain, general health, vitality, social functioning and role emotional. Measures on physical health were lower for patients with Charcot foot, but there were no differences between both groups on mental health[40].

The majority of cross-sectional studies reported that participants with diabetic foot ulcer had lower social, emotional, mental and physical health when compared to those without them and the general diabetic population[22, 25, 31, 34, 38, 39]. In addition, the number, duration and severity of ulcers were correlated with lower physical, social, emotional, vitality domains and general health[31]. One study found that diabetic foot ulcer was correlated with lower HRQOL, but it was statistically significant only on the physical functioning domain ($p<0.001$)[36]. However, it is important to note that the control group (i.e. patients without diabetic foot ulcer) in this Iranian study had low scores in all SF-36 domains compared to control groups of other studies[36].

Three studies assessed longitudinal data, assessing changes in SF-36 of patients with diabetic foot ulcer for periods varying from 8 to 18 months[27, 29, 33]. Winkley et al[33] reported that patients who had a recurrence of foot ulcer, an amputation or unhealed ulcer after 18 months had significantly lower

mental health than patients who healed but no statistically significant differences were found in their physical health. However, Nabuurs-Franssen et al[27] and Ribu et al[29] found that at the end of follow up patients with healed ulcer had better HRQOL than those with persistent ulcer, mainly in the social functioning, emotional and physical domains. While Nabuurs-Franssen et al[27] reports that healed patients improved the previously mentioned health domains and patients with persistent ulcer deteriorated, Ribu et al[29] found that only social functioning changed significantly through time for both groups and patients with persistent ulcer also reported deterioration of mental health over the period.

Studies on patients with an amputation reported significant decrements on utility scores measured by the EQ-5D[20, 28]. Clarke reported that amputation reduced the utility score by 0.280 (95%CI: -0.389, -0.170, $p<0.001$) and had greater impact than other comorbidities such as stroke and myocardial infarction[20], while Ragnarson-Tenvall showed that a major amputation decreased the index score by 0.257 ($p=0.001$)[20, 28]. However, both studies had a very small sample of amputees.

Only three studies compared different stages of foot disease (neuropathy, foot ulcer and amputation) in the same population[21, 23, 28]. One study described lower utility scores between groups with ulcer and minor amputation, both with better perceived health compared to the group with major amputation[28]. Davies, comparing foot complications, found the largest decrement in physical summary score in patients with an amputation followed by those with neuropathy, but little differences in this score were found for individuals with an ulcer[21]. The study also reported that patients treating for ulcer had the largest decrement in mental summary score, while those with an amputation were not different in this domain from patients with no foot complication[21]. Differently, Happich reported similar decrements on physical and mental summary score associated with ulcer and amputation[23].

2.3.4. Meta-analysis

We conducted a meta-analysis with the 8 health domains and summary scores of the SF-36 and SF-12 as the outcome measures. Studies were included if they presented both scores and standard deviations. We excluded the study from Ali Alzahrani[34] from the analysis as the scores were calculated differently from the other studies.

Table 2.2 shows the results of the meta-analysis comparing patients diagnosed with diabetes and with or without foot ulcer, in which heterogeneity ranged from 29 to 91%. All domains had significant heterogeneity ($p<0.10$, $I^2 \geq 50\%$), apart from the mental component summary. Four studies[22, 29, 36, 39] were included for assessment of the health domains, while 5 studies were included for analysis of summary scores[19, 21, 29, 33, 39]. Small to medium effect size were found for vitality, role emotional, mental health domains and mental component summary score, though mental health domain did not achieve statistical significance. The other health domains had medium to large effect size which were also statistically significant. Further details are found in Appendix A.

We also analyzed the differences between patients with diabetes with and without neuropathy and found only statistical significance in the phycial functioning domain and physical component summary score with small to medium effect size (Table 2.3). Only the role emotional domain presented significant heterogeneity, although there were only two studies reporting the summary scores[21, 26]. Further details on our meta-analysis are described on Appendix A.

Table 2.2. Meta-analysis of SF-36 and SF-12 domains and summary scores comparing participants with and without foot ulcer

Domain	Number of studies	Participants	Heterogeneity. I^2 (%)	Effect estimate (SMD) 95% CI	
Physical functioning	4	710	71	-0.94	[-1.28, -0.61]
Role physical	4	705	91	-0.94	[-1.54, -0.33]
Bodily pain	4	715	80	-0.54	[-0.92, -0.15]
General health	4	713	80	-0.58	[-0.97, -0.18]
Vitality	4	712	75	-0.47	[-0.82, -0.12]
Social functioning	4	715	70	-0.66	[-0.98, -0.34]
Role emotional	4	709	64	-0.36	[-0.65, -0.07]
Mental health	4	711	84	-0.42	[-0.84, 0.01]
Physical component summary	5	511	89	-0.68	[-1.30, -0.06]
Mental component summary	5	511	29	-0.28	[-0.51, -0.04]

Table 2.3. Meta-analysis of SF-36 and SF-12 domains and summary scores comparing participants with and without peripheral neuropathy

Domain	Number of studies	Participants	Heterogeneity. I^2 (%)	Effect estimate (SMD)	95% CI
Physical functioning	3	446	0	-0.25	[-0.45, -0.06]
Role physical	3	446	26	-0.11	[-0.35, 0.13]
Bodily pain	3	446	34	-0.14	[-0.40, 0.11]
General health	3	446	0	-0.16	[-0.35, 0.04]
Vitality	3	446	0	0.09	[-0.10, 0.29]
Social functioning	3	446	48	0.01	[-0.29, 0.30]
Role emotional	3	446	72	0.07	[-0.34, 0.48]
Mental health	3	446	0	0.10	[-0.09, 0.29]
Physical component summary	2	309	0	-0.39	[-0.62, -0.16]
Mental component summary	2	309	37	0.05	[-0.29, 0.39]

2.4. Discussion

This study attempted to investigate the current evidence of the impact foot problems have on HRQOL of individuals diagnosed with diabetes.This systematic review included 21 studies, mostly cross-sectional, of moderate to week methodological quality that is decreasing the generalizability and accuracy of our results. We found that diabetic foot complications are associated with impairment in HRQOL. While neuropathy was associated with lower physical functioning, patients with ulcer, a more advanced stage, had significant decrements in social, physical and mental health. Amputation was also associated with lower HRQOL, but it remains unclear, whether this condition leads to larger decrements in health domains than diabetic foot ulcers.

There was a lack of population-based studies as most studies were performed within hospitals and outpatient clinics. We also found that most studies included both types of diabetes with majority of patients being type 2. Therefore, most of our findings are more of a reflection on HRQOL in foot problems of type 2 diabetes.

There were only two studies[30, 35] with type 1 diabetic population included in our review and both found no decrements in quality of life on patients with neuropathy compared with non-neuropathy patients. A possible reason for the lack of studies on type 1 diabetes is the much lower prevalence of type 1 compared to type 2 diabetes. Both included studies[30, 35] varied in settings, duration of disease and analysis approach that call for caution while interpreting the results.

An earlier systematic review by Hogg et al analyzed the impact of foot conditions on HRQOL as a secondary objective[8]. They determined that the advancing stages of foot problems were correlated with decrements on quality of life, though caution on generalizability was required, mainly in patients with amputation[8]. Compared to Hogg's work[8], our systematic review included fewer studies as some studies included in their work did not meet our inclusion criteria. Similarly, through meta-analysis, we found that neuropathy had only small and not statistically significant effect size, whereas ulceration, a more advanced stage of diabetic foot, had a significant medium to large effect on most domains of HRQOL measured with a generic instrument. Our review also pointed to an association of lower HRQOL with amputation, but it was unclear whether this condition was different from ulceration in terms of quality of life. The studies with a group of amputees were small in sample size and had a lack of control for confounding variables. The only prospective cohort[33] following patients with diabetic foot ulcer who underwent amputation found no additional decrement on physical and mental health, though the sample size was small (26 out of 241 patients).

We found a lack of studies exlusively on diabetic patients with peripheral vascular disease and Charcot foot with the included studies prone to confounding variables and weak study design. Consequently this is limiting the validity of correlation between diabetic foot disease and lower HRQOL in our study. An explanation for lack of HRQOL measurements on peripheral vascular disease is that some diabetes studies, in order to improve statistical power at the costs of loosing information, categorize peripheral vascular disease with other comorbidities or as a macrovascular complication along with stroke and coronary artery disease.

We found that majority of investigators prefer the use of generic HRQOL measures such as the SF-36 compared to disease specific measures. The advantage is that it allows for comparison with other diabetic complications as well as other chronic conditions. The issue is that these measures may not be sensitive or responsive to specific issues of diabetes and diabetic foot conditions. Therefore, the lack of significance on some health domains of these foot conditions do not necessarily mean these conditions do not have an impact on HRQOL measurements. For that reason, it is advisable to use a specific and a generic HRQOL instrument in studies comparing diabetes complications. We also found that some authors did not describe how scores were calculated. Further, two studies calculated an overall score for the SF-36, even though the guidelines for this tool do not advise this approach[22, 36].

The strength of this study were the performance of search in different databases with assistance of a librarian and conduction of every step following the PRISMA and Chocrane handbook guidelines. Another strength was the performance of a meta-analysis, a quantitative analysis, showing the effect size of ulceration and neuropathy in different health domains. The use of standardized mean difference (SMD) has the advantage of easy calculation and interpretation. The disadvantage of this type of estimate is that it lacks accountability for differences between participants and variation of standard deviation. Some authors have suggested alternatives to SMD by using minimal important difference (MID) to standardized the mean differences, instead of the standard deviation[41, 42].

One criticism of our review is that we excluded studies that based on the self-report foot diagnosis. A result of that is the exclusion of some population-based studies with a larger sample size. On the other hand, these studies are more likely prone to information bias[43, 44], specially because neuropathy and peripheral vascular disease can be asymptomatic. Another criticism is that we pooled participants independently of their diabetes type. Participants with type 1 and type 2 diabetes will have different experiences through life and perspective on their health, as the former type usually apperas in childhood and the later is associated with other comorbidities. However, Van Acker et al[32] reported no significant difference between participants with type 1 and 2 on the impact of neuropathy in HRQOL. It was our initial intention to run sub-analysis based on the type of diabetes, but the lack of studies with type 1 participants while majority included both types impeded that.

The nature of our research question limits us to observational studies that are at higher risk of bias and confounding variables. Most included studies controlled for age, gender, diabetes duration and HbA1c. However, we found that some studies did not mention any control for confounding variables and lack of measurement of diabetic complications that could influence results. The lack of studies with higher methodological quality, prospective design with longer follow up, larger sample size of participants with amputation, peripheral vascular disease, Charcot foot within the same population limits the validity of the association and magnitude foot conditions have on HRQOL.

There are also methodological limitations in this systematic review. First, we limited to studies published in three different languages and into scientific journals. Consequently, there is a possibility of publication bias as we did not search the grey literature. Second, we did not attempt to

contact authors of included studies to improve the quality of information. Third, the authors of this review were not blinded to information of the included studies as our resources were limited. Finally, one criticism was the performance of meta-analysis even with the presence of high heterogeneity.

2.5. Conclusion

Studies have shown that diabetic foot complications are associated with decreased HRQOL and the severity of the condition correlates with lower HRQOL. However, there were few studies conducted with disease-specific instruments and comparing the different stages of diabetic foot diseases in a population-based sample.

Future cohort studies following diabetic patients and the changes of HRQOL over the evolution of the foot satus would be needed to further strenthening our findings as well as providing information from the causal relationship between them. This would improve our knowledge on the health status of these patients and what health domains could be the target in interventions leading to better well-being of diabetic population.

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Chapter 3. Health-related Quality of Life of Adults with Type 2 Diabetes Reporting Foot Problems in Alberta

3.1. Introduction

The International Diabetes Federation estimates that 415 million people have been diagnosed with diabetes in 2015 and the prevalence will rise to more than 642 million cases by 2040[1]. Type 2 diabetes represents the majority of these cases up to 91% in high-income countries[2, 3]. About 2.8% of all deaths in 2012 were attributed to diabetes, which ranked the condition as the 6th leading cause of mortality in Canada[4]. In addition, individuals with diabetes have reported lower health-related quality of life (HRQOL) compared to the general population[5]. This is due to several complications associated with diabetes such as vision impairment, renal diseases, cardiovascular problems and diabetic foot problems including ulcers. In fact, diabetes is the leading cause of non-traumatic amputations and 85% of them are caused by non-healing of diabetic foot ulcers[6].

Distal symmetrical neuropathy and peripheral vascular disease (PVD) are two important risk factors for the development of foot ulcers[7, 8]. Both conditions cause patients to loose sensitivity and have poor circulation in the lower extremities that can also delay healing time and lead to amputations[7-9].

Two literature reviews have shown that diabetic foot ulcers and amputations have a negative effect on HRQOL, especially in the physical health domain. However, studies were unclear on the impact foot problems have on mental health as they differ in clinical settings, definition of foot problems, and used HRQOL instruments[10, 11]. There is lack of evidence on the extent neuropathy and peripheral vascular disease affect HRQOL in diabetes[12]. In addition, there are no reports on HRQOL of the diabetic population with foot problems living in Alberta, Canada. It is important to assess HRQOL in the provincial level because these measurements are affected by culture and ethnicity background. Such information may also assist health-care professionals to make appropriate interventions targeting the affected health domains. The aims of this study, was to assess and compare the HRQOL between people with type 2 diabetes with and without foot problems (neuropathy, PVD, ulcer and amputation) living in Alberta.

3.2. Methods

3.2.1. Study Population

The data were obtained from the Alberta's Caring for Diabetes (ABCD) cohort study, an ongoing prospective observational study funded by Alberta Health. The overall aims of the ABCD study are to better understand the factors affecting care and outcomes in patients with type 2 diabetes in Alberta. The study included 2040 individuals over 18 years of age with type 2 diabetes, who could communicate in English and signed the consent form. The recruitment period was from December 2011 to December 2013. Further information on the design, rationale and baseline characteristics of the ABCD study sample can be found elsewhere[13, 14].

3.2.2. Measures

A self-administered questionnaire was mailed to all participants who completed the informed consent form. The survey included questions on socio-demographic, health, lifestyle and diabetes-related variables, comorbidities, care management and health-related quality of life.

Additional questions on foot complications were also included in the survey. Participants were asked to report if they have ever been diagnosed with any of the following foot problems: neuropathy, peripheral vascular disease (PVD), ulcer/infection, and gangrene/amputation.

The survey also included questions on ever being diagnosed by a health care professional on the presence of: obesity, respiratory problems, arthritis, thyroid problems, cancer, retinopathy, kidney failure, heart disease and stroke. Presence of hypertension and dyslipidemia were based on self-report of either a diagnosis by a health-care professional, or taking medications for these conditions.

3.2.3. Health-related Quality of Life

HRQOL was measured using two generic instruments: The Medical Outcome Study 12-item Short Form Health Survey version 2 (SF-12 v.2) and the 5-level EuroQol 5-Dimension Questionnaire (EQ-5D-5L)[15, 16].

The EQ-5D-5L is a preference-based measure comprised of 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 5 possible levels of severity of problems: 1

"no", 2 "mild", 3 "moderate", 4 "severe", and 5 "extreme. The Canadian scoring algorithm was used to calculate the index score, which has a possible range from -0.148 to 0.949[17]. The instrument also has the visual analogue scale (VAS): as an overall health rating scale, ranging from 0 (the worst imaginable health) to 100 (the best imaginable health). However, this scale was not used in the survey.

The SF-12v.2 is a short version of the commonly used SF-36 and measures 8 different health domains: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), energy and vitality (VT), social functioning (SF), role limitation due to emotional problems (RE) and mental health (MH)[15]. We calculated the raw scores ranging from 0 to 100 for each of the health domains, where higher scores indicate better health. Two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), are derived from these eight domains and are typically the focus of the SF-12[18]. Based on the scoring system described by Fleishman JA et al, we calculated the summary scores based on the US norm population obtained from the Medical Expenditure Panel Survey (MEPS)[18].

Participants also completed the Short Form of the Problem Areas in Diabetes Scale (PAID-5), a disease-specific instrument originally composed of 20 items measuring emotional and mental distress related to diabetes. The short form contains 5 items and studies have shown reliability and validity for use on type 2 diabetes[19, 20]. The summary scale ranges from 0 to 20 with higher scores indicating more diabetes-related distress[19].

3.2.4. Statistical Analysis

Descriptive statistics were used to verify the distribution and characteristics of the socio-demographics, health status and HRQOL variables in the sample. Chi-square, Fisher's exact, t-tests, ANOVA and non-parametric tests were used to examine the differences in proportion and means among groups as applicable. Mean imputation was used for missing values (<10% of the sample) in continuous variables (age, PCS, MCS and EQ-5D index and PAID scores). The use of mean imputation in these cases were considered not to produce bias results[21].

After carrying a univariate regression analyses, the variables that were statistically significant and/or clinically important were included as independent variables in the multiple regression

models, where the HRQOL measures (PCS, MCS, EQ-5D index and PAID-5) were dependent variables. Based on clinical pathways of ulceration and amputation[8, 9], we assumed that people with neuropathy and PVD were high-risk groups, who could develop an ulcer/infection, which could culminate into the development of an amputation. Accordingly, participants were grouped into the 6 following groups: no complications; only neuropathy; only PVD; neuropathy and PVD; ulcer, and amputation regardless of concurrent presence of ulcer. In this analysis each individual was included in only one of the foot disease categories above.

To account for the possible violation of homoscedasticity and distribution of error of the HRQOL measures, we conducted a multiple linear regression combined with robust standard error, a method that has shown to generate valid measures in large samples[22]. Furthermore, we conducted a generalized linear model with gamma distribution for EQ-5D index score. Since this different approach had similar findings with the linear regression, we opted to not report those results here. The statistical analysis was conducted with STATA 13 for Mac (www.stata.com); in all cases, a p-value < 0.05 was considered for statistical significance.

3.2.5. Ethics

The study received ethical approval by the University of Alberta Health Research Ethics Board (reference # Pro00016667).

3.3. Results

3.3.1. General Characteristics of Participants

Out of the 2040 included participants, 105 individuals were excluded from the analysis due to: unknown gender (n=13) and HRQOL was measured with other measures (i.e., SF-12v.v1 and EQ-5D-3L) (n=92). The participants excluded from the analysis were significantly more educated and had lower emotional distress measured with PAID-5 than the included participants (Table 3.1).

The average age of the included sample was 64.5 (standard deviation (SD) 10.7) with average diabetes duration of 12.6 (SD 10.0) years and average of 3.5 (SD 1.7) medical conditions. The most common foot problem was PVD (29.2%) followed by neuropathy (19.2%) and ulcer (6.1%). Few people had an amputation of limbs (1.4%) (Table 3.1).

Table 3.1. Socio-demographic and clinical characteristics of the included and excluded respondents

Characteristics	Included sample (n=1,935)	Excluded sample(n=105)	p-value
Age - mean (SD)	64.5 (10.7)	61.9 (7.4)	0.13
Gender - n(%)			0.93
- Female	875 (45.2)	42 (45.6)	
- Male	1,060 (54.8)	50 (54.4)	
Marital Status - n(%)			0.79
- Married	1,379 (71.3)	80 (76.2)	
- Not Married	556 (28.7)	25 (23.8)	
Education - n(%)			0.001
- Less than high school	285 (14.7)	3 (2.9)	
- High School or more	1,650 (85.2)	102 (97.1)	
Ethnicity - n(%)			0.25
- Caucasian	1,752 (90.5)	100 (95.2)	
- Aboriginal	46 (2.4)	2 (1.9)	
- Others	137 (7.1)	3 (2.9)	
Annual household income - n(%)			0.15
- <$80,000	1,481 (76.5)	74 (70.5)	
- >=$80,000	454 (23.5)	31 (29.5)	
Insulin use - n(%)	667 (34.5)	NA	
Foot problems			
- Neuropathy - n(%)	371 (19.2)	NA	
- PVD - n(%)	564 (29.2)	NA	
- Ulcer - n(%)	118 (6.1)	NA	
- Amputation - n(%)	28 (1.4)	NA	
Number of medical conditions* - mean (SD)	3.5 (1.7)	NA	
- Dyslipidemia - n(%)	1,558 (80.5)	NA	
- Obesity - n(%)	1,093 (56.5)	NA	
- Respiratory problems - n(%)	368 (19.0)	NA	
- Arthritis - n(%)	952 (49.2)	NA	
- Thyroid Problem - n(%)	426 (22.0)	NA	
- Cancer - n(%)	262 (13.5)	NA	
- Retinopathy - n(%)	161 (8.3)	NA	
- Kidney Failure - n(%)	86 (4.4)	NA	
- Heart disease - n(%)	384 (19.8)	NA	
- Hypertension - n(%)	1,433 (74.1)	NA	
- Stroke - n(%)	135 (7.0)	NA	
Smoking - n(%)			0.58
- Never	793 (41.0)	43 (41.0)	
- Current Smoker	199 (10.3)	14 (13.3)	
- Quit smoking	943 (48.7)	48 (45.7)	
PAID-5 - mean (SD)	4.3 (4.3)	3.3 (3.7)	<0.01

p-value: included vs excluded sample; NA: not available; PAID-5: Short form of the Problem Area in Diabetes Scale; SD: standard deviation

*The number of medical conditions was calculated excluding the diabetic foot problems and was based on the presence of the following medical conditions: dyslipidemia, obesity, respiratory problems, arthritis, thyroid problem, cancer, retinopathy, kidney failure, heart disease, hypertension and stroke

3.3.2. Health-related Quality of Life

The average PCS and MCS scores were 44.25 (10.33) and 47.87 (9.39), respectively. Individuals with foot problems had lower scores in all 8 domains of SF-12 compared to their counterparts without foot problems. Participants with PVD had lower scores in all domains than participants with neuropathy, except for the bodily pain domain. As a result, the mental and physical summary scores were lower in participants with PVD than neuropathy. Participants reporting neuropathy and PVD had lower scores in all domains and summary scores of SF-12 compared to individuals who reported just one of the conditions (Table 3.2).

The lowest scores of SF-12 were found between individuals reporting an amputation and foot ulcer, with the later recording more problems in the bodily pain, social functioning, role emotional and mental health domain. Nonetheless, the lowest physical and mental summary scores were found in individuals reporting an amputation.

Table 3.2 also shows the distribution of response for each of the five dimensions of EQ-5D-5L. We found a ceiling effect on the self-care domain and low number of individuals reporting severe problems or inability in this domain. Few people with foot problems reported no pain and most participants with ulcer reported moderate pain. Individuals reporting any foot condition also described some level of problems with mobility, depression/ anxiety and moderate to severe problems with usual activities. These individuals had lower EQ-5D index scores when compared to the control group, with participants with ulcer having the lowest score.

The overall mean PAID-5 score of our sample was 4.34 (4.35). Higher distress was found in participants with foot problems, in particular participants with ulcer followed by those with an amputation (Table 3.2).

Table 3.2. Results of the SF-12v2 and proportion of response of the EQ-5D-5L

	None (n=1,214)	Neuropathy (n=123)	PVD (n=287)	Neuro & PVD (n=186)	Ulcer (n=97)	Amputation (n=28)
SF-12v.02						
PF - mean (SD)*	75.45 (30.31)	61.79 (35.26)	53.20 (34.04)	46.85 (34.87)	44.30 (32.43)	34.82 (36.85)
RP - mean (SD)*	73.39 (27.12)	63.67 (29.73)	56.03 (29.24)	48.95 (29.76)	44.98 (27.56)	33.93 (26.76)
BP - mean (SD)*	73.82 (28.40)	60. 79 (28.77)	61.66 (30.29)	53.47 (31.05)	48.81 (29.84)	49.11 (30.03)
GH - mean (SD)*	65.94 (21.50)	57.78 (23.26)	55.04 (23.65)	49.56 (25.76)	47.70 (25.95)	42.86 (26.58)
VT - mean (SD)*	56.97 (23.86)	51.02 (23.82)	48.34 (24.77)	43.08 (23.81)	43.59 (25.60)	41.97 (18.07)

SF - mean (SD)*	80.91 (25.52)	72.36 (29.99)	71.45 (28.17)	65.88 (30.27)	58.52 (31.02)	61.65 (29.27)
RE - mean (SD)*	81.89 (22.98)	74.80 (26.15)	72.12 (26.47)	71.42 (26.14)	65.39 (31.04)	66.96 (28.30)
MH - mean (SD)*	72.99 (20.07)	69.82 (20.92)	69.16 (20.01)	66.38 (21.02)	64.70 (21.39)	66.52 (21.53)
PCS - mean (SD)*	47.02 (9.22)	42.62 (10.55)	40.87 (9.97)	38.21 (10.46)	36.37 (9.74)	33.11 (9.78)
MCS - mean (SD)*	49.30 (9.00)	46.83 (9.93)	46.28 (8.90)	44.79 (9.68)	43.35 (10.20)	43.17 (9.52)
EQ-5D-5L						
Mobility - %(n)*						
No problem	58.90 (708)	32.79 (40)	31.34 (89)	21.20 (39)	16.49 (16)	10.71 (3)
Slight problem	23.13 (278)	37.70 (46)	29.93 (85)	23.91 (44)	20.62 (20)	21.43 (6)
Moderate problem	14.23 (171)	22.13 (27)	28.17 (80)	37.50 (69)	41.24 (40)	35.71 (10)
Severe problem	3.66 (44)	6.56 (8)	9.86 (28)	16.30 (30)	20.62 (20)	32.14 (9)
Unable to walk	0.08 (1)	0.82 (1)	0.70 (2)	1.09 (2)	1.03 (1)	0.00 (0)
Self-care - %(n)*						
No problem	94.01 (1,130)	84.43 (103)	84.51 (240)	75.54 (139)	67.01 (65)	75.00 (21)
Slight problem	4.74 (57)	13.11 (16)	9.51 (27)	14.67 (27)	17.53 (17)	14.29 (4)
Moderate problem	1.25 (15)	1.64 (2)	4.58 (13)	8.15 (15)	13.40 (13)	7.14 (2)
Severe problem	0.00 (0)	0.00 (0)	1.41 (4)	0.54 (1)	2.06 (2)	3.57 (1)
Unable to do it	0.00 (0)	0.82 (1)	0.00 (0)	1.09 (2)	0.00 (0)	0.00 (0)
Usual Activities - %(n)*						
No problem	62.48 (751)	43.44 (53)	40.85 (116)	27.17 (50)	19.79 (19)	21.43 (6)
Slight problem	25.54 (307)	27.87 (34)	27.46 (78)	32.61 (60)	33.33 (32)	35.71 (10)
Moderate problem	9.32 (112)	22.13 (27)	25.00 (71)	27.72 (51)	30.21 (29)	28.57 (8)
Severe problem	1.91 (23)	4.10 (5)	5.63 (16)	10.87 (20)	13.54 (13)	14.29 (4)
Unable to do it	0.75 (9)	2.46 (3)	1.06 (3)	1.63 (3)	3.12 (3)	0.00 (0)
Pain/Discomfort - %(n)*						
No problem	33.69 (405)	13.11 (16)	16.25 (46)	8.70 (16)	10.31 (10)	3.57 (1)
Slight problem	43.43 (522)	38.52 (47)	40.99 (116)	29.89 (55)	25.77 (25)	42.86 (12)
Moderate problem	18.80 (226)	36.07 (44)	31.45 (89)	38.59 (71)	43.30 (42)	32.14 (9)
Severe problem	43 (3.58)	12.30 (15)	10.25 (29)	17.39 (32)	16.49 (16)	17.86 (5)
Extreme problem	0.50 (6)	0.00 (0)	1.06 (3)	5.43 (10)	4.12 (4)	3.57 (1)
Anxiety/Depression - %(n)*						
No problem	58.65 (705)	47.54 (58)	47.89 (136)	36.96 (68)	37.50 (36)	50.00 (14)
Slight problem	27.95 (336)	31.97 (39)	33.45 (95)	34.78 (64)	33.33 (32)	35.71 (10)
Moderate problem	11.56 (139)	18.85 (23)	16.90 (48)	21.20 (39)	18.75 (18)	7.14 (2)
Severe problem	1.66 (20)	0.00 (0)	1.76 (5)	5.98 (11)	8.33 (8)	7.14 (2)
Extreme problem	0.17 (2)	1.64 (2)	0.00 (0)	1.09 (2)	2.08 (2)	0.00 (0)
EQ-5D-5L - mean (SD)	0.835 (0.132)	0.757 (0.161)	0.755 (0.167)	0.672 (0.221)	0.652 (0.230)	0.657 (0.191)
PAID-5 - mean (SD)*	3.57 (3.92)	5.02 (4.51)	4.95 (4.43)	6.18 (4.93)	6.88 (5.04)	6.70 (4.93)

*p<0.001: Overall statistical analysis

Neuro: neuropathy; PVD: peripheral vascular disease; SF-12v2: short-form-12 version 2; PF: physical functioning; RP: role limitation due to physical problems; BP: bodily pain; GH: general health; VT: energy and vitality; SF: social functioning; RE: role limitation due to emotional problems; MH: mental health; PCS: physical component summary; MCS: mental component summary; EQ-5D-5L: Euroqol -5D Health utility index; PAID-5: Short form of the Problem Area in Diabetes Scale; SD: standard deviation

Table 3.3. Results of multiple linear regression of SF-12v2 (MCS and PCS)

Variables	SF-12v2 - MCS				SF-12v2 - PCS			
	Coefficient	SE	95%CI	p-value	Coefficient	SE	95% CI	p-value
Foot problems (ref: no foot problem)								
- Neuropathy	-1.29	0.86	(-2.98, 0.40)	0.13	-2.70	0.87	(-4.42, -0.99)	0.002
- PVD	-2.59	0.58	(-3.73, -1.46)	<0.001	-3.96	0.62	(-5.17, -2.74)	<0.001
- Neuropathy and PVD	-2.98	0.75	(-4.44, -1.51)	<0.001	-5.33	0.75	(-6.80, -3.86)	<0.001
- Ulcer	-4.58	1.02	(-6.59, -2.58)	<0.001	-8.16	1.03	(-10.18, -6.13)	<0.001
- Amputation	-3.62	1.49	(-6.54, -0.70))	0.02	-10.48	1.79	(-13.99, -6.97)	<0.001
Age	0.18	0.02	(0.14, 0.22)	<0.001	-0.01	0.02	(-0.05, 0.03)	0.73
Male	0.78	0.43	(-0.06, 1.61)	0.07	1.15	0.42	(0.32, 1.98)	0.01
Married	1.60	0.48	(0.66, 2.55)	<0.001	1.48	0.49	(0.52, 2.43)	0.003
High school or more	1.91	0.55	(0.83, 2.99)	<0.001	2.33	0.59	(1.17, 3.50)	<0.001
Income >= $80,000	1.30	0.50	(0.33, 2.29)	0.01	2.38	0.49	(1.43, 3.34)	<0.001
Race (ref: Caucasian)								
- Aboriginal	2.24	1.33	(-0.38, 4.85)	0.09	4.56	1.16	(2.29, 6.83)	<0.001
- Others	-1.15	0.72	(-2.56, 0.27)	0.11	-0.17	0.72	(-1.58, 1.24)	0.81
Smoking (ref: no smoker)								
- current smoker	-1.62	0.73	(-3.05, -0.18)	0.03	-1.68	0.72	(-3.09, -0.28)	0.02
- Past smoker	0.68	0.43	(-0.17, 1.52)	0.12	-0.39	0.43	(-1.23, 0.46)	0.37
Insulin use	-1.84	0.44	(-2.71, -0.97)	<0.001	-2.03	0.45	(-2.91, -1.15)	<0.001
Medical conditions	-1.04	0.13	(-1.30, -0.78)	<0.001	-1.82	0.13	(-2.07, -1.56)	<0.001
Intercept	37.99	1.60	(34.85, 41.12)		49.72	1.63	(46.52, 52.92)	
R-squared	0.15				0.28			

Ref: reference group; PVD: peripheral vascular disease; SF-12v2: short-form-12 version 2; MCS: mental component summary; PCS: physical component summary; SE: standard error; 95%CI: 95% confidence interval

Table 3.4. Results of multiple linear regression of EQ-5D-5L index and PAID-5 score

Variables	EQ-5D-5L index score				PAID-5 score			
	Coefficient	SE	95%CI	p-value	Coefficient	SE	95% CI	p-value
Foot problems (ref: no foot problem)								
- Neuropathy	-0.052	0.014	(-0.080, -0.024)	<0.001	1.13	0.42	(0.30, 1.95)	0.01
- PAD	-0.052	0.010	(-0.072, -0.032)	<0.001	1.56	0.28	(1.02, 2.10)	<0.001
- Neuropathy and PAD	-0.113	0.016	(-0.143, -0.082)	<0.001	2.38	0.38	(1.63, 3.14)	<0.001
- Ulcer	-0.147	0.023	(-0.192, -0.102)	<0.001	3.02	0.49	(2.06, 3.98)	<0.001
- Amputation	-0.127	0.034	(-0.192, -0.061)	<0.001	2.26	0.86	(0.57, 3.94)	0.01
Age	0.001	0.000	(0.000, 0.001)	0.05	-0.10	0.01	(-0.12, -0.08)	<0.001
Male	0.015	0.007	(0.001, 0.028)	0.04	-0.21	0.20	(-0.60, 0.18)	0.29
Married	0.009	0.008	(-0.008, 0.025)	0.30	-0.34	0.22	(-0.78, 0.10)	0.13
High school or more	0.035	0.010	(0.014, 0.055)	0.001	-0.81	0.27	(-1.35, -0.27)	0.003
Income >= $80,000	0.031	0.008	(0.016, 0.046)	<0.001	-0.66	0.23	(-1.11, -0.21)	0.004
Race (ref: Caucasian)								
- Aboriginal	0.086	0.016	(0.055, 0.117)	<0.001	-0.83	0.58	(-1.98, 0.31)	0.15
- Others	0.022	0.011	(0.002, 0.043)	0.04	0.95	0.42	(0.12, 1.77)	0.02
Smoking (ref: no smoker)								
- current smoker	-0.026	0.013	(-0.051, -0.001)	0.04	0.10	0.36	(-0.60, 0.80)	0.77
- Past smoker	-0.015	0.007	(-0.028, -0.001)	0.04	-0.40	0.20	(-0.78, -0.01)	0.05
Insulin use	-0.032	0.008	(-0.048, -0.017)	<0.001	1.07	0.21	(0.66, 1.47)	<0.001
Medical conditions	-0.027	0.002	(-0.032, -0.022)	<0.001	0.19	0.06	(0.06, 0.32)	0.003
Intercept	0.837	0.029	(0.781, 0.893)		10.38	0.78	(8.86, 11.90)	
R-squared	0.25				0.15			

Ref: reference group; PVD: peripheral vascular disease; EQ-5D-5L: Euroqol -5D Health utility index; PAID-5: Short form of the Problem Area in Diabetes Scale; SE: standard error; 95%CI: 95% confidence interval

3.3.3. Multiple Linear Regression Analysis

Table 3.3 shows the results of the regression analysis for the summary components of the SF-12. After controlling for socio-demographic and other medical conditions, participants with ulcer had the largest decrement in MCS score (-4.58, $p<0.001$) followed by patients reporting amputation (-3.62, $p=0.02$). Those with neuropathy and PVD (-2.98, $p<0.001$) had lower MCS score than individuals with either neuropathy or PVD. However, this summary score in participants with diabetic neuropathy were not statistically different from those without foot complications.

Foot problems were associated with a significant decrement in PCS scores. In particular, participants with an amputation had a 10 units lower PCS score than those without foot problems. A decrement on physical health was also found in the group reporting ulceration. Participants reporting both risk factors for ulceration had lower physical health than those without any problems. In addition, the decrements reported for PVD were around 4 points while participants with neuropathy had a decrement of 2.70 (Table 3.3).

Table 3.4 shows foot problems were statistically associated with higher PAID-5 scores, after controlling for possible confounders. Individuals with ulceration had higher decrements followed by individuals reporting both neuropathy and PVD.

Compared to subjects without foot problems, those with foot conditions had significantly lower EQ-5D index scores. Among them, subjects with ulcer had the largest decrement (-0.147, $p<0.001$) followed by those with amputation (-0.127, $p<0.001$). Neuropathy and PVD had a similar decrement of 0.05 in the EQ-5D index score. The index score, measured by the EQ-5D-5L, was better for male participants as well as those with higher education and income. Number of medical conditions, and use of insulin were significantly associated with lower index scores (Table 3.4).

3.4. Discussion

This study examined the HRQOL of adults with type 2 diabetes reporting various foot problems, and compared them to those without foot problems. We found that individuals with type 2 diabetes reporting foot problems have lower physical, mental and overall perceived health

compared to those with no foot problems. Participants reporting both risk factors (neuropathy and PVD) for ulceration had lower HRQOL measurements than participants reporting only one of them. Among foot problems, ulcer was associated with the highest distress, lowest MCS and EQ-5D-5L index scores, while amputation was associated with the largest decrement in PCS.

Our study found similar results to other studies reporting decrements on physical health of patients with ulcer and amputation[23-26]. Altenburg et al found no differences in mental health, measured with the SF-12, between patients with and without foot ulcer, while other studies reported lower mental health in patients with ulceration[23, 24, 26, 27]. The differences may be due to study settings, presence of other comorbidities and ulcer severity, etiology and duration. Our analysis found that participants with ulcer had the lowest MCS scores and the results are supported by the higher PAID-5 index score, a specific measure of distress related to diabetes.

Ragnarson-Tennvall et al found that individuals with ulceration had lower EQ-5D index score than those who underwent minor amputation, but higher than those with a major amputation[28]. An explanation for our results could be associated with a low percentage of major amputation in our sample. However, we cannot test this hypothesis as the survey did not ask about the type of amputation participants underwent. It is also important to notice that our study and the one from Ragnarson-Tennvall et al included low numbers of individuals who had an amputation[28]. Overall, studies on diabetic amputations had several methodological issues (i.e. small sample size, use of proxy HRQOL measures and highly selected patients) and further analysis are required for any conclusions[10, 28, 29].

Three studies on neuropathy reported no significant differences on MCS scores between patients with and without neuropathy, which is in line with our findings[30-32]. One explanation could be that the SF-12 as a generic measure is not able to capture mental issues specifically associated with this disease[33, 34]. Once we look at the specific measure of PAID-5, we see that this foot condition is associated with diabetes-related distress. Another point is that neuropathy is a condition that gradually changes in symptoms and manifestation through time and our analysis is based on one measure at one point in time[35].

The lower PCS scores in individuals reporting ulcer or amputation are explained by their negative effects on mobility and engagement with daily activities[33, 36]. Based on interviews, individuals with ulceration also felt more anxious and scared of further potential trauma which

compromised their physical functions[37]. Both group of individuals likewise had reduced MCS scores, which were more pronounced in those with ulceration. Problems in mental health in individuals reporting an amputation have been linked to the changes in body image, physical and social limitations[38, 39]. These patients often express lack of social activities and feelings of isolation[40]. One study found that compared to controls, amputation was associated with more negative feelings towards the foot and dissatisfaction with life[35, 41]. The same study also reported that those with ulceration had an even more significant negative feeling toward the foot than both groups formerly mentioned[41]. Possible explanations are that individuals with ulcer have stated loss of hope on treatment success, frustration and emotional instability associated with the constant visits to health-care providers, changes in dressing and use of footwear[35, 36, 41].

The true prevalence of PVD in the diabetic population remains unclear [42]. This condition's impact on HRQOL measurements is understudied, though we found that PVD decrements different domains on mental, physical and overall health.

For our analysis, we made assumptions based on the pathophysiology of ulceration and amputation in diabetes. Around 85% of amputations are preceded by ulcerations and 78% of subjects with neuropathy will develop ulcers[43, 44]. We assumed that amputation and ulceration would be the main causes of negative effects on HRQOL. On the other hand, we know that: (1) some patients could have had both amputation and ulceration at the same time, though we assume that patients reporting both, would have amputation as the main cause effecting HRQOL as did Ragnarson-Tennvall[28]; (2) similarly, we assumed that foot ulcers would cause the main and same effects on HRQOL, regardless of the presence of different risk factors (neuropathy and PVD). The study design and sample size did not allow us to have more detailed analysis and obtain evidences to further validate our assumptions and results. We also could not find longitudinal studies on HRQOL of diabetic patients at high risk further developing ulcers and amputations to compare our findings. Though we understand this type of study would require many resources, it would improve our knowledge on HRQOL and clinical pathway of foot problems.

The study strengths include the use of a large population-based sample and the use of different types of HRQOL measures. The generic measurements facilitate health professionals to compare results across different diseases. In particular, the EQ-5D-5L index measurements can further be

used in cost-effectiveness studies of new interventions on diabetic foot. The index score was based on the Canadian preference-based measures and on the 5L instruments that allow for lower ceiling effect and description of 3,125 possible health states instead of 243 found in the previous version. Another advantage is on the use of a diabetic-specific measure, the PAID-5, which assess specific concerns related to diabetes that are not capture by generic instruments.

Although, the ABCD cohort used a comprehensive recruitment using several approaches, there was a low number of the aboriginal and immigrant respondents. Our analysis showed that aboriginals had better HRQOL measurements than Caucasians, which contradicts findings from other studies[45, 46]. These results are likely due to selection bias and small number of Aboriginal people in this study.

The study also has other limitations. First, there is an association between diabetic foot problems and quality of life but we cannot infer a causal relationship as this study used cross-sectional data. Second, the characteristics and diabetic complications were self-reported and prone to information bias, especially because neuropathy and PVD are asymptomatic conditions and the prevalence of these diseases could be underestimated in our study. Third, there were not many cases of reported amputations that could limit the generalizability of our results. Fourth, the excluded sample was more educated and less distressed and this could bias our results. However, we do not know the direction and influence of this exclusion as the foot status of this population is unknown.

Another possible limitation is on the use of multiple linear regression for our statistical analysis and the violation of homoscedasticity and normal distribution of residuals. Other authors have suggested the use of generalized linear model with gamma distribution for EQ-5D index scores, which we conducted separately (Appendix B). Though the statistical significance of age, other races and past smokers were different between both models as the p-value was close to 0.05, little difference was found in the regression coefficients. Therefore, we found that the multiple linear regression coupled with robust standard error would be a valid approach and simplify the consistence and interpretation of our results. Studies around this area have demonstrated that this approach remains valid in large samples[22, 47].

Higher income and education were associated with higher HRQOL, while insulin use, diabetic complications and other medical conditions had negative effects on HRQOL measures. Other

studies in adults with type 2 diabetes have also found similar results regarding the socio-demographic variables[48-50]. Studies regarding diabetic comorbidities have varied in settings and how researchers define and categorize them. As a result, comparison of results can become an issue. We constructed models with each individual comorbidity (Appendix C) instead of a summary variable as we presented in the results section. The decrements of foot problems were smaller, but the models gave the same conclusions as the ones previously reported and little increment was seen in the explained variance given by the adjusted r-squared. In addition, some medical conditions were not statistically significant (i.e. retinopathy, hypertension). Consequently, we opted for the models with medical conditions as a continuous variable to improve the power of our analysis.

Finally, we did not include in our analysis, data on glycated hemoglobin, BMI and diabetes duration. Studies have shown that patients with controlled diabetes measured by glycated hemoglobin present better quality of life [51, 52]. Though, it remains controversial as some argue that the reason is the decrease in number of complications[53, 54]. We built other models that included diabetes duration as an independent variable (Appendix D). However, there was a large number of missing data on this variable (23.57%) and those participants were less educated, non-white, not married and more distressed as measured by PAID-5 (Appendix E). We assumed that missing data was not completely at random. Since the inclusion of this variable would decrease analytical power while increasing bias and the standard error, we decided to exclude it from our model.

3.5. Conclusion

People with diabetic foot complications report lower HRQOL compared to the diabetic patients without foot complications. These findings support the view that diabetic patients with chronic wounds and amputation need health professional assistance and community support to improve quality of life. Additionally, patients at high risk of ulceration, in which neuropathy and PVD are present, have also problems in several domains of HRQOL and there should be interventions also targeting these populations.

3.6. References

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Chapter 4. General Discussion and Conclusion

4.1. Summary of Findings

In Alberta in 2014, 171,906 individuals were estimated to have diabetes, a condition that represents a major burden in Canada[1-3]. People with type 2 diabetes are at greater risk of developing foot problems ranging from loss of protection, caused by diabetic neuropathy, to ulceration, which could ultimately lead to an amputation[4, 5]. These different conditions vary in presentation, symptomatology and could be associated with decrements in different health domains. To address the impact diabetic foot problems have on health-related quality of life (HRQOL), we performed a systematic review (Chapter 2) and a cross-sectional analysis of HRQOL among individuals with type 2 diabetes in Alberta (Chapter 3).

In chapter 2, we conducted a systematic review according to the PRISMA[6] and Cochrane handbook guidelines[7] including 21 and 8 studies for qualitative and quantitative synthesis, respectively. A total of 10 different instruments were employed, but we did not include all of them into the meta-analysis due to possibilities of greater heterogeneity and inconsistence. Only studies assessing health domains of the SF-36/12 were pooled as majority of studies used them as a measurement of effect.

We found that different foot problems (neuropathy, peripheral vascular disease (PVD), ulcer and amputation) are associated with reduced HRQOL. Neuropathy had statistically non-significant small effect sizes in most domains of the SF-36/12, apart from the small-medium effect sizes of physical functioning domain and physical summary score (PCS). On the other hand, ulcer had a small-medium effect size in vitality, role emotional, mental health and mental component summary (MCS), though mental health did not achieve statistical significance. It also had a medium-large effect size that was statistically significant in physical functioning, role physical, bodily pain, general health, social functioning and PCS. Amputation was associated with decrements on HRQOL, but results were conflicting on whether the transition of foot ulcer to amputation was associated with higher decrements in HRQOL. There was a lack of evidence for an association of HRQOL and Charcot foot and PVD. Only two studies measure this association and they were cross-sectional with the presence of confounding variables[8, 9].

To provide results in a population-based sample and HRQOL of individuals with type 2 diabetes reporting foot problems, we examined the cross-sectional data obtained from the self-administered survey from the Alberta's Caring for Diabetes (ABCD) study[10, 11] (chapter 3). It included 1,935 individuals with majority of them presenting PVD (29.15%) and neuropathy (19.17%). There were few self-report of foot ulcer (6.10%) and amputation of limbs (1.45%). Socio-demographic and clinical characteristics such as marital status, gender, education, income, medical conditions and insulin use were associated with HRQOL. Neuropathy was associated with significant decrements of PCS, EQ-5D index and PAID-5 scores. No differences were found in MCS between individuals with neuropathy and no foot complications. Individuals reporting either PVD, ulcer or amputation had statistically significant lower HRQOL measured through SF-12 (PCS, MCS), EQ-5D and PAID-5 than those with no foot complications. Participants reporting both neuropathy and PVD had more decrements on health compared to individuals reporting one of these conditions. While amputation was associated with the highest decrement on physical health with a 10-unit decrease in this SF-12 domain, patients reporting ulceration had the lowest mental and perceived health.

4.2. Discussion

This thesis has studied various foot conditions commonly found in patients with diabetes and their association with different decrements in health domains measured through generic and specific instruments. The systematic review and cross-sectional analysis showed that neuropathy is not statistically associated with lower MCS scores, but the condition had a significant impact on PCS scores in patients with diabetes. However, our analysis reported that when measured with a diabetes-specific measure and accounting for potential confounders, individuals with neuropathy presented significantly higher diabetes-related distress compared to individuals with diabetes and no diagnosed foot problems. Some authors argue for the lack of sensitivity of the SF-36/12 to capture mental issues related to neuropathy in people with diabetes[12, 13]. Interestingly, our data analysis showed significant decrements due to neuropathy in EQ-5D index score, another generic instrument. More than half of individuals with neuropathy (52.5%) reported some level of anxiety/depression. 20.5% of them had moderate to extreme problems of

anxiety/depression, while 13.4% of individuals with no foot complications reported moderate to extreme problems in this EQ-5D dimension.

The reduced EQ-5D index score in participants with neuropathy could also be due to the physical delimitation of this condition and the fact that this utility instrument has shown great psychometric properties in physical conditions[14]. Since EQ-5D has also limited evidence on mental health[14], a specific instrument for this domain, such as the PAID-5 could be an alternative or complement, though further studies in this area are necessary.

The systematic review pointed to the lack of specific HRQOL measurement for PVD in type 2 diabetes which we covered in the cross-sectional data analysis. Additionally, an important finding was that participants with both risk factors, neuropathy and PVD were associated with higher decrements on physical, mental and overall health than participants with either of the condition. Even though the true prevalence of these risk factors in the diabetic population is unknown, most individuals developing ulcer have the neuroischemic type[15, 16], an indication that the presence of neuropathy along with PVD might be a common situation in patients with diabetes and future studies on HRQOL should take this into account.

The cross-sectional analysis tried to address the magnitude of the impact amputation has on different health domains as we found conflicting results from our systematic review. Assuming loss of limbs as the endpoint of the diabetic foot clinical pathway, we can see a decrement on physical health across this pathway in which the advance of foot disease correlates with the deterioration on this health domain. A different scenario is pointed in preference-based and mental health measures as individuals with foot ulcer had worse scores in these measurements instead of those with amputation. Although, the analysis had statistically significant results, both conducted studies in this thesis had problems regarding sample size of this foot problem.

Qualitative research also supports our findings from both studies that participants diagnosed with diabetes with foot ulcers and amputation have lower perspectives on their health. A qualitative research explains that patients with diabetic foot ulcer had a very negative attitude towards the foot with requirements for extensive care and hospital visits[17]. Loss of hope on treatment success, dissatisfaction with life were seen in patients with an amputation and foot ulcer, with the later reporting more often[17, 18].

The fact that our two studies found better mental health in patients with amputation than those with an ulcer, however, does not translate into amputation being a gold standard treatment for ulceration. Our studies found significant decrements in physical, perceived health and higher distress compared to diabetic patients with no self-report of foot problems. One study reported that 50% of a sample of amputees were at high risk of psychiatric disorders as these patients felt imprisoned into their houses and socially isolated[19]. In addition, a major amputation is also associated with reduced survival rates[20, 21].

The strength of the first study lies on the conduction of a systematic review which methodically combines and synthesizes the current HRQOL literature. It has the advantage to report results based on more than one single study, find the inconsistencies and current gaps in knowledge on diabetic foot diseases and HRQOL. This systematic review attempted to cover the main scientific databases and carry a search with the guidance of an experienced librarian. The whole process was in accordance with the PRISMA[6, 22] and Cochrane handbook[7] with two independent researchers assessing and including studies to reduce research bias and opinion of a single person. The systematic review also attempted to find measurements not affected by information bias, which is likely present in the cross-sectional analysis as the results were dependent of participants' self-report.

The data analysis was the first study that we have an acknowledgment of comparing different diabetic foot problems and their HRQOL, based on different instruments, in a population of diabetes type 2 living in Alberta. It allows us to observe the health status of this population and whether different stages of foot severity should be targeted more specifically to better meet their health-care needs. The strength of this study lies in its large sample size and extensive recruitment programs to have a sample representative of the population of type 2 diabetes in Alberta. The assessment of utility measures, based on the EQ-5D-5L, can further be used in economic evaluation of interventions for diabetic foot conditions. It attempted to find an association between HRQOL measures and PVD, since the systematic view pointed to the lack of reports regarding this foot problem.

Both studies also had several limitations. The issues on the systematic review were mainly due to constrained resources as: (1) we did not search the grey literature; (2) contacted the authors for additional information; (3) restricted to articles published in three languages (English, Spanish

and Portuguese). Another concern was the conduction of meta-analysis with high heterogeneity among studies and the use of standardized mean difference as a measure of effect instead of minimal clinical difference as some other authors have suggested[23, 24].

The cross-sectional analysis had limitations worth mentioning as: (1) the use of self-report conditions; (2) possible effect of confounding variables (HbA1c, BMI and diabetes duration); and (3) exclusion of 135 participants due the use of different outcome measures that were also more educated and less distressed at the final analysis.

The systematic review and data-analysis were limited to lack of causal inference as both studies based their conclusions on cross-sectional data, and small sample size of patients with diabetes undergoing an amputation.

4.3. Conclusion and Future Research

The ABCD analysis was an attempt to cover some knowledge gaps as the lack of studies on diabetic foot disease in Alberta, lack of measurements with a disease-specific instrument and quantitative measures of the effect of PVD in HRQOL. Both studies found that diabetic foot complications are associated with lower HRQOL with the advancing conditions correlating with lower physical health. Our cross-sectional analysis results showed that while amputation had the lowest scores in physical health, ulceration was associated with the highest decrements in perceived and mental health.

There is potential to improve HRQOL in participants with diabetes reporting foot problems by preventing future deterioration of the foot and leading to worse stages of ulceration and amputation. Current guidelines recommend the screening of neuropathy with simple instruments such as the 10g monofilament, and PVD at least on a yearly basis[25-27]. There are no evidence showing that the screening per se improves HRQOL, but the detection of these early stages and proper referral could prevent development of foot ulceration and further decrements on physical and mental health described in our cross-sectional data of participants with diabetes. Early stages of diabetic foot problems such as neuropathy and PVD are not routinely checked in Alberta[10, 28]. Care on these conditions are usually neglected[10, 28] even though our results indicate experience of lower physical, mental and overall health. Community support and other effective measures

should be put into practice to improve HRQOL of the screened participants for neuropathy and/or PVD.

Another importat strategy in targeting HRQOL improvement is in understanding the effect of modifiable risk-factors on health domains in participants with diabetic foot problems. Unfortumately, the data analysis and most of the included studies of the systematic review evaluated the effects of non-modifiable factors which cannot be changed. Future research on the assessment of the effects of modifiable factors (i.e footcare and medical adherence) in HRQOL on patients with foot problems are required.

The use of generic instruments such as SF-12 and EQ-5D are very informative for policy makers as they give a general perception of individual's health and comparability to other chronic conditions. While the first mentioned measure allows for a profile of physical and mental health, the latter as a preference-based measure can further be used in economic evaluation of future interventions. Nonetheless, our study showed the importance of specific-measures and their potential use to improve policies on mental health, supporting other authors who have suggested the use of generic and specific instruments while measuring HRQOL[29, 30]. Although, we acknowledge that it comes with the costs of increase in response burden.

The findings in our studies support that medical perception on patient's health and clinical presentation such as loss of protection sensation or obstruction of blood flow are insufficient to capture the burden of foot problems in diabetes. Only when measuring the individual domains of HRQOL can we have the picture of the current situation and improve health policies and interventions offered to the population with diabetes. For example, our results question the lack of support, extension or effective interventions, mainly regarding mental health in patients with diabetes and foot problems. Reasons could be: (1) most guidelines are based on weak evidence[25-27]; (2) clinical pathways for diabetic foot are not put into practice[10, 28]; (3) current guidelines gives little importance in measuring the patient's HRQOL[25-27]; (4) lack of recommendation in treatments for mental health.

Further cohort studies with longer follow up and larger amputation sample size are still required to determine causality and the correlation of changes in HRQOL with different stages of diabetic foot problems.

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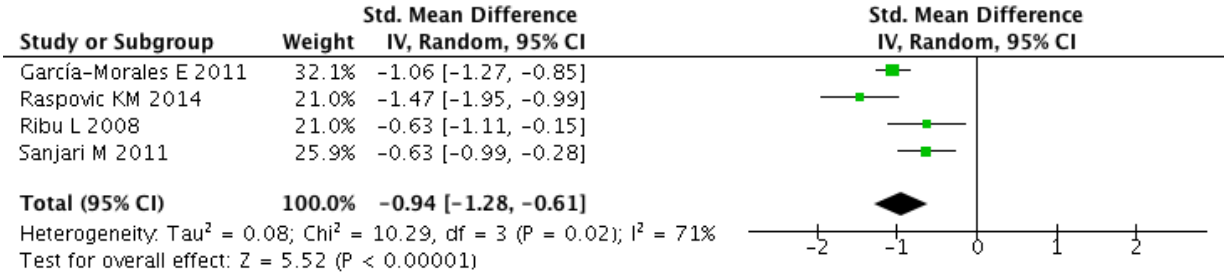
Appendix

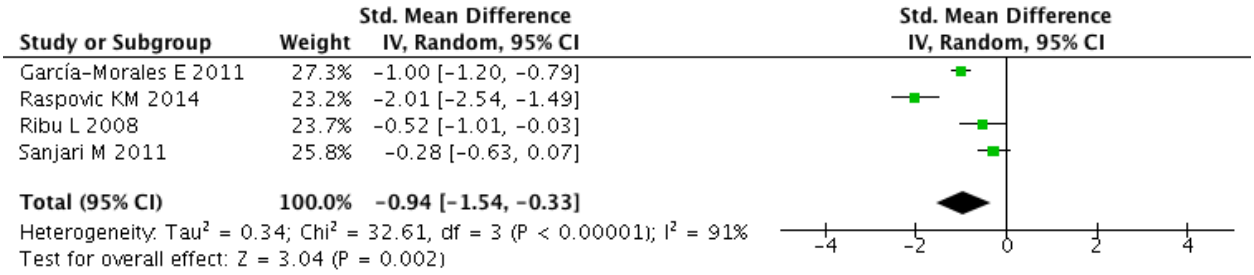
Appendix A. Results of Randon-effect Meta-analysis of SF-36/12 domains and summary scores

A.1. Meta-analsys comparing SF-36/12 domains and summary scores between individuals with and without foot ulcer

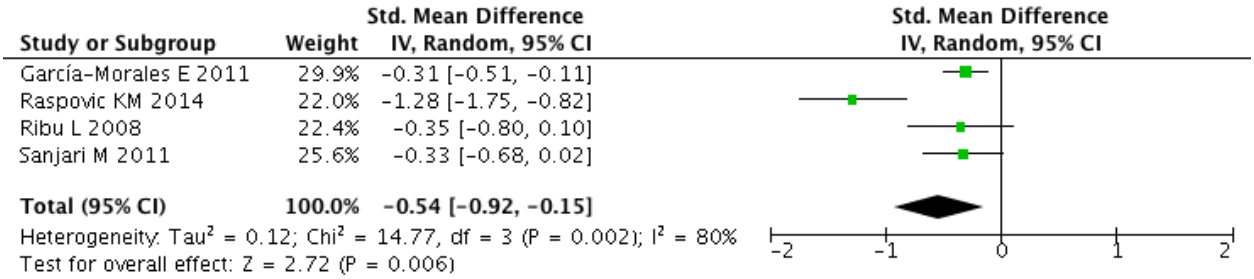
Physical functioning



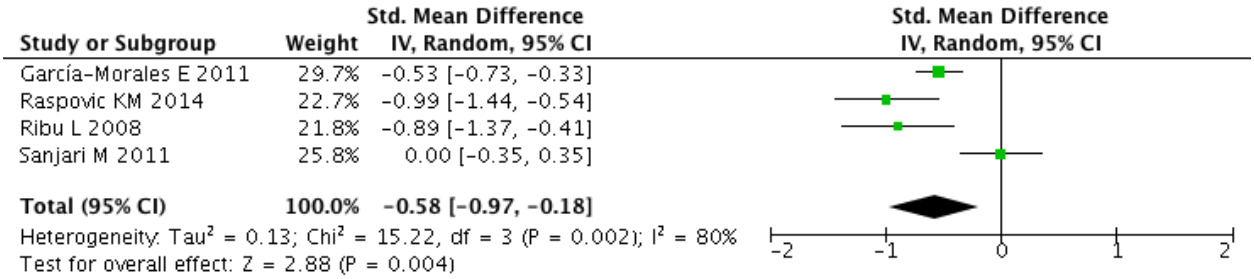
Role Physical



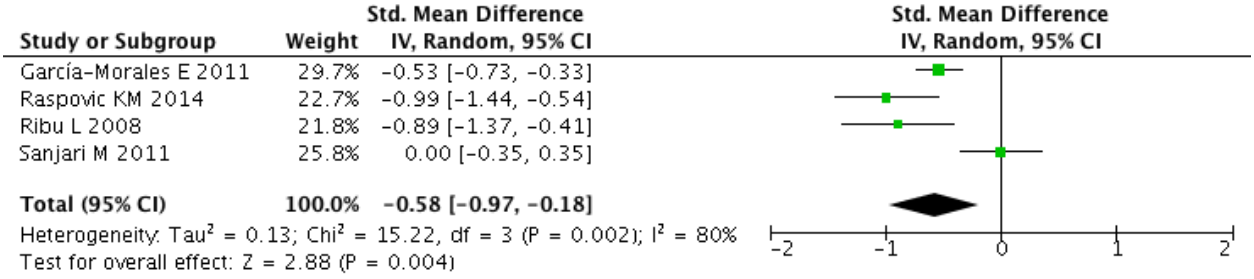
Bodily Pain



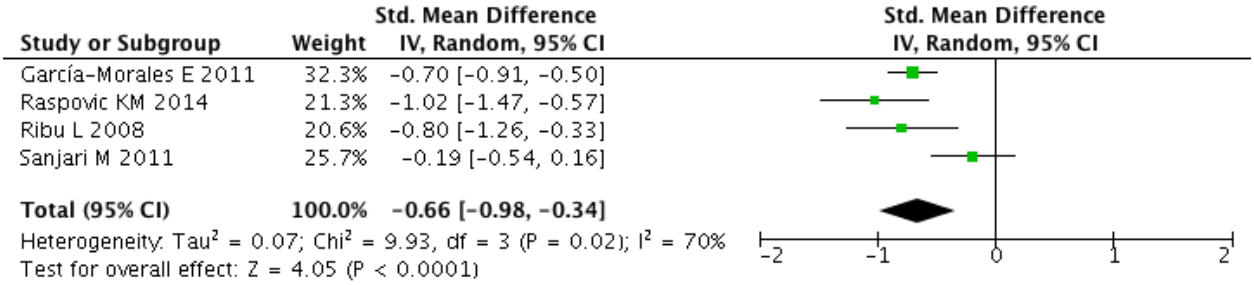
General Health



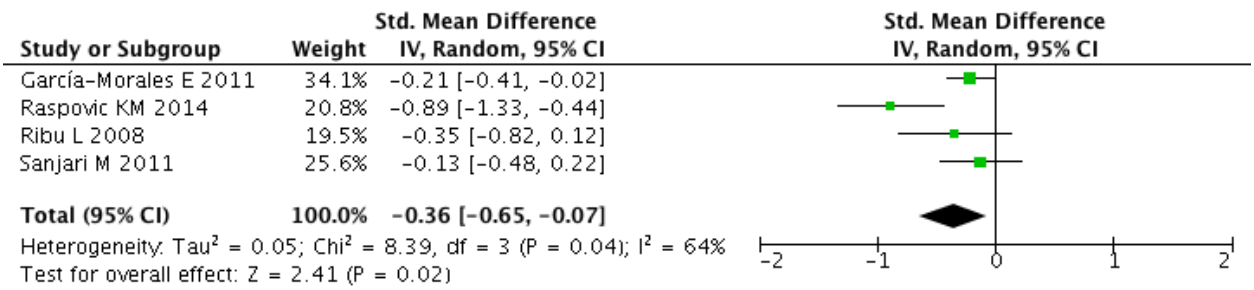
Vitality



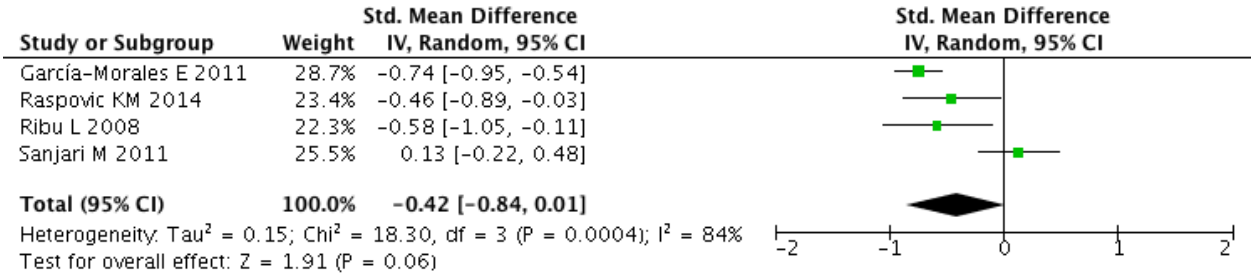
Social Functioning



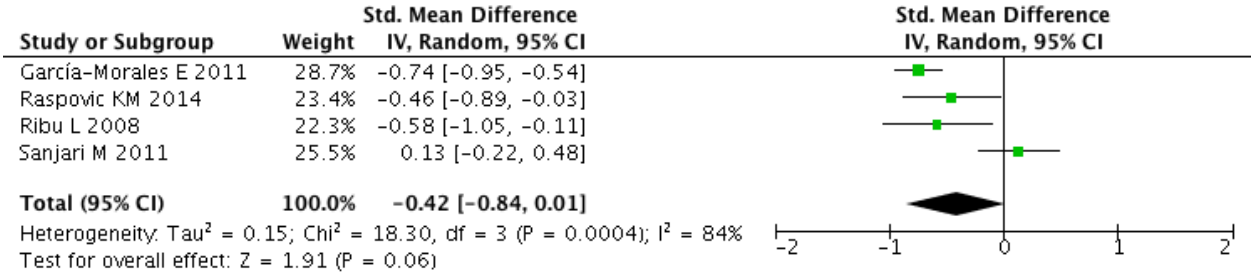
Role Emotional



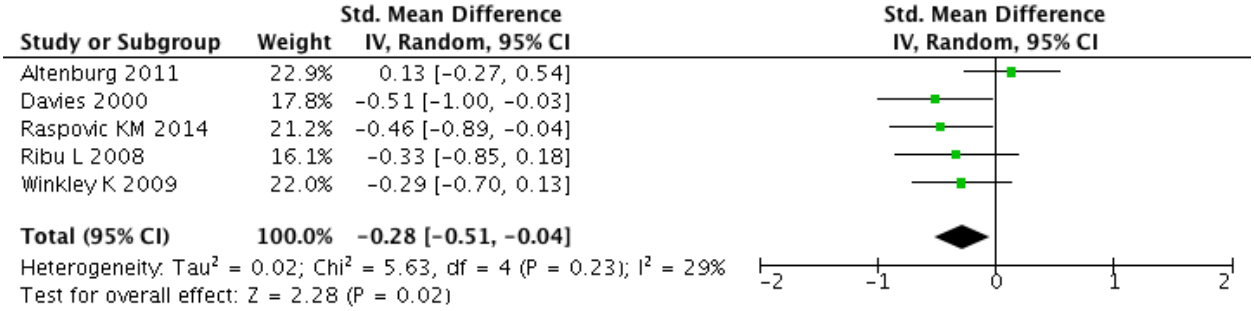
Mental Health



Physical Component Summary (PCS)

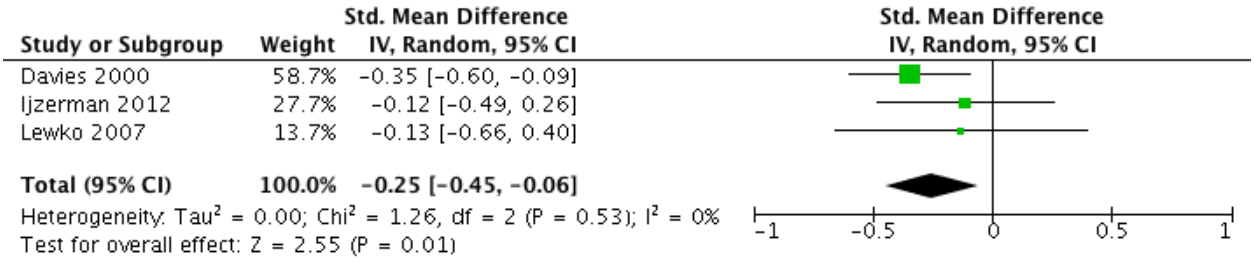


Mental Component Summary (MCS)

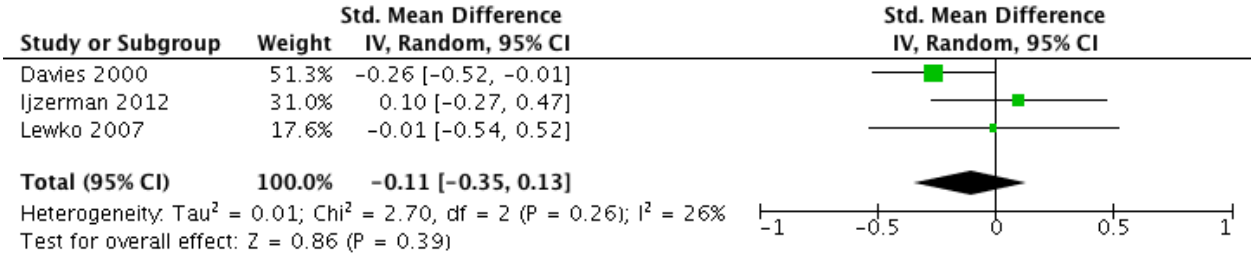


A.2. Meta-analysis comparing SF-36/12 domains and summary scores between individuals with and without neuropathy

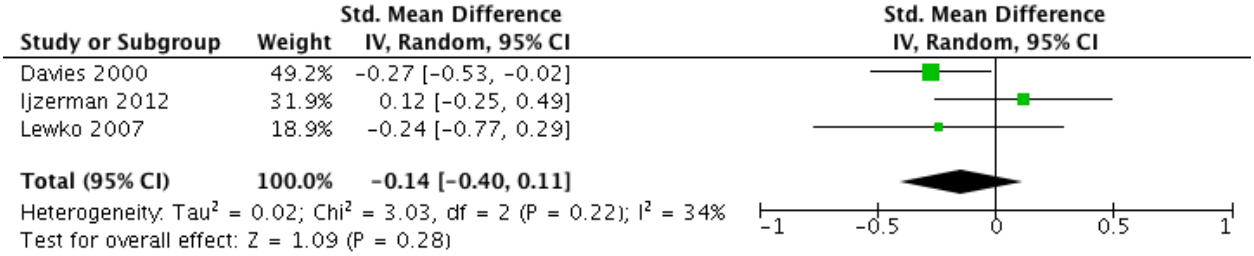
Physical Functioning



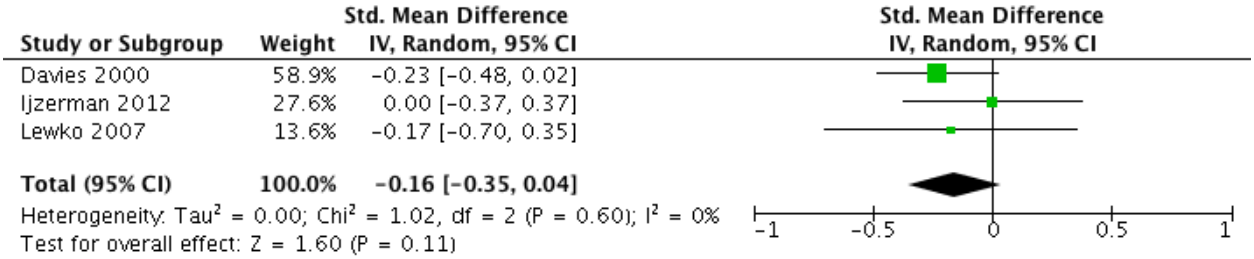
Role Physical



Bodily Pain



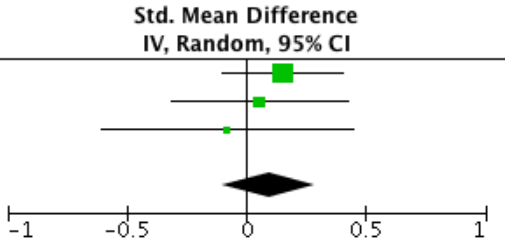
General Health



Vitality

Study or Subgroup	Weight	Std. Mean Difference IV, Random, 95% CI
Davies 2000	58.9%	0.15 [-0.10, 0.41]
Ijzerman 2012	27.5%	0.05 [-0.32, 0.42]
Lewko 2007	13.6%	-0.08 [-0.61, 0.45]
Total (95% CI)	**100.0%**	**0.09 [-0.10, 0.29]**

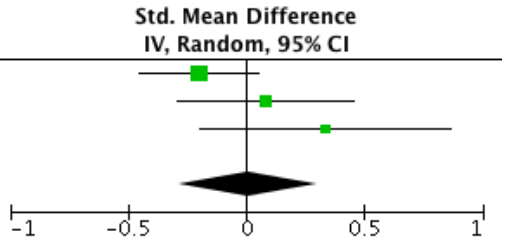
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)



Social Functioning

Study or Subgroup	Weight	Std. Mean Difference IV, Random, 95% CI
Davies 2000	45.8%	-0.20 [-0.45, 0.05]
Ijzerman 2012	33.0%	0.08 [-0.29, 0.45]
Lewko 2007	21.2%	0.34 [-0.20, 0.87]
Total (95% CI)	**100.0%**	**0.01 [-0.29, 0.30]**

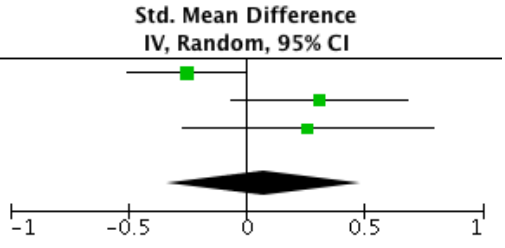
Heterogeneity: Tau² = 0.03; Chi² = 3.82, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 0.05 (P = 0.96)



Role Emotional

Study or Subgroup	Weight	Std. Mean Difference IV, Random, 95% CI
Davies 2000	39.8%	-0.25 [-0.51, 0.00]
Ijzerman 2012	33.8%	0.31 [-0.06, 0.68]
Lewko 2007	26.3%	0.26 [-0.27, 0.79]
Total (95% CI)	**100.0%**	**0.07 [-0.34, 0.48]**

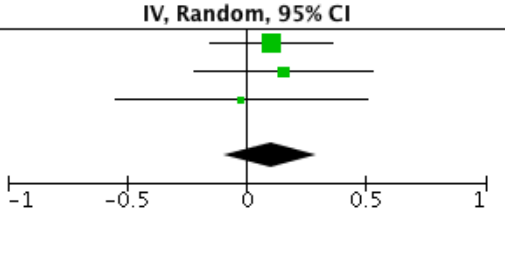
Heterogeneity: Tau² = 0.09; Chi² = 7.26, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 0.35 (P = 0.73)



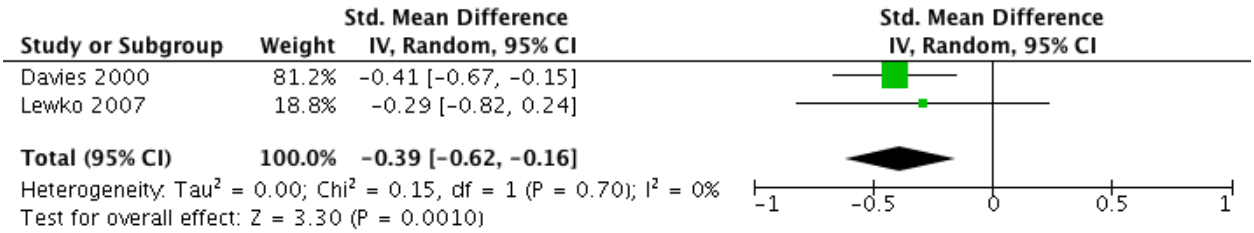
Mental Health

Study or Subgroup	Weight	Std. Mean Difference IV, Random, 95% CI
Davies 2000	59.0%	0.10 [-0.15, 0.36]
Ijzerman 2012	27.4%	0.16 [-0.22, 0.53]
Lewko 2007	13.6%	-0.02 [-0.55, 0.51]
Total (95% CI)	**100.0%**	**0.10 [-0.09, 0.29]**

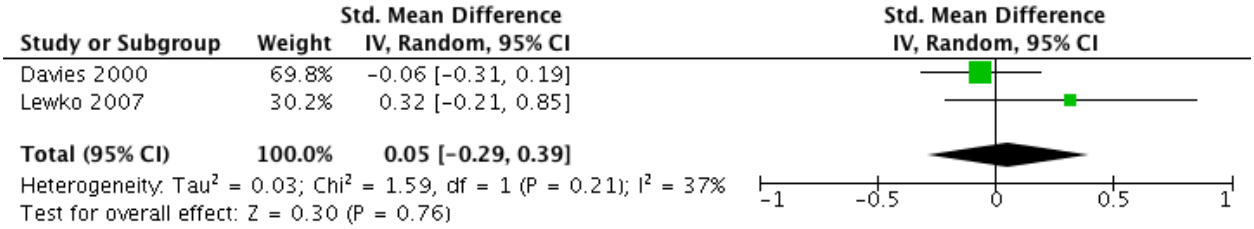
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



Physical Component Summary (PCS)



Mental Component Summary (MCS)



Appendix B. Alternative statistical analysis of EQ-5D-5L index score

Variables	EQ-5D-5L index score (robust standard error)				EQ-5D-5L index score (GLM- gamma distribution)			
	Coefficient	SE	95% CI	p-value	Coefficient	SE	95% CI	p-value
Foot problems (ref: no foot problem)								
- Neuropathy	-0.052	0.014	(-0.080, -0.024)	<0.001	-0.052	0.015	(-0.081, -0.023)	<0.001
- PVD	-0.052	0.010	(-0.072, -0.032)	<0.001	-0.055	0.011	(-0.076, -0.035)	<0.001
- Neuropathy and PVD	-0.113	0.016	(-0.143, -0.082)	<0.001	-0.119	0.012	(-0.142, -0.096)	<0.001
- Ulcer	-0.147	0.023	(-0.192, -0.102)	<0.001	-0.148	0.015	(-0.177, -0.120)	<0.001
- Amputation	-0.127	0.034	(-0.192, -0.061)	<0.001	-0.123	0.026	(-0.173, -0.072)	<0.001
Age	0.001	0.000	(0.000, 0.001)	0.05	0.001	0.000	(0.000, 0.002)	0.01
Male	0.015	0.007	(0.001, 0.028)	0.04	0.016	0.008	(0.001, 0.031)	0.04
Married	0.009	0.008	(-0.008, 0.025)	0.30	0.009	0.008	(-0.008, 0.025)	0.30
High school or more	0.035	0.010	(0.014, 0.055)	0.001	0.037	0.010	(0.017, 0.057)	<0.001
Income >= $80,000	0.031	0.008	(0.016, 0.046)	<0.001	0.034	0.010	(0.015, 0.053)	<0.001
Race (ref: Caucasian)								
- Aboriginal	0.086	0.016	(0.055, 0.117)	<0.001	0.098	0.026	(0.048, 0.148)	<0.001
- Others	0.022	0.011	(0.002, 0.043)	0.04	0.028	0.015	(-0.001, 0.056)	0.05
Smoking (ref: no smoker)								
- Current smoker	-0.026	0.013	(-0.051, -0.001)	0.04	-0.026	0.013	(0.050, -0.001)	0.04
- Past smoker	-0.015	0.007	(-0.028, -0.001)	0.04	-0.015	0.008	(-0.030, 0.001)	0.07
Insulin use	-0.032	0.008	(-0.048, -0.017)	<0.001	-0.034	0.008	(-0.049, -0.019)	<0.001
Number of medical conditions	-0.027	0.002	(-0.032, -0.022)	<0.001	-0.029	0.002	(-0.033, -0.024)	<0.001
Intercept	0.837	0.029	(0.781, 0.893)		0.820	0.029	(0.763, 0.878)	
R-squared	0.250			<0.001				

Ref: reference group; PVD: peripheral vascular disease; EQ-5D-5L: Euroqol -5D Health utility index; GLM: generalized linear model; SE: standard error; 95%CI: 95% confidence interval

Appendix C. Alternative models including medical conditions as dichotomous variables

C.1. Alternative regression analysis of SF-12v2 (MCS, PCS)

Variables	SF-12v2 - MCS				SF-12v2 - PCS			
	Coefficient	SE	95%CI	p-value	Coefficient	SE	95%CI	p-value
Foot problems (ref: no foot problem)					0.00			
- Neuropathy	-1.24	0.87	(-2.94, 0.46)	0.15	-2.45	0.87	(-4.16, -0.74)	0.005
- PVD	-2.36	0.58	(-3.50, -1.21)	<0.001	-3.45	0.62	(-4.67, -2.23)	<0.001
- Neuropathy and PVD	-2.75	0.76	(-4.25, -1.26)	<0.001	-4.90	0.75	(-6.38, -3.43)	<0.001
- Ulcer	-4.33	1.02	(-6.34, -2.32)	<0.001	-7.84	1.00	(-9.79, -5.88)	<0.001
- Amputation	-3.24	1.52	(-6.22, -0.26)	0.03	-9.95	1.79	(-13.46, -6.44)	<0.001
Age	0.17	0.02	(0.13, 0.22)	<0.001	-0.01	0.02	(-0.06, 0.03)	0.62
Male	0.57	0.43	(-0.28, 1.42)	0.19	1.20	0.43	(0.36, 2.04)	0.005
Married	1.61	0.48	(0.67, 2.55)	0.001	1.49	0.48	(0.56, 2.43)	0.002
High school or more	1.81	0.55	(0.72, 2.89)	0.001	2.07	0.59	(0.92, 3.23)	<0.001
Income >= $80,000	1.25	0.50	(0.27, 2.24)	0.01	2.24	0.48	(1.30, 3.18)	<0.001
Race (ref: Caucasian)								
- Aboriginal	2.15	1.35	(-0.49, 4.79)	0.11	4.43	1.16	(2.16, 6.70)	<0.001
- Others	-1.34	0.73	(-2.76, 0.08)	0.07	-0.35	0.73	(-1.78, 1.08)	0.63
Smoking (ref: no smoker)	0.00							
- Current smoker	-1.55	0.74	(-3.00, -0.11)	0.04	-1.46	0.72	(-2.87, -0.06)	0.04
- Past smoker	0.74	0.43	(-0.11, 1.58)	0.09	-0.14	0.42	(-0.97, 0.69)	0.74
Insulin use	-1.90	0.45	(-2.78, -1.02)	<0.001	-2.19	0.44	(-3.06, -1.32)	<0.001
Medical conditions								
- Obesity	-1.21	0.43	(-2.05, -0.38)	0.004	-2.05	0.42	(-2.88, -1.22)	<0.001
- Respiratory problems	-1.61	0.52	(-2.64, -0.59)	0.002	-2.80	0.55	(-3.88, -1.71)	<0.001
- Arthritis	-2.07	0.43	(-2.90, -1.23)	<0.001	-4.09	0.43	(-4,94, -3.25)	<0.001
- Thyroid problems	-1.34	0.52	(2.37, -0.32)	0.01	-0.60	0.53	(-1.64, 0.43)	0.25
- Cancer	-0.86	0.59	(-2.02, 0.30)	0.15	-1.21	0.62	(-2.42, 0.01)	0.05
- Retinopathy	-1.29	0.77	(-2.79, 0.21)	0.09	-0.47	0.75	(-1.94, 1.00)	0.53
- Kidney problems	-3.10	1.06	(-5.18, -1.01)	0.004	-4.59	1.14	(-6.83, -1.35)	<0.001
- Heart disease	-1.10	0.55	(-2.17, -0.03)	0.04	-2.89	0.56	(-3.99, -1.79)	<0.001
- Stroke	-0.16	0.83	(-1.79, 1.46)	0.85	-1.67	0.88	(-3.39, 0.05)	0.06
- Dyslipidemia	-0.41	0.52	(-1.42, 0.61)	0.43	-0.16	0.52	(-1.17, 0.86)	0.76
- Hypertension	0.48	0.49	(-0.47, 1.44)	0.32	-0.05	0.48	(-0.99, 0.88)	0.91
Intercept	37.64	1.72	(34.27, 41.01)		48.63	1.73		

R-squared	0.16	0.30

Ref: reference group; PVD: peripheral vascular disease; SF-12v2: short-form-12 version 2; MCS: mental component summary; PCS: physical component summary; SE: standard error; 95%CI: 95% confidence interval

C.2. Alternative regression analysis of EQ-5D-5L index and PAID-5 scores

Variables	EQ-5D-5L index score				PAID-5 score			
	Coefficient	SE	95% CI	p-value	Coefficient	SE	95% CI	p-value
Foot problems (ref: no foot problem)								
- Neuropathy	-0.049	0.014	(-0.077, -0.020)	0.001	1.13	0.42	(0.30, 1.96)	0.01
- PVD	-0.045	0.010	(-0.065, -0.026)	<0.001	1.56	0.28	(1.01, 2.10)	<0.001
- Neuropathy and PVD	-0.105	0.016	(-0.136, -0.074)	<0.001	2.23	0.39	(1.47, 2.98)	<0.001
- Ulcer	-0.140	0.023	(-0.185, -0.095)	<0.001	2.80	0.49	(1.84, 3.77)	<0.001
- Amputation	-0.118	0.034	(-0.185, -0.050)	0.001	2.02	0.87	(0.32, 3.73)	0.02
Age	0.001	0.000	(0.000, 0.001)	0.07	-0.10	0.01	(-0.12, -0.08)	<0.001
Male	0.013	0.007	(-0.001, 0.027)	0.08	-0.15	0.20	(-0.55, 0.25)	0.46
Married	0.008	0.008	(-0.007, 0.024)	0.31	-0.31	0.22	(-0.74, 0.13)	0.17
High school or more	0.031	0.010	(0.010, 0.051)	0.003	-0.79	0.28	(-1.34, -0.25)	0.004
Income >= $80,000	0.029	0.007	(0.015, 0.044)	<0.001	-0.68	0.23	(-1.13, -0.24)	0.003
Race (ref: Caucasian)								
- Aboriginal	0.082	0.016	(0.050, 0.114)	<0.001	-0.80	0.58	(-1.94, 0.34)	0.17
- Others	0.017	0.011	(-0.003, 0.038)	0.10	0.94	0.42	(0.12, 1.77)	0.03
Smoking (ref: no smoker)								
- Current smoker	-0.026	0.012	(-0.050, -0.002)	0.03	0.13	0.36	(-0.58, 0.83)	0.73
- Past smoker	-0.012	0.007	(-0.05, 0.002)	0.08	-0.38	0.20	(-0.77, 0.01)	0.06
Insulin use	-0.035	0.008	(-0.050, -0.020)	<0.001	1.02	0.21	(0.60, 1.43)	<0.001
Medical conditions								
- Obesity	-0.028	0.007	(-0.041, -0.015)	<0.001	0.22	0.20	(-0.17, 0.61)	0.26
- Respiratory problems	-0.029	0.010	(-0.048, -0.011)	0.002	0.09	0.25	(-0.39, 0.58)	0.70
- Arthritis	-0.074	0.007	(-0.088, -0.060)	<0.001	0.34	0.20	(-0.05, 0.74)	0.09
- Thyroid problems	-0.011	0.009	(-0.029, 0.007)	0.22	0.42	0.24	(-0.06, 0.89)	0.09
- Cancer	-0.019	0.011	(-0.040, 0.003)	0.09	-0.33	0.25	(-0.83, 0.17)	0.19
- Retinopathy	-0.015	0.014	(-0.043, 0.012)	0.26	0.99	0.37	(0.27, 1.71)	0.01
- Kidney problems	-0.092	0.024	(-0.140, -0.045)	<0.001	0.94	0.50	(-0.04, 1.92)	0.06
- Heart disease	-0.016	0.010	(-0.035, 0.003)	0.10	0.08	0.26	(-0.43, 0.59)	0.75
- Stroke	-0.038	0.018	(-0.072, -0.003)	0.03	0.39	0.43	(-0.46, 1.24)	0.37
- Dyslipidemia	-0.002	0.008	(-0.018, 0.015)	0.84	-0.01	0.23	(-0.46, 0.45)	0.98
- Hypertension	-0.005	0.007	(-0.019, 0.010)	0.53	-0.08	0.22	(-0.52, 0.35)	0.71

Intercept	0.825	0.030	(0.767, 0.883)	10.55	0.84	(8.89, 12.20)
R-squared	0.272			0.16		

Ref: reference group; PVD: peripheral vascular disease; EQ-5D-5L: Euroqol -5D Health utility index; PAID-5: Short form of the Problem Area in Diabetes Scale; SE: standard error; 95%CI: 95% confidence interval

Appendix D. Multiple regression results of models containing diabetes duration as a continuous variable

D.1. Regression results of SF-12v2 (MCS and PCS) with diabetes duration as a continuous variable

Variables	SF-12v2 - MCS				SF-12v2 - PCS			
	Coefficient	SE	95%CI	p-value	Coefficient	SE	95% CI	p-value
Foot problems (ref: no foot problem)								
- Neuropathy	-0.70	0.90	(-2.47, 1.06)	0.44	-3.09	0.97	(-4.99, -1.20)	0.001
- PVD	-2.50	0.66	(-3.80, -1.21)	<0.001	-3.55	0.70	(-4.93, -2.17)	<0.001
- Neuropathy and PVD	-2.73	0.81	(-4.32, -1.14)	0.001	-5.02	0.85	(-6.69, -3.36)	<0.001
- Ulcer	-5.37	1.24	(-7.80, -2.93)	<0.001	-9.21	1.25	(-11.66, -6.76)	<0.001
- Amputation	-3.67	1.71	(-7.03, -0.31)	0.03	-8.06	2.15	(-12.28, -3.85)	<0.001
Age	0.21	0.03	(0.16, 0.26)	<0.001	0.01	0.03	(-0.04, 0.06)	0.59
Male	0.74	0.49	(-0.21, 1.69)	0.13	1.15	0.47	(0.21, 2.08)	0.02
Married	1.70	0.55	(0.61, 2.79)	0.002	1.33	0.56	(0.23, 2.43)	0.02
High school or more	1.80	0.62	(0.58, 3.01)	0.004	2.97	0.68	(1.64, 4.30)	<0.001
Income >= $80,000	1.05	0.58	(-0.08, 2.19)	0.07	2.16	0.55	(1.09, 3.23)	<0.001
Race (ref: Caucasian)	0.00							
- Aboriginal	1.06	1.50	(-1.89, 4.01)	0.48	3.33	1.35	(0.67, 5.99)	0.01
- Others	-1.17	0.99	(3.12, 0.78)	0.24	0.08	0.93	(-1.74, 1.91)	0.93
Smoking (ref: no smoker)	0.00							
- Current smoker	-0.60	0.80	(-2.17, 0.97)	0.45	-0.93	0.81	(-2.53, 0.66)	0.25
- Past smoker	0.96	0.49	(0.00, 1.93)	0.05	-0.08	0.48	(-1.03, 0.86)	0.86
Insulin use	-1.81	0.52	(-2.84, -0.78)	<0.001	-2.04	0.52	(-3.06, -1.01)	<0.001
Diabetes duration	-0.02	0.02	(-0.07, 0.02)	0.31	-0.02	0.02	(-0.06, 0.03)	0.53
Number of medical conditions	-1.13	0.16	(-1.44, -0.82)	<0.001	-1.89	0.16	(-2.20, -1.59)	<0.001
Intercept	36.82	1.87	(33.16, 40.48)		48.55	1.90	(44.82, 52.28)	
R-squared	0.16				0.27			

Ref: reference group; PVD: peripheral vascular disease; SF-12v2: short-form-12 version 2; MCS: mental component summary; PCS: physical component summary; SE: standard error; 95%CI: 95% confidence interval

D.2. Regression results of EQ-5D-5L index and PAID-5 scores with diabetes duration as a continuous variable

Variables	EQ-5D-5L index score				PAID-5 score			
	Coefficient	SE	95%CI	p-value	Coefficient	SE	95% CI	p-value
Foot problems (ref: no foot problem)								
- Neuropathy	-0.051	0.015	(-0.080, -0.021)	<0.001	1.15	0.45	(0.27, 2.03)	0.01
- PVD	-0.047	0.012	(-0.069, -0.024)	<0.001	1.57	0.31	(0.96, 2.17)	<0.001
- Neuropathy and PVD	-0.102	0.017	(-0.135, -0.069)	<0.001	2.22	0.42	(1.41, 3.04)	<0.001
- Ulcer	-0.164	0.028	(-0.218, -0.110)	<0.001	2.70	0.56	(1.61, 3.80)	<0.001
- Amputation	-0.111	0.043	(-0.195, -0.027)	0.01	1.66	0.93	(-0.17, 3.48)	0.08
Age	0.001	0.000	(0.000, 0.002)	0.01	-0.09	0.01	(-0.12, -0.07)	<0.001
Male	0.013	0.008	(-0.002, 0.029)	0.09	-0.32	0.21	(-0.74, 0.10)	0.14
Married	0.012	0.009	(-0.006, 0.031)	0.19	-0.33	0.24	(-0.80, 0.14)	0.17
High school or more	0.043	0.012	(0.019, 0.068)	<0.001	-0.60	0.30	(-1.20, 0.00)	0.05
Income >= $80,000	0.026	0.009	(0.009, 0.043)	0.00	-0.48	0.25	(-0.98, 0.02)	0.06
Race (ref: Caucasian)								
- Aboriginal	0.066	0.019	(0.029, 0.102)	<0.001	-0.47	0.67	(-1.78, 0.83)	0.48
- Others	0.026	0.013	(0.001, 0.052)	0.05	0.45	0.50	(-0.53, 1.44)	0.37
Smoking (ref: no smoker)								
- Current smoker	-0.020	0.014	(-0.048, 0.007)	0.15	-0.10	0.39	(-0.86, 0.66)	0.79
- Past smoker	-0.012	0.008	(-0.027, 0.003)	0.13	-0.38	0.22	(-0.81, 0.04)	0.08
Insulin use	-0.034	0.009	(-0.052, -0.017)	<0.001	1.15	0.24	(0.69, 1.61)	<0.001
Diabetes duration	0.000	0.000	(-0.001, 0.001)	0.76	0.00	0.01	(-0.02, 0.02)	0.82
Number of medical conditions	-0.025	0.003	(-0.030, -0.019)	<0.001	0.16	0.07	(0.01, 0.30)	0.03
Intercept	0.799	0.032	(0.735, 0.862)		9.83	0.93	(8.00, 11.66)	
R-squared	0.232				0.13			

Ref: reference group; PVD: peripheral vascular disease; EQ-5D-5L: Euroqol -5D Health utility index; PAID-5: Short form of the Problem Area in Diabetes Scale; SE: standard error; 95%CI: 95% confidence interval

Appendix E. Characteristics of participants with and without missing values of diabetes duration

Outcome	Included (1,935)	Diabetes duration (1,479)	Missing diabetes duration (456)	p-value
Age - mean (sd)	64.5 (10.7)	64.7 (10.3)	64.0 (11.8)	0.25
Gender - n(%)				
- Female	875 (45.2)	683 (46.2)	192 (42.1)	0.13
- Male	1,060 (54.8)	796 (53.8)	264 (57.9)	
Marital Status - n(%)				
- Married	1,379 (71.3)	1073 (72.5)	306 (67.1)	0.02
- Not Married	556 (28.7)	406 (27.5)	150 (32.9)	
Education - n(%)				
- Less than high school	285 (14.7)	204 (13.8)	81 (17.8)	0.04
- High School or more	1,650 (85.2)	1,275 (86.2)	375 (82.2)	
Ethnicity - n(%)				
- Caucasian	1,752 (90.5)	1,374 (92.9)	378 (82.9)	<0.001
- Aboriginal	46 (2.4)	35 (2.4)	11 (2.4)	
- Others	137 (7.1)	70 (4.7)	67 (14.7)	
Annual household income - n(%)				
- <$80,000	1,481 (76.5)	1,119 (75.7)	362 (79.4)	0.1
- >=$80,000	454 (23.5)	360 (24.3)	94 (20.6)	
Insulin use - n(%)	667 (34.5)	495 (33.5)	172 (37.7)	0.09
Foot problems				0.17
- No foot problems	1,214 (62.7)	939 (63.5)	275 (60.3)	
- Neuropathy	123 (6.4)	98 (6.6)	25 (5.5)	
- PVD	287 (14.8)	212 (14.3)	75 (16.4)	
- Neuropathy and PVD	186 (9.6)	144 (9.7)	42 (9.2)	
- Ulcer	97 (5.0)	69 (4.7)	28 (6.1)	
- Amputation	28 (1.4)	17 (1.1)	11 (2.4)	
Number of medical conditions - mean (sd)	3.54 (1.6)	3.54 (1.6)	3.56 (1.8)	0.85
- Dyslipidemia - n(%)	1,558 (80.5)	1,029 (69.6)	292 (64.0)	0.03
- Obesity - n(%)	1,093 (56.5)	835 (56.5)	258 (56.6)	0.96
- Respiratory problems - n(%)	368 (19.0)	286 (19.3)	82 (18.0)	0.52
- Arthritis - n(%)	952 (49.2)	733 (49.6)	219 (48.0)	0.57
- Thyroid Problem - n(%)	426 (22.0)	338 (22.8)	88 (19.3)	0.11
- Cancer - n(%)	262 (13.5)	200 (13.5)	62 (13.6)	0.97
- Retinopathy - n(%)	161 (8.3)	111 (7.5)	50 (11.0)	0.02
- Kidney Failure - n(%)	86 (4.4)	60 (4.1)	26 (5.7)	0.14
- Heart disease - n(%)	384 (19.8)	280 (18.9)	104 (22.8)	0.07
- Hypertension - n(%)	1,433 (74.1)	1,103 (74.6)	330 (72.4)	0.35
- Stroke - n(%)	135 (7.0)	93 (6.3)	42 (9.2)	0.03
Smoking - n(%)				
- Never	793 (41.0)	592 (40.0)	201 (44.1)	0.27

- Current Smoker	199 (10.3)	152 (10.3)	47 (10.3)	
- Quit smoking	943 (48.7)	735 (49.7)	208 (45.6)	
PAID-5 score - mean (sd)	4.32 (4.3)	4.08 (4.1)	5.11 (4.9)	<0.001

PAID-5: Short form of the Problem Area in Diabetes Scale; sd: standard deviation